FIRST EDITION

NeuroPedia

NEUROPEDIA.NET

OMAR F. JBARAH
ETHAR A. HAZAIMEH

Omar F. Jbarah
Ethar A. Hazaimeh

Neuropedia.net

Literature Review Articles

Neuropedia for Training and Scientific Research

Index Number: 2023/9/4824

Book Title: Neuropedia.net

Author: Jbarah, Omar Fatehi Mohammad

Author (Other): Hazaimeh, Ethar Adeeb Mohammad

Publication Data: Amman: Neuropedia for Training and Scientific Research, 2023

Classification: 616.8

Descriptors: Nervous System//Psychiatry// Diseases// Treatment

Edition Data: First Edition

ISBN: 978-9923-9419-0-4

Omar F. Jbarah
Ethar A. Hazaimeh

Neuropedia for Training and Scientific Research
Amman – Jordan

ISBN 978-9923-9419-0-4

Neuropedia for Training and Scientific Research ©

This work is protected by copyright law. The Publisher reserves all rights, whether for the entire material or any part of it. This includes, but is not limited to, the rights of translation, reproduction, reuse of images, public recitation, broadcasting, reproduction on microfilm, or in any other physical form, as well as the transmission, storage, and retrieval of information, electronic adaptation, and the use of computer software, whether through current or future technologies.

The use of general descriptive terms, registered trademarks, or service marks in this publication does not imply that they are free from the applicable protective laws and regulations, even if no specific disclaimer is provided.

The publisher, authors, editors and reviewers have made every effort to ensure that the information and guidance in this book are accurate at the time of publication. However, no warranties, explicit or implicit, are made by the publisher, authors, or editors regarding the contents or for any potential errors or omissions.

Dedication

To all the doctors and students who contributed to the launch and continued success of **Neuropedia.net**.

To our esteemed mentors in the Departments of Neurosurgery and Neurology at King Abdullah University Hospital, Irbid, Jordan.

To the passionate students in all medical fields who inspire and drive this endeavor forward.

To our beloved families, for their unwavering support and encouragement.

To our precious daughter, Talia, whose presence fills our lives with joy and purpose.

Omar F. Jbarah

Preface

The journey of **Neuropedia** began in 2020 with a vision to advance scientific research and medical training in the field of neuroscience. What started as a small initiative has grown into a thriving global platform, bringing together doctors, researchers, and students from various medical disciplines, all united by their passion for the brain and its complexities.

This book is a special collection of all the articles originally published on **Neuropedia.net**, written by dedicated medical students and meticulously reviewed by specialists in their fields. It is a testament to the hard work, dedication, and passion of everyone involved—students, professionals, and mentors—who have contributed their time and knowledge to make this endeavor a reality.

Our mission with this publication is twofold: to offer an in-depth exploration of Neurosurgery, Neurology, Psychiatry and Neuroscience topics while fostering a spirit of collaboration and curiosity among the next generation of medical professionals. Each chapter has been carefully curated to provide insights into both foundational knowledge and cutting-edge advancements, making this book a valuable asset for learners at various stages of their careers.

Lastly, this book is dedicated to all those who have played a role in making Neuropedia a success, to our families for their constant encouragement, to our beloved daughter Talia, and in loving memory of my mother, whose spirit continues to inspire us.

It is our hope that this book will serve as a foundation for continued learning, innovation, and collaboration in the ever-evolving field of neuroscience. May it inspire, educate, and empower all those who turn its pages.

With gratitude,

Omar F. Jbarah
Founder and General Director of Neuropedia

Acknowledgments

The editors would like to extend their heartfelt thanks to every student who contributed to the articles in this book. Your passion, dedication, and commitment to the field of neuroscience are the foundation of this work, and without you, this book would not have been possible.

We also want to express our deep gratitude to everyone who has worked tirelessly to sustain Neuropedia's success. Your hard work, vision, and perseverance have been crucial in driving the empowerment of neuroscience-related research, not only in our region but across the globe.

A special thanks goes to **Haneen Bani Hani** and **Rahmeh Adel** for their tremendous efforts in finalizing and reviewing this book. Your dedication and attention to detail have been instrumental in bringing this project to completion.

Your contributions have made Neuropedia a platform of excellence, fostering collaboration and innovation in neuroscience and neurosurgery worldwide.

With sincere appreciation,

The Editors

About This Book

This book represents the full collection of scientific content from **Neuropedia.net**, originally published in its online version. It is designed to provide a comprehensive resource for medical professionals, students, and researchers in the fields of neuroscience, neurology, neurosurgery, and psychiatry.

The book is divided into four main chapters:

1. **Neurosurgery**
2. **Neurology**
3. **Psychiatry**
4. **Neuroscience**

Each chapter contains multiple articles, carefully written by medical students and reviewed by specialists in the field. These articles include the latest updates and cutting-edge scientific content for each topic, offering a thorough exploration of current advancements and trends.

This book is a testament to the hard work and dedication of the Neuropedia community, aimed at fostering knowledge, research, and innovation in the neurological sciences.

* Some pictures, diagrams, and tables in this book may not appear as clear as intended. For a clearer view and full access to these visuals, please refer to the original articles on our website: www.Neuropedia.net.

Contents

Neurosurgery 12

1. Spinal Biomechanics and Basics of Spinal Instrumentation
2. Epidemiology of Traumatic Brain Injury
3. Blunt Cerebrovascular Injury.
4. Radiotherapy Techniques.
5. Biomechanical basis of traumatic brain injury.
6. Carotid Body Tumors.
7. Carotid Occlusive Artery Disease - Carotid Artery Stenosis.
8. Non-Atherosclerotic Carotid Artery Lesions.
9. Neural Tube Defects.
10. Chiari Type I Malformation.
11. Dandy Walker Syndrome.
12. Low grade glioma.
13. Epidural Hematoma.
14. Cerebral Vasospasm.
15. Central Nervous System Primitive Neuroectodermal Tumor (PNET).
16. Arachnoid Cyst.
17. Craniopagus Twins.
18. Brown Sequard Syndrome.
19. Brain abscess.
20. Pineal Gland Anatomy and Tumors.
21. arachnoid cysts.
22. Intraventricular Brain Hemorrhage
23. Normal Pressure Hydrocephalus (NPH).
24. Spondylodiscitis
25. Skull fractures.
26. Choroid Plexus Tumors.
27. Bow Hunter Syndrome
28. Epidural Abscesses.
29. Intraventricular Central Neurocytoma.
30. Encephalocele

31. Brainstem Cavernoma.
32. Dysembryoplastic Neuroepithelial Tumor (DNET).
33. Glioblastoma Multiforme (GBM).

Neurology.....380

1. Parkinson's Disease.
2. Spinal Cord Infarction.
3. Meningitis
4. Alzheimer’s Disease.
5. Cerebral palsy.
6. Guillain barre syndrome.
7. Migraine
8. Trigeminal Autonomic Cephalalgias (TACs)
9. Ischemic Stroke.
10. Multiple Sclerosis.
11. Intracerebral Hemorrhage (ICH).
12. Neuromyelitis Optica Spectrum Disorder (NMOSD).
13. Myasthenia gravis.
14. Causes of Ischemic Stroke.
15. Management of Multiple Sclerosis Relapses.
16. Adult Focal Epilepsy.
17. Status Epilepticus.
18. History of Epilepsy.
19. Trigeminal Neuralgia.
20. Management of Acute Ischemic Stroke.
21. Phases and Phenotypes of Multiple Sclerosis.
22. Cerebral Venous Thrombosis (CVT).
23. Rehabilitation for Patients with Multiple Sclerosis.
24. Transverse Myelitis.
25. Neurological Manifestations of COVID-19
26. Huntington's Disease.
27. Physiotherapy Intervention for Spinal Cord Injury.
28. Secondary Stroke Prevention.
29. Occipital Neuralgia
30. Foot Drop.
31. Central Pontine Myelinolysis.
32. Vagus nerve stimulation (VNS).
33. Chorea and its Most Common Associated Pathologies.
34. McArdle's Disease.
35. Chronic Migraine.

36. Hereditary spastic paraplegia.
37. Charles Bonnet syndrome.
38. Dystonia
39. Internuclear Ophthalmoplegia.
40. Creutzfeldt- Jakob disease (CJD)
41. Benign paroxysmal positional vertigo (BPPV).
42. Transient Global Amnesia (TGA).
43. The Role of Physical Exercise in Neuroplasticity.
44. Blepharospasm
45. Medication Overuse Headache (MOH).
46. Highly Aggressive Multiple Sclerosis.

Psychiatry.....871

1. Somatic Symptom Disorder.
2. Specific Phobia.
3. Personality Disorders Cluster A.
4. Social Anxiety Disorder.
5. Major Depressive Disorder.
6. Posttraumatic Stress Disorder (PTSD).
7. Bipolar Disorder.
8. Illness Anxiety Disorder.
9. Substance/Medication- Induced Bipolar Disorder (BPD).
10. Obsessive-Compulsive Disorder (OCD).
11. Persistent depressive Disorder (PDD).
12. Attention-Deficit Hyperactivity Disorder (ADHD).
13. Conversion Disorder.
14. Hoarding Disorder.
15. Psychological Child Abuse & Maltreatment.
16. Generalized Anxiety disorder.
17. Schizophrenia
18. Central Sleep Apnea.
19. Delirium
20. Bulimia Nervosa.
21. Binge Eating disorder (BED).
22. Factitious Disorder.
23. Depersonalization/Derealization Disorder.
24. Pica Disorder.
25. Narcolepsy.
26. Neuroleptic Induced Parkinsonism.
27. Rumination Disorder.

28. Avoidant/Restrictive Food Intake Disorder (ARFID).
29. Female Sexual Interest / Arousal Disorder.
30. Anorexia Nervosa.
31. Neuroleptic Malignant Syndrome.
32. Disinhibited social engagement disorder (DSED).
33. Obstructive Sleep Apnea.
34. Premenstrual Dysphoric Disorder (PMDD).
35. Acute Stress Disorder (ASD).
36. Erectile Disorder
37. Tourette Syndrome.
38. Dissociative Amnesia.
39. Medication-induced Akathisia.
40. Delusional Disorder.
41. Medication-induced acute dystonia.
42. Genito-pelvic pain/penetration disorder (GPP/PD).
43. Panic Disorder.

Neuroscience.....1201

1. Brain Hemorrhage.
2. Disorders of the Neuromuscular Junction.
3. Meninges, Ventricular System, and Cerebrospinal Fluid.
4. Cerebral ischemia
5. Alzheimer's Disease
6. Cerebral edema
7. Amyotrophic Lateral Sclerosis (ALS)
8. Cholinergic Agonists
9. The Autonomic Nervous System
10. Adrenergic Agonists
11. Multiple Sclerosis
12. Antipsychotic Drugs.
13. Autonomic Nervous System
14. Synthesis of Adrenergic Neurotransmitters
15. Parkinson's Disease
16. Acquired Metabolic and Toxic Disturbances.
17. Adrenergic Antagonist
18. Neuronal Storage Diseases
19. ICP Monitoring: Types and Indications
20. *The use of stem cell therapy in the treatment of neurological disorders.*

Neurosurgery

Article topic: Spinal Biomechanics and Basics of Spinal Instrumentation.

Author: Yasser Banat.

Editor: Zain Alsaddi, Phillip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Overview

The spinal column is a complex system that holds the spinal cord, nerve roots, and vertebral arteries. It handles transferring electrical messages between the upper and lower limbs. This article will review the fundamental concepts of spinal anatomy and physiology, energy transfer, and the parameters of spinal alignment, as well as implant the properties needed to plan a surgical procedure.

Spinal Anatomy and Physiology

The spinal column consists of three regions: The highly mobile, lordotic cervical segment supporting the head; The hypomobile, kyphotic, thoracic spine; The mobile, lordotic lumbar segment carries 60-75% of the body weight. The spine is divided into the four following components: vertebral bodies (VBs), intervertebral (IV) disks, facet joints, and ligamentous structures.

The vertebral body, as shown in Figure 1, is the main load-bearing structure of the spine. As the spine transitions caudally, the vertebral body's width increases. This is due to the need for increased load bearing. Moreover, the vertebral bodies are at their largest within the lower lumbar spine, so correspondingly can accept a larger pedicle screw diameter than the thoracic spine.

The intervertebral disk is analogous to a shock absorber, which acts to stabilize the spine. Each disk comprises a hydrated core of proteoglycans assembled in a loose collagen network called the nucleus pulposus and surrounded by a fibrocartilaginous ring called the annulus fibrosus to provide structural support (1).

Facet joints perform two functions. They control the direction and amplitude of the axial movement and share the load bearing of the vertebral body. The ligaments of the spine

provide stability. Bone-to-bone attachments provide tension and translational support (1).

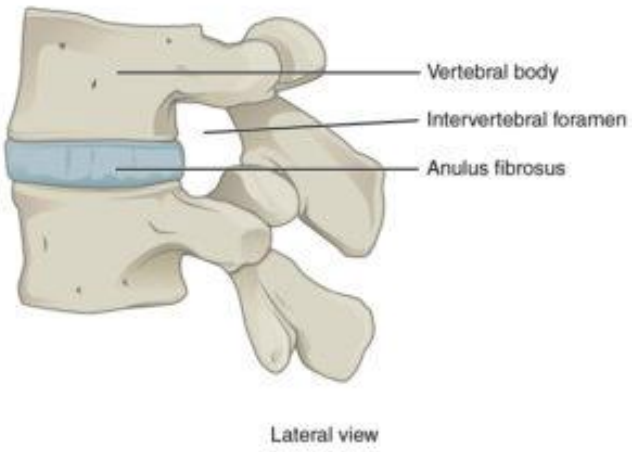


Figure 1: Lateral view of lumbar spine (2)

Pain and Energy Transfer

Trauma to the spine, whether acute or chronic, occurs secondary to excessive potential or kinetic energy that exceeds the vertebrae's and soft tissue's absorptive capacity, resulting in mechanical failure. Thus, failure of the normal spine or instrumented spine will occur if an energy transfer exceeds the structural capacity of the spine and its construct. Pain in the lower back and neck is one of the most common medical problems in adults (3).

Finding factors that may increase the risk for or predispose individuals to developing back pain is important in trying to reduce the prevalence and the social impact of this problem. Many studies have attempted to identify the contribution of multiple demographics, physical, socioeconomic, psychological, and occupational factors to the development of spine pain. Some of these factors are summed up in Box 1. (4)

Box 1. Risk factors for back pain

Demographic factors
Age
Gender
Socioeconomic status and education level

Health factors
Body mass index (BMI)
Tobacco use
Perceived general health status

Occupational factors
Physical activity, such as bending, lifting, or twisting
Monotonous tasks
Job dissatisfaction

Psychologic factors
Depression

Spinal anatomy factors
Anatomic variations
Imaging abnormalities

Figure 2: Risk Factors (4)

Spinal Alignment Parameters

Postural changes play an important role in stress distribution across all segments of the spine. To meet the evolutionary demand of the upright posture, sagittal curves have evolved to distribute the normal physiologic loads applied to the spine (7). There are three curvatures in the spine from cranial to caudal: cervical lordosis, thoracic kyphosis, and lumbar lordosis.

- **Cervical parameters:** The lower cervical part is measured between C2 lower C7 endplates. The cervical spine may have lordosis or kyphosis or could be neutral depending on the value of the C7 slope.
- **Thoracic parameters:** Thoracic kyphosis is measured between the upper T1 endplate and the lower T12 endplate.
- **Lumbar parameters:** lumbar lordosis is measured between the point of inflection of lumbar lordosis to thoracic kyphosis and the upper S1 endplate. (8)

When the alignment is being evaluated, it is important to measure thoracic kyphosis, lumbar lordosis, and coronal curves on x-ray. Coronal curves are measured using the Cobb angle, in which an angle between the end vertebrae of a deformity is measured through the intersection of two lines parallel to the endplate of the superior and inferior vertebrae, as in (figure 3). (5, 6)

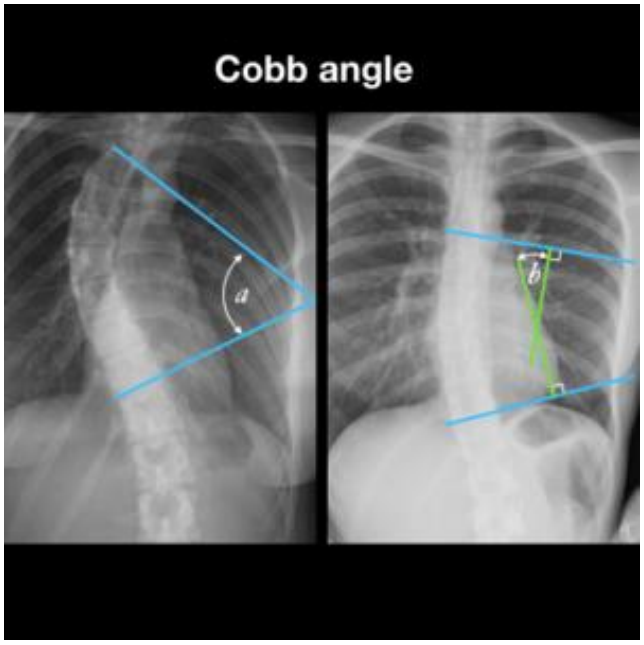


Figure 3: Cobb angle (6)

Kinetics and Kinematics

Studying kinematics is insufficient since it involves analyzing a subject's motion without considering the underlying forces, whereas kinetics incorporates the subject's mass and subsequent loading into the motion analysis to determine the relationship between the underlying forces and associated deformation. These results are expressed using the previously discussed curves. Whether designing implants or planning a surgical construct as a spine surgeon, it is important to account for the expected loading of the construct based on the local anatomy and patient's parameters, such as weight and activity level. This planning is critical in preventing any implant failure (9).

Figure 4: Cervical spine implants (11)

Implant Properties Required to Plan a Surgical Construct

A spinal implant is a device that is used to relieve back pain and manage disorders related to the spine, as seen in Figure 3. They are used to provide better pain relief, improve function and quality of life, as well as restore a long-lasting height for the vertebral body (10).

Commonly used materials in spinal implants include stainless steel, titanium, and cobalt chromium, each having distinct properties. The two most important properties to consider are stiffness and toughness or yield strength.

The choice of which spinal implant material to use depends on two key factors: patient bone quality and expected demands on a spinal construct. Bone quality is worse among osteoporosis patients, elderly patients, renal disease patients, smokers, and osteomyelitis patients (9). Implant failure results from fatigue through repetitive stress and strain on the implant.

Recent Study: The Effect of Sitting Posture on the Load on Spinal Joints

Lower back pain is a common problem among most people, especially the ones who work in the office. A study was conducted to show the relation between the sitting posture and musculoskeletal diseases of the spine. It reported that people sit 8 hours a day. The pressure between intervertebral discs while sitting is twice the amount while standing. Figure 4 shows normal spinal curvatures.

Figure 5: Normal spine curvatures (13)

The sample contained 20 students tested in three different postures, slump, lordosis, and flat, to evaluate the moment and the AP (anterior posterior) force on two main regions in the spine, which are the cervicothoracic and lumbosacral joints. The posture of the arms was taken into account as well (arms on chest, arms forward).

Results showed that the moment and the AP reaction force at both joints were much smaller in the lordosis and the flat postures compared to the slump posture. Also, the cervicothoracic joint loads decreased in the arms-on-chest posture. Consequently, flat or lordotic spinal curvature with arms near the axial line of the trunk is suggested to be a desirable sitting posture (12).

References

1. Izzo R, Guarnieri G, Guglielmi G, et al. Biomechanics of the spine. Part I: spinal stability. Eur J Radiol. 2013;82:118-126.
2. Case courtesy of OpenStax College, Radiopaedia.org. From the case rID: 42770

3. Andersson GB. Epidemiology of low back pain. Acta Orthop Scand Suppl 1998;281:28–31.
4. Rubin, D. I. Epidemiology and Risk Factors for Spine Pain. Neurologic Clinics, 2007; 25(2); 353–371.
5. Goldberg CJ, Kaliszer M, Moore DP, et al. Surface topography, Cobb angles, and cosmetic change in scoliosis. Spine. 2001;26: E55-E63.
6. Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org. From the case rID: 49374
7. Ames CP, Smith JS, Scheer JK, et al. Impact of spinopelvic alignment on decision making in deformity surgery in adults: a review. J Neu¬rosurg Spine. 2012;16:547-564.
8. Le Huec, J. C., W. Thompson, Y. Mohsinaly, C. Barrey, and A. Faundez. Sagittal Balance of the Spine. European Spine Journal. 2019; 28(9): 1889–1905.
9. Youmans, Julian R, and H R. Winn. Youmans Neurological Surgery. Philadelphia, PA: Saunders, 2011. Internet resource.
10. Cornelis, Francois H., Quentin Joly, Maud Nouri-Neuville, Mohamed Ben-Ammar, Bruno Kastler, Adrian Kastler, Nicolas Amoretti, and Olivier Hauger. Innovative Spine Implants for Improved Augmentation and Stability in Neoplastic Vertebral Compression Fracture. Medicina. 2019; 55(8).
11. Case courtesy of Dr Roberto Schubert, Radiopaedia.org. From the case rID: 16687
12. Yuri Kwon-Ji-Won Kim-Jae-Hoon Heo-Hyeong-Min Jeon-Eui-Bum Choi-Gwang-Moon Eom. The Effect of Sitting Posture on the Loads at Cervico-thoracic and Lumbosacral Joints. Technology and Health Care. 26(1): 409–18.
13. Case courtesy of Assoc Prof Craig Hacking, Radiopaedia.org. From the case rID: 83007

Article topic: Epidemiology of Traumatic Brain Injury

Author: Noor Alosta.

Editor: Zain Alsaddi.

Reviewer: Hassan AbuShukair, Omar Jbarah.

Overview

Traumatic brain injury (TBI), usually referred to as "the silent epidemic" [1], is a critical health and socioeconomic problem that affects every society. Its incidence is thought to be rising sharply worldwide due to the increased use of motor vehicles in middle and low-income countries.[2]

TBI remains a major public health concern as it is one of the greatest contributors to mortality and disability globally among all trauma-related injuries. Alongside its effect on the physical, psychological, and financial aspects of the individual, it also inflicts a burden on society.[3]

Definitions

As defined by the Centers for Disease Control and Prevention (CDC), epidemiology is the study of the determinants and distributions of health-related events in a specific population. Just like any other health issue, knowing the epidemiology of TBI is crucial to carry out successful primary preventive measures.
Incidence of a specific condition refers to the occurrence rates of new cases of that condition or disease in a population over a specific period, according to the CDC. Therefore, the incidence of TBI measures its risk within a certain period. However, the prevalence of TBI measures the whole volume of people with TBI (including the incidence) at a known point in time or a period.

Mortality rate measures the number of deaths because of a specific disease in a given population compared to the overall size of that population in a chosen unit of time, which is usually one year. In contrast, the fatality rate of TBI refers to the number of deaths from TBI in relation to the number of patients suffering from TBI, expressed in a percentage. Thus, both the case fatality and mortality rates can be used as a rough estimate for the severity and outcome of a given condition or injury.

Limitations and Gaps in Studying the Epidemiology of TBI [4]

Efforts to measure the magnitude of the problem posed by TBI are limited by some factors. First, there's a variation in the definition of TBI, as it is a heterogeneous disorder with multiple forms of presentation. It has been defined as brain damage that results from external forces as a consequence of direct impact, rapid acceleration or deceleration, a penetrating object (e.g., gunshot), or blast waves from an explosion. The nature, intensity, direction, and duration of these forces determine the pattern and extent of damage.[2] Cases where subtle behavioral or neuropsychological changes and injury-associated altered mental state were reported after a possible trivial injury. As a result, the inclusion criteria that include the presence of post-traumatic confusion or loss of consciousness as well as the presence of post- traumatic findings on imaging (CT or MRI) upon admission is variable in different studies. All which results in a different estimate of the incidence and mortality rate, which cannot be compared between different studies.

Second, the total number of people suffering from TBI is underreported, as most of such patients have mild brain injuries and thus refrain from seeking medical treatment. Moreover, hospital recordings of unattended and emergency department-treated TBIs might be less consistent than the accurately reported cases of admitted patients. Other challenges include cases where TBI is undiagnosed or overlooked because it is masked by an underlying, more severe health condition. More bias is introduced because some pre-hospital fatal TBIs are not accounted for.

Third, the monitoring of TBI epidemiology is seldom performed in a standardized way and is absent in many parts of the world. The epidemiologic dates are mostly retrospective, retrieved from regularly collected administrative sources; for example, "in the United States, CDC data are based on data from three different national sources: the National Vital Statistics System, the National Hospital Discharge Survey, and the National Hospital Ambulatory Medical Care Survey. In Europe, standard epidemiologic monitoring is lacking. Finland, however, has the oldest nationwide register in the world (established in 1967), and the computer-based Finnish Hospital Discharge Register provides some of the most reliable data within the European Union. Current initiatives include the Trauma Audit and Research Network (https://www.tarn.ac.uk), established in the United Kingdom, whose aim is to collect data to inform acute response to trauma, and the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI; https://www.center-tbi.eu), which is establishing a TBI registry of 15,000 to 25,000 patients from across Europe, as well as collecting detailed data on the clinical course of injury, treatment, and outcome for 5400 patients."[4]

Even though these studies may provide insight into epidemiologic patterns, they were not designed to measure accurate data on incidence rates.

Fourth, when data is being collected, they are often identified by codes of the International Classification of Diseases (ICD), which are more pathologically based in the ICD-9 (ninth edition) classification, while it is more clinically oriented in the ICD-10(tenth edition). However, neither classification system measures reliable information about the severity of an injury, as both are primarily intended for administrative use and thus have substantial limitations.

Classification of Traumatic Brain Injury

Biochemical and pathological consequences of TBI are initiated by the physical insult. Therefore, the clinical manifestations of TBI depend largely on the nature of the insult. For example, many open-head injuries are caused by objects that penetrate the skull and damaging brain tissue. On the contrary, closed head injuries are associated with blunt or accelerative forces.[5]

The classification of TBI follows clinical severity and is assessed primarily with the Glasgow Coma Scale. [6] Its a scale with a score that ranges from 3 to 15 that consists of the sum of three component scores (eye, verbal, and motor scales) and offers a rapid evaluation of the severity of the brain injury (Table 1).[7] A score of 13-15 is considered a mild TBI, while 9-12 is moderate, and a score ≤8 is classified as severe.[8]

In addition to the Glasgow Coma Scale, TBI is further evaluated by various imaging modalities in order to establish the severity of structural damage in the brain. TBI can be classified into primary and secondary injuries.[9] Primary injuries occur at the time of the injury as a direct result of the traumatic impact, resulting in epidural or subdural-hematomas, micro-vascular injuries, contusions, and diffuse axonal injury. Secondary injuries occur hours or days later and are generally a result of a complex cascade of biochemical events that often manifest as cerebral edema, elevated intracranial pressure, ischemia, and infarction.[9]

Table 1: The Glasgow Coma Scale*.

	Score					
Response	1	2	3	4	5	6
Eye	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sound	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extensions to painful stimuli	Abnormal flexion to painful stimuli	Flexion/withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

*Based on Teasdale and Jennett (1974).

The Effect of Traumatic Brain Injury from a Global Perspective

Table 2 worldwide Incidences of Traumatic Brain Injury.	
Region	**Incidence per 100, 00 population/ year of study.**
USA	• 470.6 in adults aged ≥75 years • 145.5 for adults aged 65-74 • 89.5 for adults aged 55-64 (2014) [13]
EU	For all TBI severities and all ages, crude incidence rates in Europe ranged from 47.3 per 100,000, to 694 per 100,000 population per year (in country-level studies) and 83.3 per 100,000, to 849 per 100,000 population per year (in regional-level studies). (2015) [14] In another study, it was estimated that across Europe there is an average incidence of approximately 235 per 100,000, with most countries experiencing an incidence in the range of 150–300 / 100,000 per year. (2005) [15]
UK	An overall rate of 453 per 100,000 was found for all head injuries in the UK, of which 40 per 100,000 (10.9%) were moderate to severe. (2006) [16] • In Scotland the rate of continuous hospital stays as a result of TBI in was 446.4 / 100,000 in men and 194.8 / 100,000 in women. (2009) [17]
New Zealand	The total incidence of TBI per 100,000 person-years was 790 cases (2013) [18], of which ; • Incidence of mild TBI was 749 cases. • Moderate to severe TBI was 41 cases.
Australia	Incidence rates were estimated to be 99.1/100,000 population. 2019 [19]
Taiwan	The age-adjusted incidence rate of head injury in Taiwan was 382/100 000; 499/100 000 of which for males and 244/100 000 for females. (1995) [20]
India	The annual incidence rate of head injuries is approximately 55 per 100,000 (2008). [21]

Pakistan	The annual incidence of head injured patients admitted to various neurosurgical centers in Pakistan was 50 per 100,000 populations per year. (2001) [22]

TBI is considered a major health and socioeconomic problem affecting all societies worldwide. In the United States alone, the cases of TBI in 2014 were estimated to be 1,565,000. The Emergency department witnessed 2,000,000 patient visits, approximately 300,000 hospital admissions, and 51,000 deaths annually, along with the associated costs that may reach approximately $76.5 billion or even higher. [10]
The World Health Organization (WHO) forecasts that by the year 2030, TBI will be a leading cause of disability and death across the world. [11]
Brain trauma accounts for roughly one-third of all deaths from TBI and for the majority of permanent disabilities.[12] For each death, there will be dozens of hospitalizations, hundreds of emergency department admissions, and thousands of doctor appointments. A significant percentage of people who survive their injuries incur temporary or permanent disability across social, cognitive, behavioral, and physical functioning aspects.

Incidence and Population at Risk

The epidemiologic data that is reported in the literature should be interpreted with caution because of limitations and gaps in knowledge of the epidemiologic characteristics of TBI. Table 2 summarizes the most recent incidence rates reported around some regions of the world.

The above table illustrates the variation in reported incidence rates, primarily caused by varying definitions of injury and different inclusion criteria, in addition to sampling errors and actual differences. [23]
The CDC uses the ICD codes to identify cases of TBI and collects data on TBI-related emergency department visits, hospitalizations, and deaths. In a report published in 2010 by Faul and associates,[24] they collected CDC data for the years 2002 to 2006 and concluded that an estimated 1.7 million people sustain TBI annually. Of these, only 0.7% ended up in the emergency department, while 16.3% were hospitalized and 3% died.

The TBI rates in the United States increased from 616 in 2005 to 824 per 100,000 in 2010. The large increase was correlated chiefly to increased TBI-related visits to emergency departments, mainly by children and older adults. This may indicate that the increase is related to improved diagnostic methods or to an increase in the awareness of the importance of TBI among the general population. However, it is still uncertain.[25]

In Europe, a study by Tagliaferri and associates reported an overall incidence of 235 per 100,000, derived from a systematic review of 23 reports on national and regional epidemiologic studies of TBI. Wide variation was found in reported incidences, ranging from 20 per 100,000 for neurosurgical cases only to 546 per 100,000, including emergency department visits, hospital discharge, and coroner reports.[26] Nevertheless, major variations across studies were shown, with extremes ranging from 47.3 per 100,000 to 546.0 per 100,000.[27,28]
Similarly, In Australia, a pattern of varying incidence rates has been described; estimated annual rates varied widely from 57 per 100,000 to 322 per 100,000.[29] This range of estimates is broad and is influenced by significant methodological variation among studies.
Incidence rates from Asian countries, on the other hand, are infrequently published. In India, for instance, an incidence of 120 per 100,000 was found among hospital-based victims. [30] A more conservative estimate in 2002 was given by Gururaj [31], who reported that nearly 1.5 million to 2 million individuals sustain a TBI annually.

Population at Risk

A study by Albrecht. et al. in 2019 provided evidence that over a 4-year period of following up with older adults, any severe to moderate injury is associated with increased mortality risk.
Specifically, older injured adults are at higher risk of death from accidental and thus preventable causes, suggesting that proper intervention could reduce mortality.[32] Elderly patients, military personnel, and children (aged 0-4 years) were found to be at particular risk for TBI. [33] [34] Another study in New Zealand found that children and adolescents (aged 0-14 years) and young adults (aged 15-34 years) constituted almost 70% of all TBI cases.[18]
A study by Morrel et al. indicated that a large percentage of people detained in penitentiary institutes reported a history of “head” injury.[35] In another study done by Ivins and associates, it was reported that up to 23% of service members on noncombat active duty had suffered some form of TBI during their military service. [36] It was stated by Ling and Eklund that explosive blasts had emerged as a leading cause of combat-related TBI. [37] The overall incidence rate of TBI among service members on active duty more than doubled between the years 2000 (720.3 per 100,000) and 2011 (1811 per 100,000), which may reflect an actual increase in TBI but may also reflect the deployment of an increased number of members, along with increased awareness of the need to seek out care and to improve recognition and diagnosis.[38]

Causes of TBI

The major causes of TBI are transportation accidents, falls, and gunshot wounds that are caused by misadventure, violence, or carelessness and reflect societal behavior.

Gilbert stated that the motorcar "had emerged as the most persistent killer in the western world." [39] Road traffic injuries place an enormous strain on any country's health care system and national economy in general. The mechanism of TBI sustained in road traffic accidents in high-income countries is markedly different from that in low- and middle-income countries. In high-income countries, the victims are commonly young adult drivers, while in low- and middle-income countries, the victims are much more frequently vulnerable road users (e.g., pedestrians, cyclists, motorcyclists, and users of public transport). The observation that vulnerable road users are the primary victims of TBI suggests that it is possibly not so much reckless driving but rather unawareness of traffic risks in the general population. Accordingly, perhaps it may be better to aim prevention campaigns in these countries more towards the general population. For example, in Pakistan,[40] most people who sustain TBI in road traffic incidents are pedestrians hit by a vehicle and people falling from a moving vehicle.
In a study by Hyder and colleagues, they summarized the epidemiologic characteristics of TBI in a worldwide context and reported that, in general, 62% of TBIs are caused by road traffic accidents, approximately 24% by violence, 8% by falls, and only 4% result from work- and sports-related injuries.[41]
Other causes of trauma also showed regional variations and changing trends. In the United States, for instance, injuries related to firearms exceeded those from road traffic incidents for the first time in 1990, and this trend contrasted with the decrease in deaths from road traffic incidents[42], and more than half of cranial gunshot wounds represented suicidal attempts.[43]
Sport and recreation-related TBIs are being recognized more frequently. In the United States, the CDC estimated that between 1.6 and 3.8 million sports-related TBIs occur yearly; including injuries for which no medical care was sought.[44] Particular attention is being focused on secondary prevention because repetitive concussions may have cumulative effects resulting from increased vulnerability of the brain after earlier injury. A study conducted in New Zealand found that 21%of all TBIs have been sustained during a sports-related activity; the highest rates were observed in rugby, cycling, and equestrian activities.[45]

Mortality Rates

Because of the huge variability in data collection and lack of standardization, comparison of mortality rates between different studies, even the ones done in the same region, is nearly impossible.

The average mortality rate in Europe is reported to be approximately 15 per 100,000.[46]However, this rate ranges from 5.2 per 100,000 in a population in France[47] in which only in-hospital deaths after severe TBI were counted, to 24.4 per 100,000 in a province in Italy in which all in-hospital and pre-hospital deaths were recorded.[48]Another study in Europe showed that crude mortality rates ranged from 9

to 28.10 per 100,000 population per year (on a country-level studies), and 3.3 to 24.4 per 100,000 population per year (for regional-level studies.).[49]
In the United States, Adekoya and colleagues and Rutland-Brown and associates reported a decrease in TBI related deaths from 24.6 in 1997 to 17.5 per 100,000 in 2003.[50][51] A more recent study by Coronado and associates reported a decrease in TBI-related deaths by 8.2% during the period 1997 through 2007 in the United States.[52] The decreases in death and disability rates after TBI in western society are considered to be the result of collective effects of proper prevention, improvement of emergency health systems, trauma organization and implementation of guidelines. However, in patients older than 75 years, a significant increase in TBI-related deaths was found.[52]
In Australia, despite a 40% increase in population and an increase in the number of registered vehicles by 120%, the fatality rate from road traffic accidents decreased by 47% between 1970 and 1995.[53] This decrease coincided with the recognition of the importance of public education and the implementation of a uniform code of road safety, backed by legislation and police reinforcement. However, opinion is divided; some authors believe that there has been no clear decrease in mortality since the 1990s. [54]
In a more recent study of hospitalized traumatic brain injury in the state of New South Wales, Australia; mortality rate was estimated to be of 5.9 per 100,000 populations. [55]
Evidence of elevated long-term risk for premature mortality in people experiencing a TBI have has also been revealed. This is particularly in cases of suicide attempts, injuries, and assaults, even after adjustment for socio-demographic and familial factors 6 months after injury.[56]
The average life expectancy is decreased by 9 years after inpatient rehabilitation from TBI.[57] Among people who have suffered a TBI, the annual mortality rate remains high, up to approximately seven folds, for at least 13 years.[58]

References

1. Rusnak, M. (2013). Traumatic brain injury: Giving voice to a silent epidemic. *Nature Reviews. Neurology*, *9*(4), 186–187.
2. Maas, A. I. R., Stocchetti, N., & Bullock, R. (2008). Moderate and severe traumatic brain injury in adults. *The Lancet. Neurology*, *7*(8), 728–741.
3. Rubiano AM, Carney N, Chesnut R, Puyana JC (2015). Global neurotrauma research challenges and opportunities. *Nature*527:S193–S197
4. Youmans, Julian R, and H R. Winn. Youmans Neurological Surgery. Philadelphia, PA: Saunders, 2017. 'epidemiology of traumatic brain injury' ; 2749.
5. Young, L., Rule, G. T., Bocchieri, R. T., Walilko, T. J., Burns, J. M., & Ling, G. (2015). When physics meets biology: low and high-velocity penetration, blunt impact, and blast injuries to the brain. *Frontiers in Neurology*, *6*, 89.
6. Maas, A. I. R., Stocchetti, N., & Bullock, R. (2008). Moderate and severe traumatic brain injury in adults. *The Lancet. Neurology*, *7*(8), 728–741.
7. Teasdale, G., Murray, G., Parker, L., & Jennett, B. (1979). Adding up the Glasgow Coma Score. *Acta Neurochirurgica. Supplementum*, *28*(1), 13–16.
8. Jain, S., & Iverson, L. M. (2020). *Glasgow Coma Scale*.
9. Currie, S., Saleem, N., Straiton, J. A., Macmullen-Price, J., Warren, D. J., & Craven, I. J. (2016). Imaging assessment of traumatic brain injury. *Postgraduate Medical Journal*, *92*(1083), 41–50.
10. Rutland-Brown, W., Langlois, J. A., Thomas, K. E., & Xi, Y. L. (2006). Incidence of traumatic brain injury in the United States, 2003. *The Journal of Head Trauma Rehabilitation*, *21*(6), 544–548.

11. Mathers, C. D., & Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, *3*(11), e442.
12. Thornhill, S., Teasdale, G. M., Murray, G. D., McEwen, J., Roy, C. W., & Penny, K. I. (2000). Disability in young people and adults one year after head injury: prospective cohort study. *BMJ (Clinical Research Ed.)*, *320*(7250), 1631–1635.
13. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, <https://www.cdc.gov/traumaticbraininjury/data/tbi-hospitalizations.html>March 29, 2019.
14. Brazinova, A., Rehorcikova, V., Taylor, M. S., Buckova, V., Majdan, M., Psota, M., Peeters, W., Feigin, V., Theadom, A., Holkovic, L., & Synnot, A. (2018). Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. *Journal of Neurotrauma*.
15. Tagliaferri, F., Compagnone, C., Korsic, M. *et al.*A systematic review of brain injury epidemiology in Europe. *Acta Neurochir (Wien)* **148,** 255–268 (2006).
16. Yates, P. J., Williams, W. H., Harris, A., Round, A., & Jenkins, R. (2006). An epidemiological study of head injuries in a UK population attending an emergency department. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(5), 699–701.
17. Shivaji, T., Lee, A., Dougall, N. *et al.*The epidemiology of hospital treated traumatic brain injury in Scotland. *BMC Neurol.* **14,** 2 (2014).
18. Feigin, V. L., Theadom, A., Barker-Collo, S., Starkey, N. J., McPherson, K., Kahan, M., Dowell, A., Brown, P., Parag, V., Kydd, R., Jones, K., Jones, A., & Ameratunga, S. (2013). Incidence of traumatic brain injury in New Zealand: a population-based study. *The Lancet. Neurology*, *12*(1), 53–64.
19. Pozzato, I., Tate, R. L., Rosenkoetter, U., & Cameron, I. D. (2019). Epidemiology of hospitalised traumatic brain injury in the state of New South Wales, Australia: a population-based study. *Australian and New Zealand Journal of Public Health*, *43*(4), 382–388.
20. Chiu, W. T., Hung, C. C., & Shih, C. J. (1995). Epidemiology of head injury in rural Taiwan -a four year survey. *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia*, *2*(3), 210–215.
21. Yattoo, Gh, and Amin Tabish. (2008). "The profile of head injuries and traumatic brain injury deaths in Kashmir." *Journal of trauma management & outcomes* 2,1 5.
22. Raja, I. A., Vohra, A. H., & Ahmed, M. (2001). Neurotrauma in Pakistan. *World Journal of Surgery*, *25*(9), 1230–1237.
23. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol*. 2013;9: 231-236.
24. Faul M, Xu L, Wald MM, et al.(2010). *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002- 2006 (Blue Book)*. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control
25. Centers for Disease Control and Prevention. *Traumatic brain injury in the United States: Fact sheet*. <http://www.cdc.gov/ traumaticbraininjury/get_the_facts.html>; 2014 Accessed 05.10.16.
26. Tagliaferri F, Compagnone C, Korsic M, et al.2006.A systematic review of brain injury epidemiology in Europe. Acta Neurochir (Wien).148:255-268.
27. Pérez K, Novoa AM, Santamariña-Rubio E, et al. (2012)Incidence trends of traumatic spinal cord injury and traumatic brain injury in Spain, 2000-2009. Accid Anal Prev.46:37-44.
28. Andersson EH, Bjorklund R, Emanuelson I, et al. Epidemiology of traumatic brain injury: a population based study in western Sweden. Acta Neurol Scand. 2003;107:256-259.
29. Hillier SL, Hiller JE, Metzer J. Epidemiology of traumatic brain injury in South Australia. Brain Inj. 1997;11:649-659.
30. Channabasavanna S, Guruaj G, Das B, et al. Epidemiology of Head Injuries in Bangalore [project report PR/3/93]. Bangalore: National Institute of Mental Health and Neurosciences; 1993.
31. Gururaj G. Epidemiology of traumatic brain injuries: Indian scenario. Neurol Res. 2002;24:24-28.
32. Albrecht JS, Al Kibria GM, Greene CR, Dischinger P, Ryb GE. Post-Discharge Mortality of Older Adults with Traumatic Brain Injury or Other Trauma. J Am Geriatr Soc. 2019 Nov;67(11):2382-2386
33. Faul M, Xu L, Wald MM, et al. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002- 2006 (Blue Book). Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
34. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol. 2013;9:231-236.
35. Morrell RF, Merbitz C, Jain S. Traumatic brain injury in prisoners.J Offender Rehabil. 1998;27:1-8.
36. Ivins BJ, Schwab KA, Warden D, et al. Traumatic brain injury in theUS army paratroopers: prevalence and character. J Trauma. 2003;55:617-621
37. Ling GS, Ecklund JM. Traumatic brain injury in modern war. Curr Opin Anaesthesiol. 2011;24:124-130.
38. Centers for Disease Control, National Institutes of Health, Departmentof Defense, and Department of Veterans Affairs Leadership Panel. Report to Congress on Traumatic Brain Injury in the United States: Understanding the Public Health Problem among Current and Former Military Personnel. Atlanta: Centers for Disease Control and Prevention, National Institutes of Health, U.S. Department of Defense, and U.S. Department of Veterans Affairs; 2013.
39. Gilbert M. A History of the Twentieth Century, Vol. 1: 1900-1933. London: Harper Collins; 1997.
40. Raja IA, Vohra AH, Ahmed M. Neurotrauma in Pakistan. World J Surg. 2001;25:1230-1237.
41. Hyder AA, Wunderlich CA, Puvanachandra P, et al. The impact of traumatic brain injuries: a global perspective. Neurorehabilitation. 2007;22:341-353.
42. Sosin DM, Sniezek JE, Waxweiler RJ. Trends in death associated with traumatic brain injury, 1979 through 1992. JAMA. 1995;273:1778-1780.

43. Aarabi B, Alden TD, Chestnut RM. Management and prognosis of penetrating brain injury—guidelines. J Trauma. 2001;51(suppl):S1-S86
44. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology andimpact of traumatic brain injury: a brief overview. J Head TraumaRehabil. 2006;21:375-378.
45. Theadom A, Starkey NJ, Dowell T, et al., on behalf of the BIONICResearch Group. Sports-related brain injury in the general population:an epidemiological study. J Sci Med Sport. 2014;17:591-596.
46. Tagliaferri F, Compagnone C, Korsic M, et al. A systematic review of brain injury epidemiology in Europe. *Acta Neurochir (Wien)*. 2006;148:255-268.
47. Masson F, Thicoipe M, Aye P, et al. Epidemiology of severe brain injuries: a prospective population-based study. *J Trauma*. 2001;51: 481-489.
48. Servadei F, Ciucci G, Piazza G, et al. A prospective clinical and epidemiological study of head injuries in northern Italy: the Comune of Ravenna. *Ital J Neurol Sci*. 1988;9:449-457.
49. Brazinova A, Rehorcikova V, Taylor MS, Buckova V, Majdan M, Psota M, Peeters W, Feigin V, Theadom A, Holkovic L, Synnot A. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. J Neurotrauma. 2018 Dec 19
50. Adekoya N, Thurman DJ, White DD, et al. Surveillance for traumatic brain injury deaths—United States 1989-1998. *MMWR Surveill Summ*. 2002;51(10):1-16.
51. Rutland-Brown W, Langlois JA, Thomas KE, et al. Incidence of traumatic brain injury in the United States, 2003. *J Head Trauma Rehabil*. 2006;21:544-548.
52. Coronado VG, Xu L, Basavaraju SV, et al. Surveillance for traumatic brain injury-related deaths—United States, 1997-2007. *MMWR Surveill Summ*. 2011;60(5):1-32.
53. Atkinson L, Merry G. Advances in neurotrauma in Australia 1970- 2000. *World J Surg*. 2001;25:1224-1229.
54. Rosenfeld JV, Maas AI, Bragge P, et al. Early management of severe traumatic brain injury. *Lancet*. 2012;380:1088-1098.
55. Pozzato, I., Tate, R.L., Rosenkoetter, U. and Cameron, I.D. (2019), Epidemiology of hospitalised traumatic brain injury in the state of New South Wales, Australia: a population-based study. Australian and New Zealand Journal of Public Health, 43: 382-388.
56. Fazel S, Wolf A, Pillas D, et al. Suicide, fatal injuries, and other causes of premature mortality in patients with traumatic brain injury: a 41-year Swedish population study. *JAMA Psychiatry*. 2014; 71:326-333.
57. Harrison-Felix CL, Pretz CR, Hammond F, et al. Life expectancy following inpatient rehabilitation for traumatic brain injury in the United States. *J Neurotrauma*. 2015;2432:1893-1901.
58. McMillan TM, Teasdale GM, Weir CJ, et al. Death after head injury: the 13 year outcome of a case control study. *J Neurol Neurosurg Psychiatry*. 2011;82:931-935

Article Title: Blunt Cerebrovascular Injury.

Author: Nancy Abu Amoud.

Editors: Zain Alsaddi.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Keywords: Cartotid Injury, Vertebral Injury, Stroke.

Overview

Blunt cerebrovascular injury (BCVI) is a range of intracranial or extracranial traumatic injuries to the carotid and vertebral arteries in around 1-2% of patients presenting with blunt trauma to the head, neck, and chest. Although uncommon, it may lead to high mortality and morbidity as a devastating brain injury. [8, 9] It is important to note that ischemic stroke occurs in a generous part of patients with BCVI at a rate of 10% as reported in studies. [7]

Etiology and Pathogenesis

High energy, non-penetrating trauma causes cerebrovascular injury resulting in defects in one or more of the arterial walls. [7] This results in intimal tear that exposes the collagen of the endothelium, thus starting platelet aggregation to create a healing thrombus, which could induce stenosis or vessel occlusion. Having that said, an intimal tear could produce a space for dissecting blood to narrow or occlude the vessel or even for a traumatic aneurysm. [5]

Multiple injury mechanisms have been suggested, longitudinal stretching of the artery with subsequent partial or complete failure of arterial mural integrity is the main suspected mechanism.[12] Direct injury to the carotid or vertebral arteries can be caused via displacement of bone fragments from skull base or cervical spine fractures.[4, 12] Carotid injury could be caused by intra-oral trauma, or direct blow to the neck (e.g.; impact against a steering wheel, seatbelt or near hanging).[12] Blunt vertebral injuries have been associated with facet-joint dislocations, subluxations, as well as fractures extending into the foramen transversarium.[4]

In most cases, the potential mechanisms of stroke in BCVI are thromboembolism and hemodynamic insufficiency. Although, research shows that thromboembolism is the more likely mechanism of injury supported by analysis of vascular lesions and the presence of micro emboli in patients with BCVI. [6]

Clinical presentation

Most BCVI are asymptomatic lesion discovered on screening CT angiography based on screening criteria. [13] For symptomatic BCVIs, presentation is often like that of spontaneous dissections, with the classic triad of neck/head pain, Horner syndrome, and brain ischemia. Other presentations could involve headache or neck pain, cranial nerve palsies, distal ischemia, spinal cord ischemia, traumatic fistulae, or hemorrhage/ hematoma. [5]

Risk factors and screening

Multiple screening tools have been developed to identify patients at risk of BCVI, modified Memphis criteria and Denver criteria. The recommended criteria are the expanded Denver screening criteria, which encompass indicators from the Memphis screening tool. [3]

The expanded Denver screening criteria for BCVI [3]

CT angiography is indicated if one or more of the criteria are present.

Signs/symptoms of BCVI

- Arterial hemorrhage from neck/nose/mouth
- Cervical bruit in patients < 50 years
- Expanding cervical hematoma
- Focal neurological deficit
- Neurological exam incongruous with head CT findings Stroke on secondary CT scan

Risk factors for BCVI

(High-energy transfer mechanism plus):

- Le Fort II or III Mandible fracture
- Complex skull fracture/basilar skull fracture/occipital condyle fracture
- Severe traumatic brain injury (TBI) with GCS < 6
- Cervical spine fracture, subluxation or ligamentous injury at any level
- Near hanging with anoxic brain injury
- Seat belt abrasion with significant swelling, pain or altered mental status
- TBI with thoracic injury
- Scalp degloving
- Thoracic vascular injury

- Blunt cardiac rupture
- Upper rib fracture

Imaging [1, 10]

Digital subtraction angiography (DSA) is the imaging gold standard for detection of BCVI due to its high sensitivity and ability to detect collateral circulation. However, it falls behind due to its failure to provide information about vessel wall, and the associated complication rate of 1.3%, since it is an invasive technique. Arterial dissection, thromboembolism, and IV contrast-induced renal injury are possible complications for DSA. Therefore, its use is limited for patients with equivocal or negative CTA findings with strong clinical suspicion or when therapeutic intervention is needed.

Computed tomography angiography (CTA) is considered the screening choice for BCVI, with sensitivity and specificity reaching 100% with the use of 16-sections or higher CT scans. Moreover, it is cheaper, widely available, non-invasive and saves time in reaching diagnosis and observation of non-vascular injuries.

Magnetic resonance angiography (MRA) is not recommended as a single tool for diagnosis with a reported sensitivity of 50%. However, it is useful for detection of dissections and intramural hematoma and therefore could be used as a complimentary tool to CTA.

Duplex sonography has little role and is an inappropriate tool for screening of BCVIs, with a sensitivity rate of 38.5%.

In conclusion, digital subtraction angiography (DSA) remains the gold standard in detecting BCVI, but it is time-consuming and not offered by all institutions. Thus, the recommended imaging study is CT angiography of the precerebral carotid and vertebral arteries reaching through the base of the skull together with the circle of Willis. [3]

Grading

The Biffl/Denver scale is a commonly used grading system which describes injury according to angiography on a scale from I to V. [11] The risk of stroke increases with the increasing grade. [2]

- grade I: vessel wall irregularity or dissection with <25% stenosis
- grade II: dissection or intramural hematoma with ≥25% stenosis, intraluminal thrombus, or raised intimal flap
- grade III: pseudo aneurysm

- grade IV: complete vessel occlusion
- grade V: transection with free extravasation and/or high flow arteriovenous fistula

Figure 1: (Abu Mughli, 2020) (1) Biffl grade I injury. Sagittal CTA showing small intimal flap of the right cervical ICA, with <25% stenosis (A). Biffl grade II injury, coronal CTA showing moderate left sided extracranial ICA dissection with intramural hematoma causing >25% stenosis (B). Biffl grade III injury. Follow up imaging showing pseudo aneurysm on coronal imaging of a 31-year-old male with a history of polytrauma 6 days prior with initial scanning revealing Biffl grade II (C). Biffle grade IV injury. Left vertebral artery occlusion on axial image (D). Biffle grade V injury. DSA showing left vertebral artery irregularity at C3 level, at C2/3 level there is complete artery occlusion with an AV fistula draining into enlarged epidural veins (E).

Management

The management of BCVIs is still controversial. [5] Due to the nature of ischemic stroke being identified primarily as thromboembolic in origin, antithrombotic therapy is the primary method of treatment. Studies report the use of anticoagulation (42.8%), antiplatelet (32.5%) or both (17.1%). [7] It is of importance to note that many patients with BCVI have polytrauma and require surgery. Therefore, the increased risk of bleeding must be weighed with the risk of ischemic stroke in these patients. [7] The use of antiplatelet therapy as an alternative to anticoagulation has shown a favorable risk for complications with equivalent if not superior neurologic outcomes. [5]

Endovascular and surgical treatments are reserved for patients with severe injury (grade V), or patients with pseudo aneurysm (grade III), which if not treated, commonly does not resolve. Options include stenting, resection, and embolization. [1]

Prognosis

Overall mortality rates depend on the injured artery; reports show 7–21% mortality for carotid artery injury and 4-8% for vertebral artery injury. Similarly, stroke rates related to BCVI also depend on the injured artery; infarctions are more likely to occur with carotid artery injuries than injuries in vertebral arteries reported at 26-41% and 14-24% respectively. [11]

Additionally, stroke rate increases with increasing injury grade regarding carotid artery injury, while stroke rate in vertebral artery injury is not remarkably influenced by injury grade. [11]

External links

- Endovascular reconstruction of enlarging traumatic internal carotid artery pseudoaneurysm –Video: **https://youtu.be/uCypcsBvOZ4**
- Open Repair of Carotid Artery Pseudoaneurysm (Rahimi, MD, Rojo, MD, & Mohamed, MD) — Video: **https://youtu.be/xuvCsWb6_YE**

References

1. Abu Mughli, R., Wu, T., Li, J., Moghimi, S., Alem, Z., Nasir, M. U., Abdellatif, W., & Nicolaou, S. (2020). An Update in Imaging of Blunt Vascular Neck Injury. *Canadian Association of Radiologists journal = Journal l'Associationcanadienne des radiologistes*, *71*(3), 281–292. https://doi.org/10.1177/0846537120909468
2. Biffl, W. L., Moore, E. E., Offner, P. J., Brega, K. E., Franciose, R. J., & Burch, J. M. (1999). Blunt carotid arterial injuries: implications of a new grading scale. *The Journal of trauma*, *47*(5), 845–853. https://doi.org/10.1097/00005373-199911000-00004
3. Brommeland, T., Helseth, E., Aarhus, M., Moen, K. G., Dyrskog, S., Bergholt, B., Olivecrona, Z., & Jeppesen, E. (2018). Best practice guidelines for blunt cerebrovascular injury (BCVI). Scandinavian journal of trauma, resuscitation and emergency medicine, 26(1), 90. https://doi.org/10.1186/s13049-018-0559-1
4. Cothren CC, Moore EE, Biffl WL, Ciesla DJ, Ray CE Jr, Johnson JL, Moore JB, Burch JM. Cervical spine fracture patterns predictive of blunt vertebral artery injury. J Trauma. 2003 Nov;55(5):811-3. doi: 10.1097/01.TA.0000092700.92587.32. PMID: 14608149.
5. Fusco, M. R., & Harrigan, M. R. (2011). Cerebrovascular dissections: a review. Part II: blunt cerebrovascular injury. Neurosurgery, 68(2), 517–530. https://doi.org/10.1227/NEU.0b013e3181fe2fda
6. Griessenauer, C. J., Fleming, J. B., Richards, B. F., Cava, L. P., Curé, J. K., Younan, D. S., Zhao, L., Alexandrov, A. V., Barlinn, K., Taylor, T., & Harrigan, M. R. (2013). Timing and mechanism of ischemic stroke due to extracranial blunt traumatic cerebrovascular injury. Journal of neurosurgery, 118(2), 397–404. https://doi.org/10.3171/2012.11.JNS121038
7. Harrigan M. R. (2020). Ischemic Stroke due to Blunt Traumatic Cerebrovascular Injury. Stroke, 51(1), 353–360. https://doi.org/10.1161/STROKEAHA.119.026810
8. Hoffman, H., Bunch, K. M., Protas, M., & Chin, L. S. (2020). Risk Factors and Outcomes Associated with Blunt Cerebrovascular Injury in Patients with Mild or Moderate Traumatic Brain Injury. *Annals of vascular surgery*, S0890-5096(20)30623-3. Advance online publication. https://doi.org/10.1016/j.avsg.2020.07.031
9. Kobata H. (2017). Diagnosis and Treatment of Traumatic Cerebrovascular Injury: Pitfalls in the Management of Neurotrauma. Neurologia medico-chirurgica, 57(8), 410–417. https://doi.org/10.2176/nmc.oa.2017-0056
10. Nagpal, P., Policeni, B. A., Bathla, G., Khandelwal, A., Derdeyn, C., &Skeete, D. (2017). Blunt Cerebrovascular Injuries: Advances in Screening, Imaging, and Management Trends. AJNR. American journal of neuroradiology, 39(3), 406–414. Advance online publication. https://doi.org/10.3174/ajnr.A5412
11. Rutman, A. M., Vranic, J. E., &Mossa-Basha, M. (2018). Imaging and Management of Blunt Cerebrovascular Injury. *Radiographics : a review publication of the Radiological Society of North America, Inc*, *38*(2), 542–563. https://doi.org/10.1148/rg.2018170140

12. Sliker C. W. (2008). Blunt cerebrovascular injuries: imaging with multidetector CT angiography. Radiographics: a review publication of the Radiological Society of North America, Inc, 28(6), 1689–1710. https://doi.org/10.1148/rg.286085521
13. Winn, H. R. (2017). *Youmans and Winn Neurological Surgery*. Elsevier. https://books.google.jo/books?id=z3q7wAEACAAJ

Article topic: Radiotherapy Techniques.

Author: Saif Yahya Smadi.

Editor: Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Keywords: Intensity-modulated therapy (IMRT), Brachytherapy, Stereotactic body radiotherapy (SBRT), Stereotactic radiosurgery (SRS), Charged particle therapy.

Overview

Cancer is a worldwide public health problem; it accounts for a quarter of deaths exceeding heart diseases as the leading cause of death for people under 85 years old. Radiotherapy is a valuable tool in the management of cancer. More than 50% of cancer patients with localized tumors receive radiotherapy as part of their therapy, either alone or combined with other types of management such as chemotherapy and surgery. [1] In this article, we are going to briefly discuss some radiotherapy techniques.

Intensity-modulated radiotherapy

Intensity-modulated radiotherapy (IMRT) is a radiotherapy treatment that provides a high dose of radiation to the tissue affecting the tumor but with minimal dose to the nearby normal tissue. There is an obvious relationship between tumor control and radiation dose, but the radiation dose is usually limited by the tolerance of the surrounding structures. In some cases, the use of this technique allows more normal tissue to survive than other techniques [2].

IMRT treatment plans are produced using an inverse planning system that uses computerized techniques to distribute the intensities across the target volume [3]. Therefore, this technique is found to be proper for head and neck cancers which are found near many critical organs as the brainstem, eyes, spinal cord, optic nerves, lacrimal glands, cochlea, and mandible [4][5]. A newly published systematic review identified 10 comparative studies of IMRT and 2D-RT in nasopharyngeal carcinoma, they concluded that IMRT yields a lower incidence of late toxicities and thus it may be an effective treatment for patients with nasopharyngeal carcinoma [6].

This technique improved the target conformity, increased the normal tissue sparing, and enabled dose escalation. On the other hand, the biggest downside of IMRT is the increase in total body irradiation dose, in addition to that, it is a complex and time-

consuming procedure that requires a long time, this long time may interfere with the patient's comfort and positioning. [2][7]

Brachytherapy

Brachytherapy is a particular type of radiation therapy that requires the placement of an emitting radiation source close to the tumor or adjacent tissue at risk of having the microscopic disease. Brachytherapy applicators are specifically designed for different anatomic sites like body cavities and tissues. [8]

Implanted radon (Rn) in the brain of a patient who was suffering from a pituitary mass was the first use of brachytherapy for brain tumors by Dr. W.O Lodge in 1936. [9] Iodine-125 brachytherapy is an Important therapeutic method that enhances the survival of patients with gliomas [10][11]. Recently, it has been suggested that the use of I^{125} brachytherapy be effective in patients with recurrent gliomas. [12][13] A new study published in 2020 states that I^{125} brachytherapy could be an effective method in recurrent high-grade gliomas (HGG) even without the use of radiotherapy and/or chemotherapy [14].

The main limitation of this procedure is that it is invasive, meaning that it requires a short procedure in the operating room to place the source. Another important aspect is the quality of the implantation. Certainly, inappropriate placement of the source may expose the tumor to under dosage or too much toxicity especially if the source is close to a critical organ [15].

Figure1: prostatic brachytherapy, Case courtesy of Dr Chris O'Donnell [32].

Stereotactic body radiotherapy

Stereotactic body radiotherapy (SBRT) is a radiation method of delivering a high dose of external radiotherapy beam to small tumor targets very precisely with a high level of accuracy [16]. Stereotactic body radiotherapy development began in the 1990s in Stockholm at Karolinska Institute [17].

Compared with other external beam radiation therapies, this technique has many advantages, the use of high dose radiation, the delivery of one to five fractions in a few days, decreasing the treatment overall time, and improving the treatment response [18]. On the other hand, missing the target tumor can cause damage to the surrounding normal tissues, and because SBRT radiation fraction is higher in dose compared to other types of external beam radiation therapies the potential damage is also higher [19].

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) was first introduced in 1951 by Lars Leksell as an alternative for whole-brain radiotherapy. [20][21] SRS uses multiple beams of protons, gamma rays, and high-energy x-rays. [22] This technique works by radiation-induced DNA damage by free radicles and ions. [23]

It is a non-invasive, outpatient procedure that does not require general anesthesia. Under local anesthesia, a special helmet produces gamma rays fixed to the patient's skull. [23] Stereotactic radiosurgery (SRS) is considered suitable for brain metastasis and primary tumors, such as vestibular schwannomas, meningiomas, pituitary tumors, and other tumors that are resistant to conventional whole-brain radiation therapy (WBRT). [24][25]

The use of this technique is contraindicated in large lesions or too many lesions, the single-fraction SRS is often limited to small lesions. [26] A randomized trial compared SRS followed by conventional radiotherapy with carmustine (chemotherapy) versus only conventional radiotherapy with carmustine for patients with glioblastoma showed no improvement in the outcome or the overall quality of life. [27]

Figure2: Brainstem glioma, Case courtesy of Assoc Prof Frank Gaillard [33].

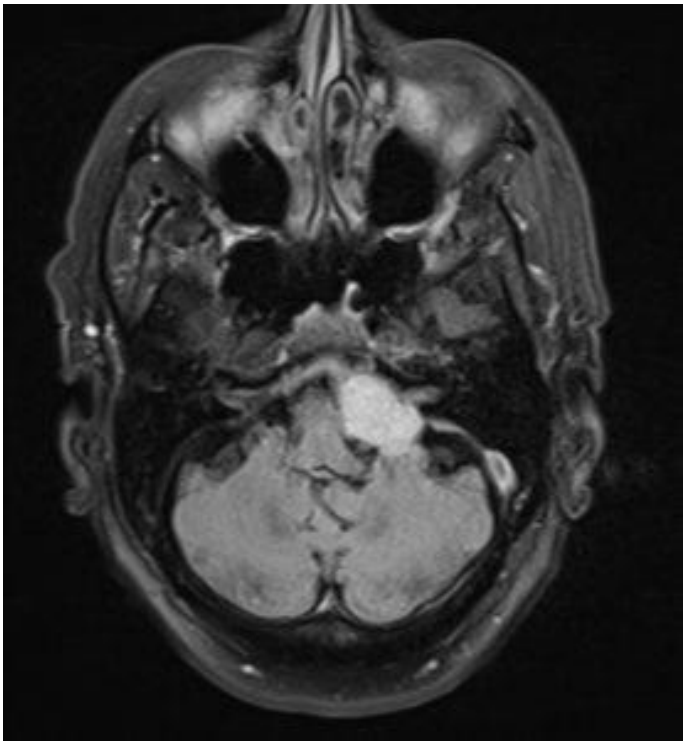


Figure3: Cerebellopontine angle meningioma, Case courtesy of Dr Mostafa El-Feky [28].

Charged particle therapy

Robert R. Wilson was the first one who proposed that accelerated protons could be used in the treatment of localized tumors in 1946. In 1950 was the first clinical use of this technique for pituitary hormone suppression in metastatic breast carcinoma. [29]

Unlike X-Ray irradiation, which is absorbed by the body and shows an exponential decrease in the radiation dose with increasing tissue depth, this technique deposits little energy at the body's surface [30]. Therefore, charged particle therapy produces the same dose of radiation to a tumor, this will minimize the radiation received by nearby normal nonmalignant tissues [31].

Charged particle therapy is useful in treating tumors surrounded by radiosensitive tissues and in situations where surgical access is limited. A small number of studies have made comparisons between X-rays and charged particle therapy. Although there are supporting advantages for charged particle therapy the cost-benefit ratio is still debatable. [30]

External Links:

Brachytherapy

https://www.youtube.com/watch?v=GfuFgyULt7w

Stereotactic radiosurgery

https://www.youtube.com/watch?v=HZQ8puGlsIw

Charged particle therapy

https://www.youtube.com/watch?v=MS590Xtq9M4

References

1. Thariat J, Myint AS, Vuong T, Gérard JP. for the benefit of patients. Nat Rev Clin Oncol [Internet]. 2012;10(1):52–60. Available from: http://dx.doi.org/10.1038/nrclinonc.2012.203
2. Taylor A, Powell MEB. Intensity-modulated radiotherapy - What is it? Cancer Imaging. 2004;4(2):68–73.
3. Purdy JA. Intensity-modulated radiotherapy: Current status and issues of interest. Int J Radiat Oncol Biol Phys. 2001;51(4):880–914.
4. Shuch, Brian; Linehan, B. W. M.L.; Srivasan R. O ncologist G. 2012;0031(0):1051–62.
5. Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: Promises and pitfalls. J Clin Oncol. 2006;24(17):2618–23.
6. Du T, Xiao J, Qiu Z, Wu K. The effectiveness of intensity-modulated radiation therapy versus 2D-RT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis. PLoS One. 2019;14(7):1–14.
7. Rehman J ur, Zahra, Ahmad N, Khalid M, Noor ul Huda Khan Asghar HM, Gilani ZA, et al. Intensity modulated radiation therapy: A review of current practice and future outlooks. J Radiat Res Appl Sci [Internet]. 2018;11(4):361–7. Available from: https://doi.org/10.1016/j.jrras.2018.07.006
8. Petereit DG, Frank SJ, Viswanathan AN, Erickson B, Eifel P, Nguyen PL, et al. Brachytherapy: Where has it gone? J Clin Oncol. 2015;33(9):980–2.
9. Lodge WO. Treatment of Intrasellar Tumours by Radon. Br Med J. 1936;2(3963):1257–8.

10. Wen PY, Iii EA, Black PM, Fine HA, Riese N, Levin JM, et al. Long term results of stereotactic brachytherapy used in the initial treatment of patients with glioblastomas. Cancer. 1994;73(12):3029–36.
11. Suchorska B, Ruge M, Treuer H, Sturm V, Voges J. Stereotactic brachytherapy of low-grade cerebral glioma after tumor resection. Neuro Oncol. 2011;13(10):1133–42.
12. Larson DA, Suplica JM, Chang SM, Lamborn KR, McDermott MW, Sneed PK, et al. Permanent iodine 125 brachytherapy in patients with progressive or recurrent glioblastoma multiforme. Neuro Oncol. 2004;6(2):119–26.
13. Suchorska B, Hamisch C, Treuer H, Mahnkopf K, Lehrke RE, Kocher M, et al. Stereotactic brachytherapy using iodine 125 seeds for the treatment of primary and recurrent anaplastic glioma WHO° III. J Neurooncol [Internet]. 2016;130(1):123–31. Available from: http://dx.doi.org/10.1007/s11060-016-2214-x
14. Wang C, Liu S, Peng L, Zhang K, Li W, Zhang H, et al. Permanent iodine-125 brachytherapy for patients with progressive or recurrent high-grade gliomas. BMC Cancer. 2020;20(1):1–8.
15. Chargari C, Deutsch E, Blanchard P, Gouy S, Martelli H, Guérin F, et al. Brachytherapy: An overview for clinicians. CA Cancer J Clin. 2019;69(5):386–401.
16. Potters L, Kavanagh B, Galvin JM, Hevezi JM, Janjan NA, Larson DA, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guideline for the Performance of Stereotactic Body Radiation Therapy. Int J Radiat Oncol Biol Phys. 2010;76(2):326–32.
17. Tipton KN, Sullivan N, Bruening W, Inamdar R, Launders J, Uhl S, et al. No Title. Rockville (MD); 2011.
18. Tipton KN, Sullivan N, Bruening W, et al. Stereotactic Body Radiation Therapy [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 May. (Comparative Effectiveness Technical Briefs, No. 6.) Executive Summary. Available from: ht.
19. Meyer JL, Verhey L, Xia P, Wong J. New Technologies in the. 2007;40:1–17.
20. Grandhi R, Lunsford LD. The past , present and future of Gamma Knife radiosurgery for brain tumors : the Pittsburgh experience. 2012;437–45.
21. The journey from proton to gamma knife 7. 215:67–75.
22. Baschnagel A, Wolters PL, Camphausen K. Neuropsychological testing and biomarkers in the management of brain metastases. 2008;12(Table 1):1–12.
23. Harris L MDJ. PubMed [Internet]. 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542166/
24. Suh JH. Stereotactic Radiosurgery for the Management of Brain Metastases. 2010;1119–27.
25. Chang EL, Selek U, Hassenbusch SJ 3rd, Maor MH, Allen PK, Mahajan A, et al. Outcome variation among “radioresistant” brain metastases treated with stereotactic radiosurgery. Neurosurgery. 2005 May;56(5):936–45.
26. Haw EDS, Cott CHS, Ouhami LUISS, Inapoli ROD, Line ROK, Oeffler JAYL, et al. SINGLE DOSE RADIOSURGICAL TREATMENT OF RECURRENT PREVIOUSLY IRRADIATED PRIMARY BRAIN TUMORS AND BRAIN METASTASES : FINAL REPORT OF RTOG PROTOCOL 90-05. 2000;47(2):291–8.
27. Ouhami LUISS, Eiferheld WES, Rachman DAB, Odgorsak ERBP, Asik MAWE, Ustig ROL, et al. RANDOMIZED COMPARISON OF STEREOTACTIC RADIOSURGERY FOLLOWED BY CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE TO CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE FOR PATIENTS WITH GLIOBLASTOMA MULTIFORME : REPORT OF RADIATION THERAPY ONCOLOGY GROUP 93-05 PROTOCOL. 2004;60(3):853–60.
28. Radiopedia. Cerebellopontine angle meningioma [Internet]. Available from: https://radiopaedia.org/cases/cerebellopontine-angle-meningioma-14?lang=gb
29. Durante M, Loeffler JS. Charged particles in radiation oncology. Nat Rev Clin Oncol [Internet]. 2010;7(1):37–43. Available from: http://dx.doi.org/10.1038/nrclinonc.2009.183
30. Loeffler JS, Durante M. Charged particle therapy-optimization, challenges and future directions. Nat Rev Clin Oncol [Internet]. 2013;10(7):411–24. Available from: http://dx.doi.org/10.1038/nrclinonc.2013.79
31. Durante M, Orecchia R, Loeffler JS. Charged-particle therapy in cancer: Clinical uses and future perspectives. Nat Rev Clin Oncol [Internet]. 2017;14(8):483–95. Available from: http://dx.doi.org/10.1038/nrclinonc.2017.30
32. Radiopedia. prostatic brchytherapy [Internet]. Available from: https://radiopaedia.org/articles/brachytherapy?lang=gb
33. Radiopedia. brainstem glioma [Internet]. Available from: https://radiopaedia.org/articles/diffuse-brainstem-gliomas-1?lang=gb

Title: Biomechanical basis of traumatic brain injury.

Author: Sara M. AlQuran.

Editor: Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Keywords: Traumatic brain injury, Biomechanics, acceleration, Blast injury, impact injury, impulsive injury.

Overview

Traumatic brain injury (TBI) is a large entity of diseases that results from an external insult to the brain by a mechanical force that may lead to either permanent or temporary loss of the brain's cognitive, psychological or physical functions (1).

In 2016, more than 3.5 million people were reported to live with a disability from TBI, and around 1.7 million new cases occur each year in the US, which causes a huge economic burden (2).

Etiology

The causes of TBI vary according to the age of the patient. For example, in people younger than 75 years old road traffic accidents are the most common cause, while falling is the major cause in people older than 75 years old (3). Violence and abuse contribute to about 20% of TBIs and 3% can be attributed to sports injuries (4).

Biomechanics

To understand biomechanics of TBI it is crucial to understand the head-brain anatomy complex and the protective layers that first meet the trauma. Scalp, the most outer layer, is a 1-1.5 cm thick multi-layer of skin, connective tissue and pericranium that absorbs and redistributes the load before reaching the skull. Beneath the scalp is the neuro-cranial bone plates, the CSF holding the brain, the meninges, the vasculature and finally the brain (5). The brain is held in place by several structures such as the tentorium, parasagittal bridging veins, perisinusoidal granulations, and cranial nerves (6).

The brain is one of the softest tissues in the body (7). Characteristics and behaviour of the brain upon the application of force depend on its mechanical properties. The brain is described as a viscoelastic material, meaning that it displays both elastic properties upon being affected by high load forces and viscous properties with low load forces (8).

Furthermore, the brain is heterogeneous in nature, the white and grey matter differ in characteristics and response to the force, with the white matter being stiffer (9). These mechanical characteristics and behaviour are affected by age and diseases (10).

From the above mentioned, the impact of injury is determined by three factors:

1. The amount of mechanical load that has been experienced by the head during the injury.
2. The estimate of the transferred load into mechanical injury such as stress or strain.
3. The tissue mostly affected, predicted depending on the characteristics of tissue and cell tolerance (11). the response and the behaviour of biological material under stress and force is determined by not just the amount of stress but by the rate and speed at which it is applied (8)

Physical Powers and Injury Mechanisms

Forces applied to the head can either be static, meaning that force is applied over a period of less than 200 milliseconds, or dynamic, meaning that it is applied quickly over a period of typically less than 50 milliseconds. The brain is commonly affected by dynamic forces in three ways: impact injury, impulsive injury, or blast pressure (8).

As seen in Figure 1, impact injury is caused by striking the head with an object. On the other hand, impulsive injury results from the movement of the head because of the movement of another body part. Blast wave injury happens due to the propagation of pressure waves from a blast exposure (12).

Figure 1: Types of Dynamic loading (8)

Injuries can be further classified into open (penetrating) or closed (non-penetrating). Open injuries fortunately resemble an exceedingly small portion, since their results are

catastrophic, and the damage occurs due to the physical penetration and transection of the tissue by the foreign body (13). Closed injuries are caused by contact and inertial forces. Contact forces are due to the direct impact of trauma while inertial forces are due to the acceleration of the head. Usually, the injury happens due to the combination of these forces as they rarely happen in isolation (12).

There are three diverse types of acceleration that affect the skull and the head: translational, rotational, and angular acceleration. As shown in the diagram, in the translational type, also known as linear, the centre of gravity in the head will move in a straight line without rotation and this usually results in focal injury, while in rotational acceleration, there is no movement of the centre but the head will rotate around it resulting in diffuse shear strain. Lastly, the angular type is a combination of both rotational and linear properties, and the centre of gravity moves in an angular manner. Angular type is the most common type responsible for the bulk of TBI cases (14).

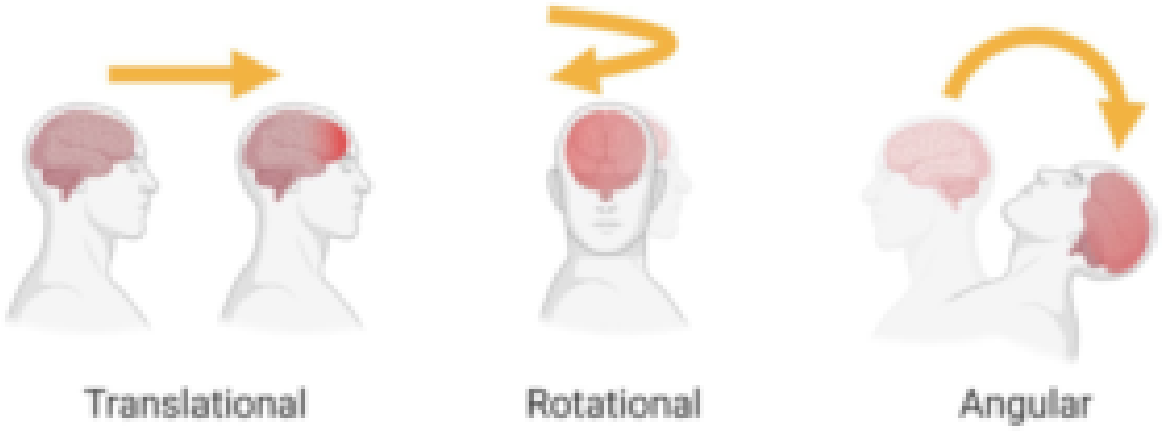


Figure 2: Types of Head Acceleration (8).

Events Taking Place in the Brain in Response to Trauma

The biomechanical investigations have found that the energy transferred to the head results in the creation of three-dimensional linear and rotational accelerations (3). In case of linear acceleration, the head will get acceleration when trauma affects it. Due to the brain's inertia, it will first lag interacting with the interior lining of the skull (15). The brain moves anteriorly inside the cranial cavity, meeting the anterior cranial basal structures especially the sphenoid ridges, so the surface injuries and contusion are most found at the bases of frontal lobes and the tips of temporal lobes (6).

This movement will cause damage. The coup contusions result from the direct slapping effect against the skull, while the contrecoup result from the re-bouncing of the brain

(16). The damage is explained by the fact that the movement of the parenchyma induces slight changes in the intracranial pressure causing short-lived pressure gradients; positive pressure is on the coup sites along with negative pressure at the contrecoup sites (17). Due to this pressure gradient, cavitation bubbles will develop in negative pressure in the contrecoup site, and these bubbles may cause local tissue damage (18). On the other hand, in case of rotational acceleration, there is a different mechanism of injury (19). Rotational acceleration is thought to cause shear strain resulting in more diffuse injury (20).

The above-mentioned processes and events happen in both impact and impulsive injuries. These injuries rarely happen in isolation.

Events Taking Place in the Brain due to a Blast Injury?

There are different theories that explain the mechanisms of injury in a blast-wave shock, despite the absence of any penetration and any object hitting the head. All these theories have evidence supporting them and others confounding (21).

First, the acceleration mechanism: it is argued that linear and rotational acceleration and their resultant pressure gradients have been implemented in the process (22), although scientists have found that the duration of acceleration in a blast injury will not reach the threshold of causing damage to the brain (21).

Second, the direct cranial transmission of pressure waves has also been implemented in the injury mechanism (23) along with the thoracic mechanism theory that suggests the transmission of pressure waves from the thorax along with the vasovagal activation that may have a role in causing brain injury (24).

References

1. Dawodu, T. J. S. D. (2019, November 9). Traumatic Brain Injury (TBI) - Definition, Epidemiology, Pathophysiology: Overview, Epidemiology, Primary Injury. Medscape. https://emedicine.medscape.com/article/326510-overview
2. Dixon, K. J. (2017). Pathophysiology of Traumatic Brain Injury. Physical Medicine and Rehabilitation Clinics of North America, 28(2), 215–225. https://doi.org/10.1016/j.pmr.2016.12.001
3. Karton, C., & Blaine Hoshizaki, T. (2018). Concussive and subconcussive brain trauma: the complexity of impact biomechanics and injury risk in contact sport. Sports Neurology, 39–49. https://doi.org/10.1016/b978-0-444-63954-7.00005-7
4. Traumatic Brain Injury: Hope Through Research | National Institute of Neurological Disorders and Stroke. (2020, February). National Institute on Neurological Disorders and Stroke. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Traumatic-Brain-Injury-Hope-Through
5. Bandak, F. A., Ling, G., Bandak, A., & De Lanerolle, N. C. (2015). Injury biomechanics, neuropathology, and simplified physics of explosive blast and impact mild traumatic brain injury. Handbook of Clinical Neurology, 89–104. https://doi.org/10.1016/b978-0-444-52892-6.00006-4
6. Md, R. W. H. (2016). Youmans and Winn Neurological Surgery, 4-Volume Set (Youmans Neurological Surgery) (7th ed.). Elsevier.
7. Moore, S. W., Roca-Cusachs, P., & Sheetz, M. P. (2010). Stretchy Proteins on Stretchy Substrates: The Important Elements of Integrin-Mediated Rigidity Sensing. Developmental Cell, 19(2), 194–206. https://doi.org/10.1016/j.devcel.2010.07.018
8. Keating, C. E., & Cullen, D. K. (2021). Mechanosensation in traumatic brain injury. Neurobiology of Disease, 148, 105210. https://doi.org/10.1016/j.nbd.2020.105210

9. Braun, J., Guo, J., Lützkendorf, R., Stadler, J., Papazoglou, S., Hirsch, S., Sack, I., &Bernarding, J. (2014). High-resolution mechanical imaging of the human brain by three-dimensional multifrequency magnetic resonance elastography at 7T. *NeuroImage*, *90*, 308–314. https://doi.org/10.1016/j.neuroimage.2013.12.032
10. Murphy, M. C., Huston, J., &Ehman, R. L. (2019). MR elastography of the brain and its application in neurological diseases. NeuroImage, 187, 176–183. https://doi.org/10.1016/j.neuroimage.2017.10.008
11. Meaney, D. F., Morrison, B., & Dale Bass, C. (2014). The mechanics of traumatic brain injury: A review of what we know and what we need to know for reducing its societal burden. Journal of Biomechanical Engineering, 136(2), 021008. https://doi.org/10.1115/1.4026364
12. Meaney, D. F., & Cullen, D. K. (2016). Biomechanical Basis of Traumatic Brain Injury. In H. R. Winn (Ed.),Youmans and Winn Neurological Surgery (7th ed., pp. 2755–2764). Elsevier.
13. Kim, J., Bandak, F., & de Lanerolle, N. (2015). Neuropathology of Traumatic Brain Injury: Comparison of Penetrating, Nonpenetrating Direct Impact and Explosive Blast Etiologies. Seminars in Neurology, 35(01), 012–019. https://doi.org/10.1055/s-0035-1544240
14. Ommaya, A. K., Goldsmith, W., & Thibault, L. (2002). Biomechanics and neuropathology of adult and paediatric head injury. British Journal of Neurosurgery, 16(3), 220–242. https://doi.org/10.1080/02688690220148824
15. Rowson, S., Bland, M. L., Campolettano, E. T., Press, J. N., Rowson, B., Smith, J. A., Sproule, D. W., Tyson, A. M., & Duma, S. M. (2016). Biomechanical Perspectives on Concussion in Sport. Sports Medicine and Arthroscopy Review, 24(3), 100–107. https://doi.org/10.1097/jsa.0000000000000121
16. El Sayed, T., Mota, A., Fraternali, F., & Ortiz, M. (2008). Biomechanics of traumatic brain injury. Computer Methods in Applied Mechanics and Engineering, 197(51–52), 4692–4701. https://doi.org/10.1016/j.cma.2008.06.006
17. A.C. Johnson, P.G. Young, The analysis of pressure response in head injury, in:C2006 Digital Human Modeling for Design and Engineering Conference, July 2006, Lyon, France, 2006. SAE paper no. 2006-01-2368.
18. E. Brennen, Cavitation in biological and bioengineering contexts, in: FifthInternational Symposium on Cavitation, Osaka, Japan, 2003.
19. King AI, Yang KH, Zhang L, Hardy W, Viano DC. Is head injury caused by linear or angular acceleration? IRCOBI Conference. 2003:1–12.
20. Gennarelli TA, Thibault LE, Ommaya AK. Pathophysiologic responses to rotational and translational accelerations of the head. SAE Technical Paper Series. 1972; 720970:296–308.
21. Courtney, A., & Courtney, M. (2015). The complexity of biomechanics causing primary blast-induced traumatic brain injury: A review of potential mechanisms. Frontiers in Neurology, 6, 221. https://doi.org/10.3389/fneur.2015.00221
22. Goldstein, L. E., Fisher, A. M., Tagge, C. A., Zhang, X.-L., Velisek, L., Sullivan, J. A., Upreti, C., Kracht, J. M., Ericsson, M., Wojnarowicz, M. W., Goletiani, C. J., Maglakelidze, G. M., Casey, N., Moncaster, J. A., Minaeva, O., Moir, R. D., Nowinski, C. J., Stern, R. A., Cantu, R. C., … McKee, A. C. (2012). Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Science Translational Medicine, 4(134), 134ra60. https://doi.org/10.1126/scitranslmed.3003716
23. Chavko, M., Koller, W. A., Prusaczyk, W. K., & McCarron, R. M. (2007). Measurement of blast wave by a miniature fiber optic pressure transducer in the rat brain. Journal of Neuroscience Methods, 159(2), 277–281. https://doi.org/10.1016/j.jneumeth.2006.07.018
24. Bhattacharjee, Y. (2008). NEUROSCIENCE: Shell Shock Revisited: Solving the Puzzle of Blast Trauma. Science, 319(5862), 406–408. https://doi.org/10.1126/science.319.5862.406

Article topic: Carotid Body Tumors.

Author: Layan Abuqayyas.

Editor: Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Overview

The carotid body is a small organ, measuring 2-6mm, located in the dorsal aspect at the bifurcation of the Carotid Artery bilaterally (1). Carotid artery tumors are a type of neuroendocrine tumors (NET) that arise from the paraganglionic neurons derived from embryonic neuronal tissue. Carotid Body tumors are the most common head and neck paraganglioma (2).

Etiology and Pathogenesis

The carotid bodies are composed of non-chromaffin cells from which tumors descend. They are divided into functional and non-functional. Most tumors are non-functional and the rare cases of functional non-chromaffin cell tumors release catecholamines like norepinephrine and epinephrine.

Due to the proximity of the carotid body to major blood vessels, tumors are highly vascular and certain growth factors are implicated in their angiogenic physiology: Vascular Endothelial Growth Factor (VEGF) and Platelet Derived Endothelial Cell Growth Factor (PD-ECGF). Moreover, the prevalence in females is higher than males (2:1) and more at higher altitudes (2000m above sea level) due to tumors expressing estrogen receptors and hypoxia acting as an environmental trigger to the genetics (3).

CBT can occur in sporadic and familial forms, and various oncogenes are culprits in both forms of occurrences. Sporadic tumors are unilateral in 95% of cases. Gardner and colleagues performed seminal genetic studies and found an increased expression of (c-myc, bcl-2, and c-jun) in the tumors. Further confirmation on the role of oncogenes was proven by Wang and colleagues, where the oncoprotein (bcl-2) was studied and found to tend to deregulate cell death, therefore, playing a vital role in the formation of the carotid body tumors.

The succinate dehydrogenase (SDH) mutation is linked to an earlier age of onset, multiple paragangliomas, and a positive family history. This mutation is present in both forms with increased incidence in familial cases (83%) than in sporadic (11%) (4).

Clinical presentation

CBTs are mostly benign tumors which present as an asymptomatic anterior neck mass, but if they grew large enough, they may have a mass effect that present with signs and symptoms of fullness, dysphagia, odynophagia, tongue weakness or atrophy. This is attributed to the proximity of the carotid body to the Vagus and Hypoglossal nerves (seen in 10%) (1).

The functional variant of CBT is relatively rare (4%) (3), and the release of catecholamines causes a presentation with symptoms of headache, flushing, palpitations, or increased blood pressure and heart rate (1).

Workup and Diagnosis

CBTs are named after clinical examination or found incidentally on imaging. The differential diagnoses for masses in the high cervical area include carcinoma, lymphadenopathy, leiomyomas, and branchial cleft cysts. Thus, a cervical MRI with and without contrast can help differentiate CBT (3) **(Fig.1)**. Color flow carotid duplex has become the ideal screening test for CBTs, where a well-circumscribed hypoechoic mass is seen splaying the carotid bifurcation. Other radiographic modalities that can be used to support the diagnosis: CT with or without contrast, and ultrasound (1).

The highly vascular nature of the tumor is problematic if surgical resection is done without angiography **(Fig.2)**, as it is needed to delineate the exact blood supply for the tumor. The ascending pharyngeal artery is the biggest contributor in most cases, and the superior thyroid artery plays a minor role. Variations in the vascularity should be assessed carefully (3).

Once the mass is confirmed to be a CBT, endocrine workup is prompted, especially in patients with high blood pressure or palpitations (3).

Classification

Shamblin and associates created a three-group system for CBT according to the location and important landmarks. Group I tumors are at the bifurcation between the ICA and ECA with no vessels or nerves traversing the tumor, they are easily dissectible. Grade II is partially associated with the ECA and ICA, they invade the adventitia, but do not completely enclose the arteries. Grade III tumors completely enclose the ICA and may invade the adventitia all the way to the muscularis. Grade III is the hardest to resect due to the superior laryngeal and hypoglossal nerves traversing the tumor, and the need for ICA reconstruction (3).

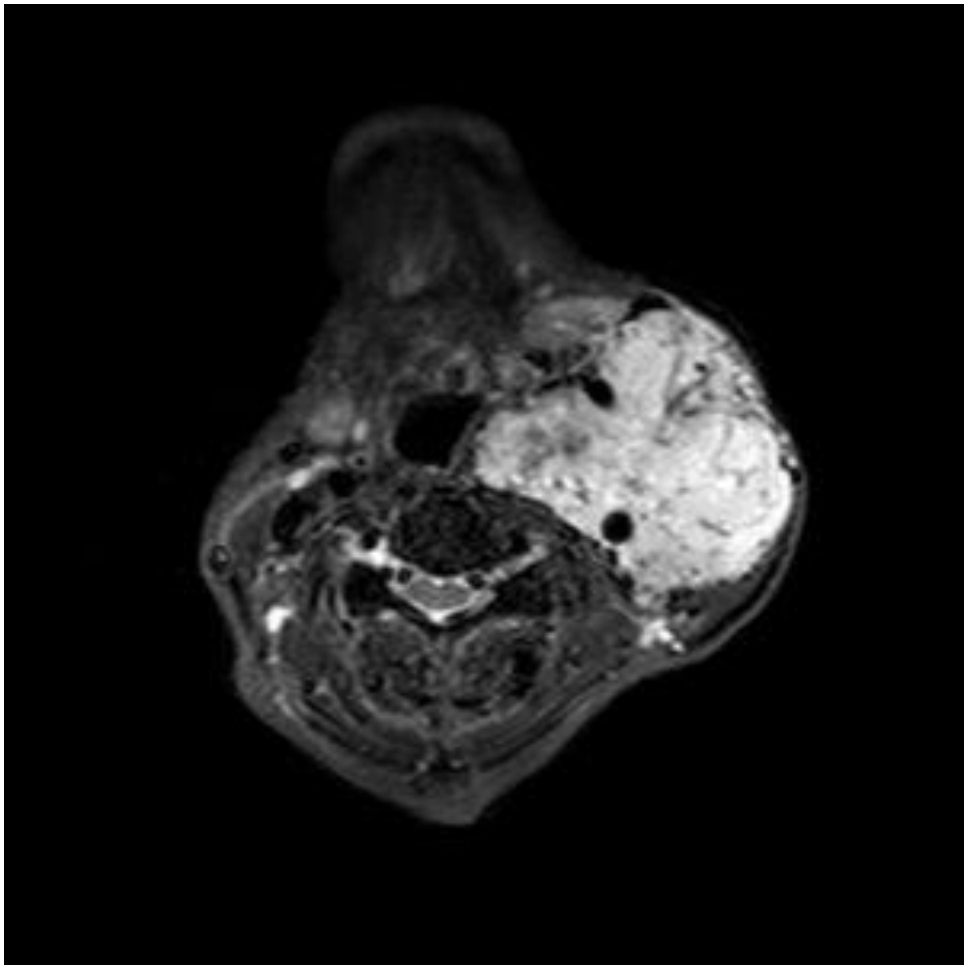


Fig.1: Axial MRI T1 showing a large enhancing vascular conglomerate soft tissue mass splaying the external and internal carotid arteries sitting between them, representing a carotid body tumor. Case courtesy of Dr. HanniMakky (5).

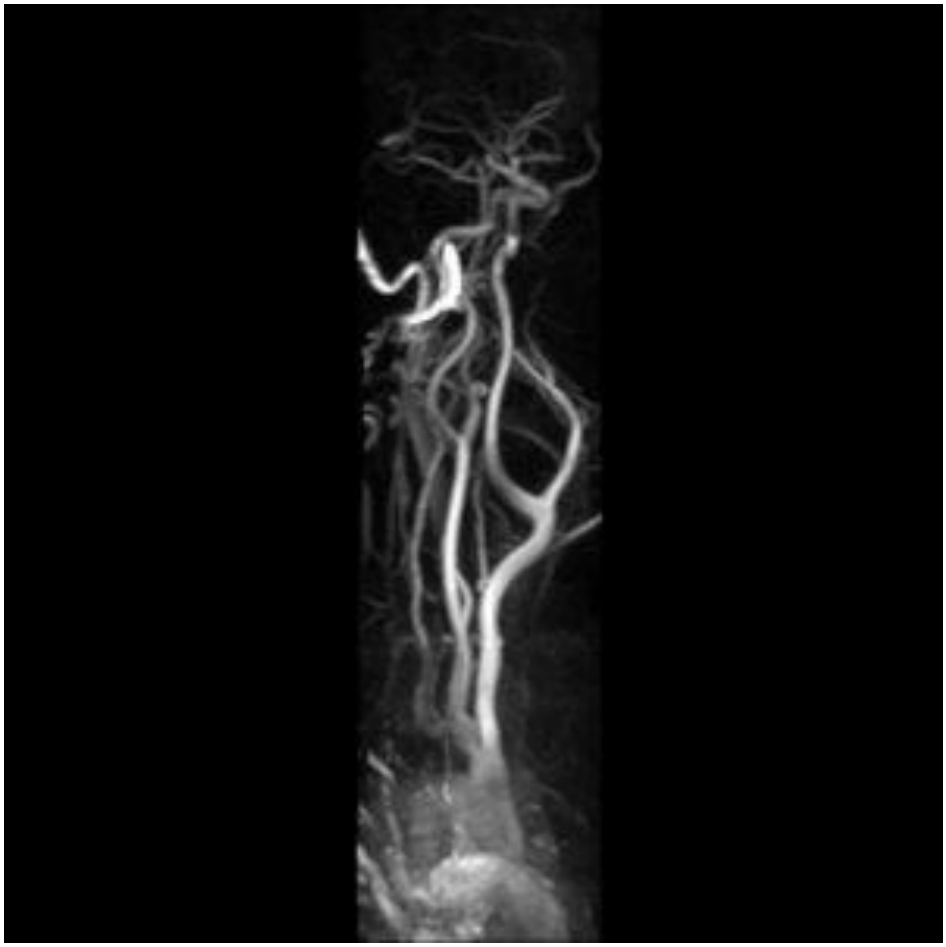


Fig.2: Angiography showing a large enhancing vascular conglomerate soft tissue mass splaying the external and internal carotid arteries sitting between them, representing a carotid body tumor. Case courtesy of Dr. HanniMakky (5).

Treatment

Preoperative planning is crucial to assess endocrine abnormalities due to catecholamine release. These patients should be given alpha-blockade two weeks prior to surgery and further beta-blockade to control heart rate and arrhythmias. Diagnostic cerebral angiography is done to assess for collateral cerebral blood flow. (3)

Evaluation of tumor extent horizontally and vertically, neural involvement, and infiltration of the ICA and other blood vessels is warranted to reduce morbidity and mortality. (4)

Smaller tumors (2-3cm) are resected easily, while bigger ones may require embolization to decrease the risk of blood loss (3). Embolization is indicated for larger tumors, Shamblin group III and tumors with cranial extension (6). Superselective catherization is done after angiography to embolize the smaller vessels supplying the tumor without

disrupting blood flow through the major vessels. Surgery is done no later than 48 hours after embolization to decrease soft tissue inflammation (3). Embolizaton carries the risk of transient ischemic attacks and stroke (6).

Tumors of grade III that encase the ICA may not be good candidates for surgical resection. Therefore, balloon occlusion testing is done to assess the possibility of resection and its effect on the ICA. The cerebral blood flow is assessed continuously intraoperatively using Compressed Spectral Array Electroencephalography (CSA-EEG) and a decrease in the cerebral blood flow may cue the surgeon to perform intraoperative shunting (3).

The incision will depend on the group. Group I and II may be resected with a curvilinear incision along the middle part of the tumor, or a straight incision along the sternocleidomastoid. For Group III, a radial neck T incision is recommended to properly view the tumor. **(Fig.3)**. Bilateral tumors are operated separately, with removal of the largest one first (1).

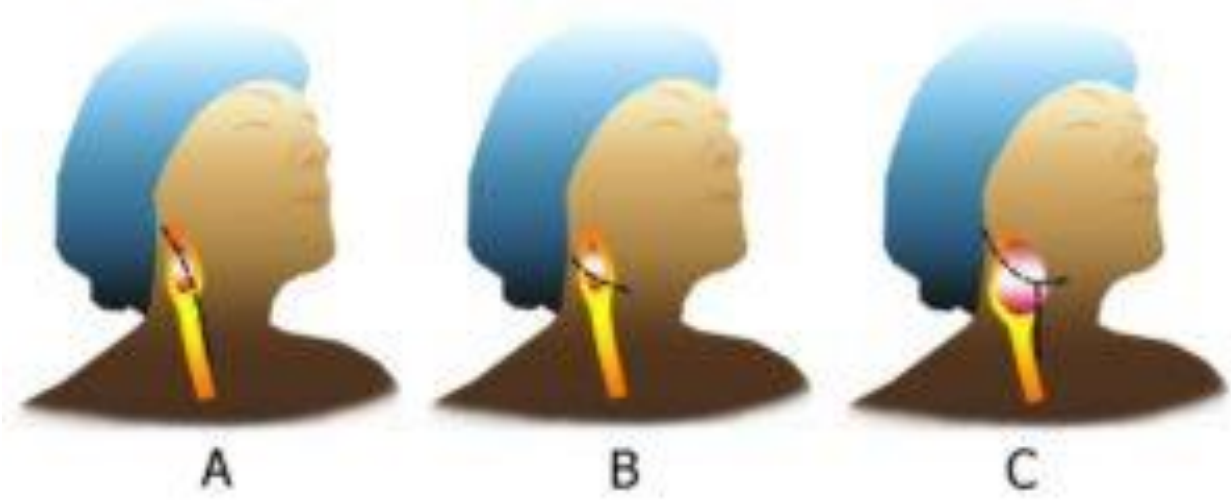


Fig.3: A and B for grade I and II, C for grade III (7).

Upon exposure, identifying the vagus and hypoglossal nerves is important as the hypoglossal nerve may be superior and posterior to the tumor. In group III, the nerves traversing the tumor may be damaged and surgery will be difficult and associated with irreversible damages. In larger tumors extending higher in the neck, or patients with shorter necks, exposure higher up the extracranial ICA is necessary.

Superiorly, the oblique incision is continued anterior to the tragus up to the root of zygoma. Mobilization of the parotid gland is done to ensure the safety of the lower division of the facial nerve, followed by tracking of the hypoglossal nerve along its course between the ECA and ICA and mobilization of it. Inferiorly, the stylohyoid and digastric muscles along with the stylomandibular ligament are divided to expose the distal ICA (3).

Radiotherapy is considered for patients at higher risk to undergo surgical resection due to extensive involvement, anesthetic risks, and multiple tumors. It helps reduce the tumor size and stops the growth (1).

Prognosis

The benign etiology of most CBTs makes their prognosis related to the local invasion of vascular and nervous structures. Prognosis depends on the preoperative measures done; to decrease mortality and morbidity, along with surgical complications (3).

Some CBTs are malignant (5-10%) and distant metastasis may occur in rare cases to lymph nodes, bone, lung, liver, pancreas, thyroid, renal, brain, and breast. The treatment modality in local malignant CBT is surgical. However, in distant metastasis, it is yet to be identified (2).

External Resources:

1. Carotid Body Tumor Excision (CharudattaBavare, MD, M. MujeebZubair MD) - YouTube
2. CAROTID BODY TUMOR - RESECTION WITHOUT EMBOLIZATION - YouTube
3. Resection of a Carotid Body Tumor - YouTube

References

1. Hoang VT, Trinh CT, Lai TAK, Doan DT, Tran TTT. Carotid body tumor: a case report and literature review. J Radiol Case Rep. 2019 Aug;13(8):19–30.
2. Xing J, Cheng Y, Ying H, Guan M, Jia N, Bai C. Systemic treatment of a metastatic carotid body tumor: A case report and literature review. Medicine (Baltimore). 2020 Nov;99(47):e22811–e22811.
3. Kliot M, Magistretti PJ, Friedlander RM, Haglund MM. Introduction and General Neurosurgery Oncology Pediatrics. 2017. 5720 p.
4. Prasad SC, Paties CT, Pantalone MR, et al. Carotid Body and Vagal Paragangliomas: Epidemiology, Genetics, Clinicopathological Features, Imaging, and Surgical Management. In: Mariani-Costantini R editor. PAMA [Internet]. B (AU): CP 2019 J 2. C 5. A from: https://www. ncbi. nlm. nih. gov/books/NBK543230. doi: 10. 15586/paraganglioma. 2019. ch. No Title.
5. Case courtesy of Dr Hani Makky ALSALAM, Radiopaedia.org rID: 7571. CBT mri. 10th Nov 2009.
6. Fan D, Luster S, Eid IG, Saied Calvino A. A multidisciplinary approach to carotid body tumors surgical management. J Surg case reports. 2020 Mar;2020(3):rjaa030–rjaa030.
7. Davis FM, Obi A, Osborne N. Carotid Body Tumors. In: Hans S editor. EC and VADS 2018. pp. 253–260. No Title.

Article topic: Carotid Occlusive Artery Disease - Carotid Artery Stenosis.

Author: Yusra Ghassan (Moh'd Akram) Arafeh.

Editor: Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Anatomy

The vascularization of the brain and the spinal cord depends entirely on two sources: the right and left vertebral arteries, which arise from the right and left subclavian arteries and the right and left internal carotid arteries, which arise at the base of the neck where the common carotid arteries bifurcate into external and internal carotid arteries.

After arising from the subclavian arteries, the vertebral arteries then proceed superiorly and travel across the posterior arch of C1, subsequently entering the foramen magnum. When meeting at the base of the pons they join to form the basilar artery in the midline. The basilar artery being the main blood supply to the brainstem. The basilar artery eventually forms the Posterior Cerebral Circulation.

Regarding the latter, the internal carotid arteries form two major arteries, the anterior and middle cerebral arteries, which form the Anterior Cerebral Circulation. The Anterior and Posterior Cerebral Circulations form the arterial ring called the Circle of Willis.

The internal carotid arteries and their branches supply blood to the frontal lobe and the lateral surface of the temporal and parietal lobes. Those areas are majorly responsible for the control of logical thinking, personality. It is also where the primary motor and sensory areas reside [1].

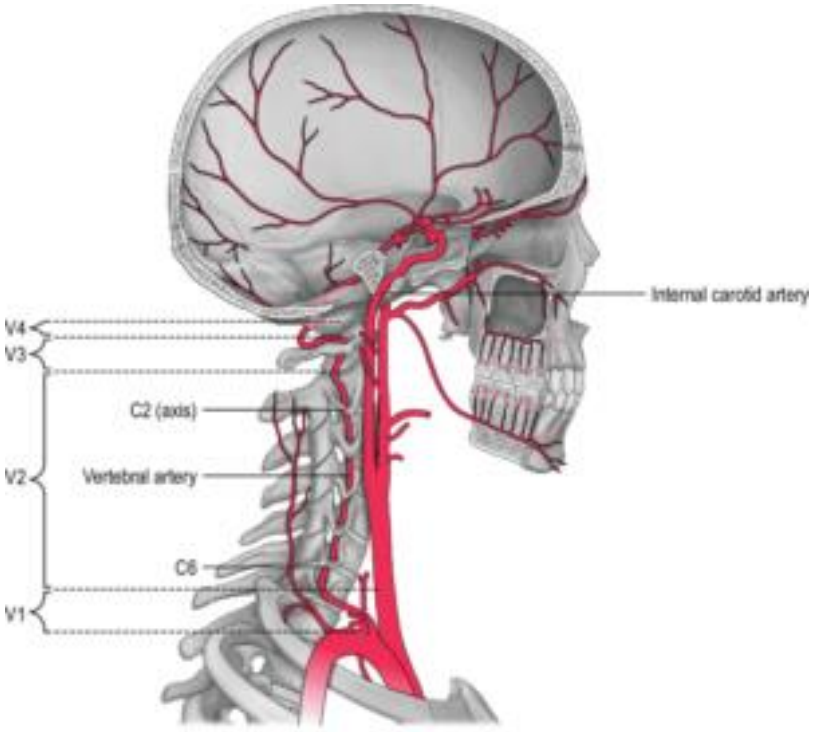


Figure 1: Brain blood supply and vertebral artery segments

Pathophysiology

Carotid occlusive artery disease, also called Carotid artery stenosis, is the progressive narrowing of the carotid arteries which could result in severe consequences. The mentioned stenosis or narrowing is mostly secondary to the development of atherosclerosis. Atherosclerosis is described to be a disease of the arterial intima; it is a pathological progressive process characterized by the build up of atheromatous plaques inside the vessels [3].

This plaque is made up of cholesterol, fat, calcium and other substances circulating in the bloodstream. Overtime, the presence of the plaque gradually reduces the lumen of the vessel. This decreases the blood flow through the affected vessels, which according to the size and area of the lesion results in a wide spectrum of symptoms [4]. In the cervical carotid artery, the bifurcation of the common carotid artery creates shear stress secondary to the turbulence and high-pressure of the arterial blood flow. This subsequently causes endothelial damage and recurrent inflammatory cascades. The recurrent bouts of inflammation lead to progressive deposition of plaque. This is followed by secondary migration of mononuclear cells and lymphocytes and consequent stimulation of smooth muscle cells in the arterial media to migrate and proliferate. Moreover, lipids, most notably by low-density lipoproteins, are taken up and deposited by the macrophages. Lipid-laden macrophages, or foam cells, continue to accumulate alongside calcium and other substances. Gradually, this compromises the integrity of the carotid arterial lumen and decreases the cerebral blood supply. Furthermore, if a

portion of the carotid plaque happens to rupture and migrate distally into the intracranial circulation, partial or complete obstruction of the blood flow can occur secondary to the breaking off and the lodging of the thromboembolism.

Strokes—a term that refers to the death or dysfunction of brain tissue due to vascular disease. Ischemic stroke remains a leading cause of death and disability in the developed world. Carotid artery stenosis is relatively common, and the atherosclerotic plaques formed are a source of emboli that can cause disturbance to the cerebral blood flow.

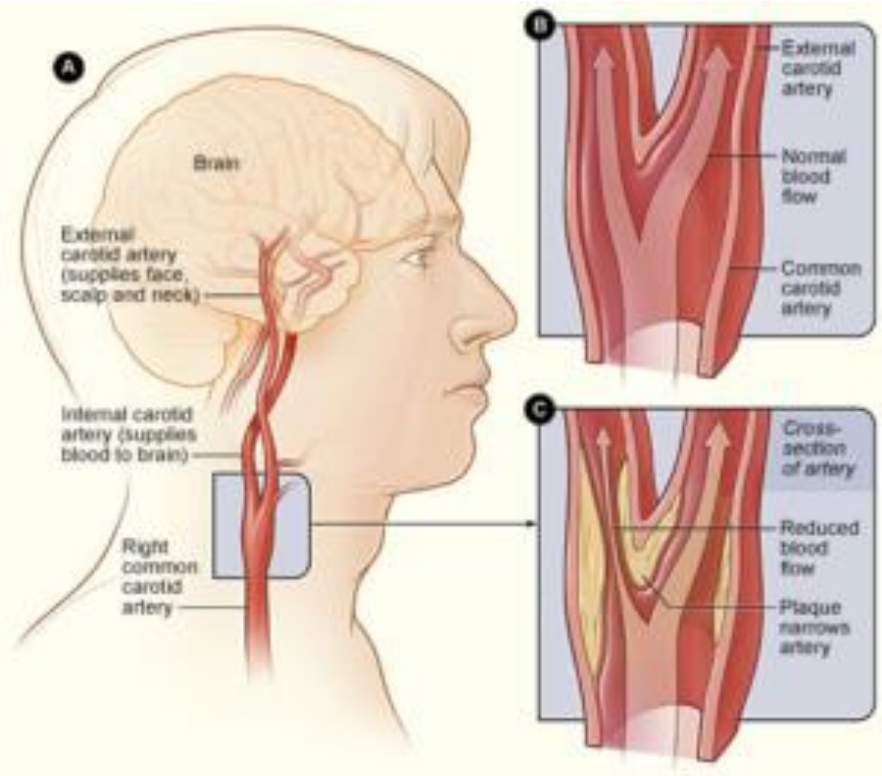


Figure 2: **A:** it shows the location of the right carotid artery in the head and neck. **B:** shows the inside of a normal carotid artery that has normal blood flow. **C:** shows the inside of a carotid artery that has plaque build up and reduced blood flow [5].

Presentation and complications

The clinical presentation of a stroke or TIAs is composed of a wide spectrum of signs and symptoms. Due to the significance and the consequences of such a thromboembolic event, recognizing the signs and symptoms of a symptomatic carotid stenotic disease is critical.

The most common neurological examination findings include dysarthria, facial weakness, contralateral hemiparesis or hemiplegia, or a pronator drift.

One neurological symptom experienced by the patients is Amaurosis fugax, an acute, atraumatic monocular visual loss described as a curtain being lowered over the patient's symptomatic eye caused by marginal perfusion related to diminished retinal blood flow or retinal micro-emboli.

10% to 15% of those who experience a stroke have a history of a sentinel TIA. The consequence of the thromboembolic event is highly dependent on the size and the vessel blocked.

The most affected vessel by thromboembolic events is the middle cerebral artery. Manifestation of an infarction in the territory supplied by the MCA is variable due to its large area. These manifestations mostly include contralateral weakness and hemisensory loss. If the lesion were on the dominant side, this would lead to aphasia. While a lesion was on the nondominant side, would more likely present as hemineglect and apraxic syndromes.

Infarctions in the anterior cerebral arteries lead to contralateral weakness that is more profound on the lower extremities compared to the upper extremities.

Infarctions in the ACA that supplies the frontal lobe will cause cognitive or psychiatric disturbances.

The anterior choroidal artery supplies the posterior limb of the internal capsule, the posterolateral thalamus, and the lateral geniculate body, infarctions of which present clinically as the triad of contralateral hemiparesis, hemisensory loss, and hemianopsia (visual field cut).

The classic deficit in posterior cerebral artery infarctions is a contralateral visual field cut. Yet, it is noted that sensory or visual disturbances or deficits are rare [6][7].

Work up and Diagnostic Imaging

There are several neuroimaging modalities that can be used to diagnose, localize, and measure the degree of the carotid artery stenosis. However, the most frequently used screening tool for the detection of the carotid artery stenosis is the doppler ultrasonography, which uses real-time imaging to detect changes in the velocity of the flow of the blood through the vessel in question. Moreover, the patient is usually asymptomatic, and the setting is usually non-emergent. It is requested by the physician after the detection of a carotid bruit in a physical examination. Remarkable elevation in the velocity of the flow is associated with significant reduction of the arterial lumen, and thus, is usually the finding of a symptomatic carotid artery stenosis case.

There are other common modalities like Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA) that are used in an emergency setting or to confirm the findings of the doppler ultrasound. CTA is particularly useful in a patient with a pacemaker or a stent. However, the gold standard imaging modality for exact calculations of the degree of the stenosis is Digital Subtraction Angiography (DSA) that is a fluoroscopy technique used in interventional radiology. It can be used on the carotid arteries bilaterally and on the vertebral arteries as well. [8]

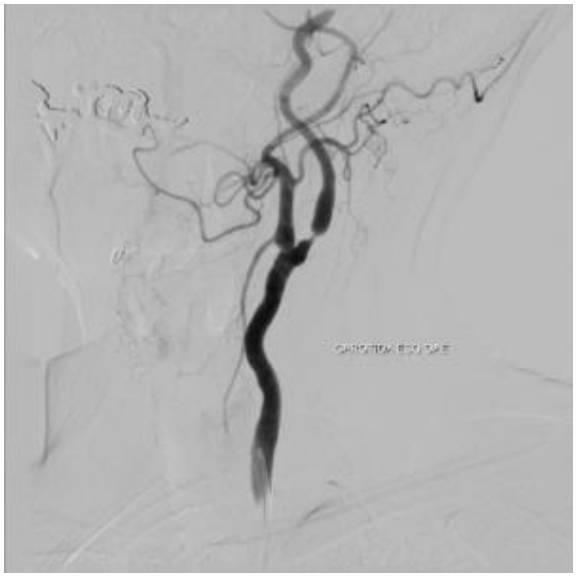
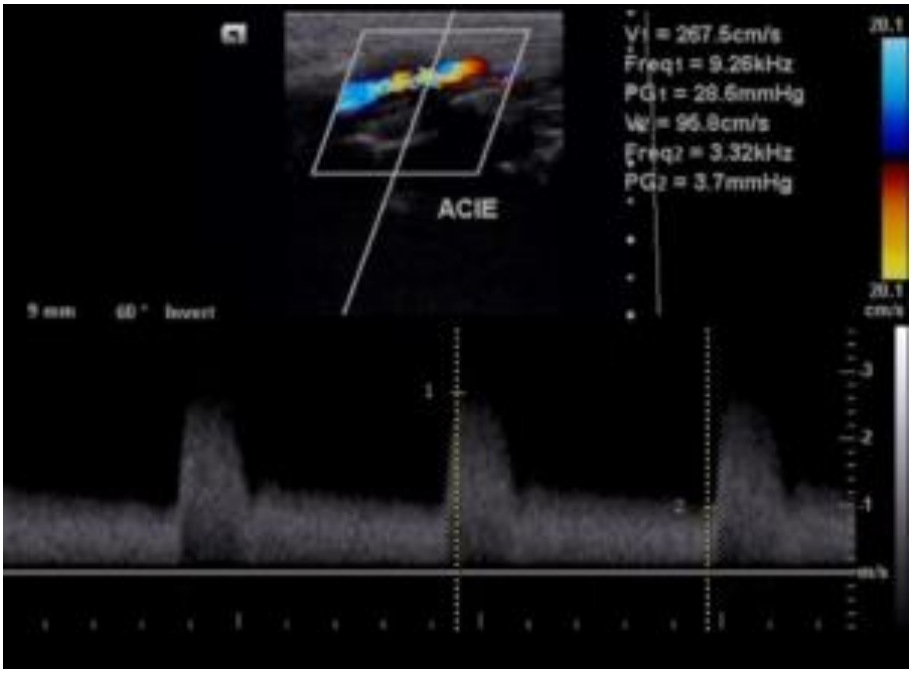


Figure 3: Angiography study confirms stenosis greater than 70% in the left ICA.[9]

Figure 4: Carotid Doppler study demonstrates bilateral atherosclerotic mixed plaques on bulbs (calcified and hypoechoic), being more important on the left, where it is sub-occlusive (near occlusion of the ICA) [9].



Left ICA PSV is greater than 230 cm/sec (267.5 cm/sec). Left CCA PSV is 81.9 cm/sec. ICA/CCA index > 2. [9]

Treatment and Management

To minimize the incidence of ischemic strokes in patients diagnosed with carotid artery stenosis, there are standard treatment algorithms that are dependent on everyone's modifiable and nonmodifiable risk factors. Treatment of carotid artery stenosis includes medical and surgical approaches.

Regarding medical management as an approach, the pharmacologic mainstay is platelet antiaggregating.

Aspirin's mechanism of action is characterized by irreversible inhibition of platelet cyclooxygenase, which later thwarts the production of thromboxane A2. Moreover, thromboxane A2 works as a vasoconstrictor and a platelet aggregation inducer. Thus, by inhibiting the production of thromboxane A2 we prevent further exacerbation of the stenotic lesion, or complete sudden blockage of the arterial lumen.

Studies have shown that one-hour post-ingestion of a single aspirin results in 98% inhibition of the formation of thromboxane A2 and, thus, prevents its aftermath from taking place. Adding to that, randomized trials of platelet antiaggregating therapy in patients with history of transient ischemic attack or stroke showed 25% reduction in the risk of nonfatal stroke and death from a vascular cause [10]. This reduction of risk was independent of patient's age, sex, and any other risk factors.[11]

After undergoing the carotid endarterectomy, which is the traditional surgical approach to this disease, aspirin has been associated with reduction in mortality rates and is a standard of care for patients suffering from this disease, regardless of whether the medical or the surgical approach was the mainstay of their treatment. However, the medical evidence is still in controversy regarding the dosage of aspirin that is associated with the best outcome for patients. Nonetheless, studies that were trying to evaluate its efficacy have utilized doses ranging from 30 to 1500 mg/day [12].

In the Aspirin in Carotid Endarterectomy trial, a total of 2804 patients who had undergone the surgery were randomized to compare the benefits of low-dose aspirin (81 to 325 mg/day) and high-dose aspirin (650 to 1300 mg/day). The goal of the trial was to assess the risk reduction in stroke, myocardial infarction, and death secondary to vascular causes. Three months postoperatively, the risk reduction was 6.2% to 8.4% favouring the high-dose aspirin group [13].

Also, another antiplatelet aggregate is Ticlopidine. Regarding the mechanism of action, it consists of inhibiting the adenosine phosphate pathway. It was not tested or studied specifically for patients with carotid stenotic disease. However, its usage has led to reduction in the risk of stroke, myocardial infarction, or death secondary to a vascular cause after a cardio-embolic stroke. It was reported that the relative risk of subsequent strokes, whether fatal or nonfatal, have been reduced by 12%; in comparison with aspirin [14-15]. Nonetheless, the dose recommended for ticlopidine to be beneficial in this condition is 250 mg twice daily.

However, the side effects profile thwarts its widespread implementation. The worrisome side effects include significant hematologic side effects including reversible neutropenia and thrombotic thrombocytopenic purpura.

Clopidogrel, an adenosine diphosphate receptor antagonist, is also used for medical management. In a study that included 19,000 patients suffering from a vascular disease secondary to atherosclerosis, a Clopidogrel of 75 mg/day was found to be more effective than 325 mg of aspirin in the risk reduction for a subsequent stroke, myocardial infarction, or death secondary to a vascular cause [16]. In patients who suffered from strokes, there was a relative risk reduction of 7.3% in favour of Clopidogrel.

Considering the favourability of Clopidogrel, the side effects profile is relatively benign, when compared to ticlopidine and aspirin, which is responsible for increased incidences of gastrointestinal bleed and gastric or duodenal ulcers. However, the tests did not test the effects of Clopidogrel use on patients with isolated carotid artery stenosis.

Dipyridamole is a phosphodiesterase inhibitor. It works by increasing the levels of intracellular cyclic adenosine monophosphate. Its side effects profile consists of gastrointestinal distress and headaches, neither of which cause significant impairment.

A study called the European Stroke Prevention Study 2 (ESPS-2) randomized patients with documented previous TIA or stroke to a treatment with low-dose aspirin, modified release dipyridamole, a combination of both agents, or a placebo. The study reported that the combination of the two agents reduced the stroke rate. Suggesting that the dipyridamole has a synergic effect when used with aspirin [17].

Clinicians use combinations of platelet antiaggregant therapy but there's still controversy regarding their superiority to one agent therapy in the prevention of stroke. There have been studies evaluating the usage of platelet glycoprotein IIb-IIIa receptor inhibitors for cardiovascular disease. However, more trials are required to evaluate their validity in carotid artery stenosis. Warfarin has also been utilized in stroke prevention in patients with non-valvular atrial fibrillation. Warfarin is undoubtedly effective in decreasing the incidence of stroke in patients who suffer from cardiogenic emboli, but their effectiveness with atherothrombotic TIA or stroke is yet to be evaluated. However, some clinicians use it for severe internal carotid stenosis.

The surgical standard of care at most institutions for the definitive treatment is CEA. Endovascular treatments such as catheter-based procedures, such as carotid artery stenting have also been performed for carotid artery stenosis.

The results of the Stenting and Angioplasty with Protection in Patients at High Risk of Endarterectomy and Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) suggested that carotid artery stenting with the use of a distal protection device is a superior therapeutic intervention for high-risk patients who met the surgical criteria outlined previously by the NASCET [19-23].

In 2010, the European International Carotid Stenting Study reported an increase in the incidence of strokes after undergoing the carotid endarterectomy procedure, despite the usage of distal protection devices. However, stenosis can recur after the stenting procedure.

Regardless of the number of trials conducted evaluating the medical and surgical managements and differentiating between stenting and CEA. No neurosurgical procedure has demonstrated better outcomes in the treatment of carotid artery stenosis than CEA. It is also widely believed in the surgical community that CEA is superior to medical management alone for symptomatic patients with greater than 50% carotid stenosis and for asymptomatic patients with greater than 60% carotid stenosis [24,25].

Risk factors and Prevention

There are several modifiable risk factors for stroke. Most prevalently is hypertension. Studies and evidence-based medicine has confirmed that control of blood pressure reduces the patient risk of stroke. [26] Even a reduction in diastolic blood pressure of 5

to 6 mm Hg has the capacity to decrease the risk of stroke by almost 42%. Also, control of isolated systolic hypertension decreases the risk of stroke by 36%. [27-28]

Cardiologists advise that systolic blood pressure greater than 140 mm Hg, and diastolic blood pressure greater than 90 mm Hg requires treatment, whether in the form of lifestyle modification or medical therapy.

Diabetes mellitus increases the risk of stroke. This increase is secondary to hyperinsulinemia which propagates the formation of plaques and accelerates the atherosclerosis of large arteries. It has been reported that serum glucose levels less than 126 mg/dL are optimal [26], [29], [30].

Nonetheless, other modifiable risk factors for an ischemic stroke are heavy alcohol consumption and cigarette smoking. [31] Interestingly, studies have shown that light to moderate alcohol drinking demonstrates a protective effect. It was also documented that individuals who drink lightly had a lower incidence of experiencing an ischemic stroke in comparison to those who indulge in heavy alcohol consumption, or those who are abstinent. Preferably, patients should be encouraged to quit smoking.

References

1. Purves D, Augustine GJ, Fitzpatrick D, et al., editors. Neuroscience. 2nd edition. Sunderland (MA): Sinauer Associates; 2001. The Blood Supply of the Brain and Spinal Cord.
2. Kerry, Roger & Taylor, Alan. (2010). Haemodynamics.
3. Ross R. The pathogenesis of atherosclerosis: an update. N Engl JMed. 1986;314:488-500.
4. Yamazaki M, Uchiyama S. Pathophysiology of carotid stenosis. Brain Nerve. 2010;62:1269-1275.
5. https://surgery.ucsf.edu/conditions--procedures/carotid-artery-disease.aspx
6. North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med.1991;325:445-453.
7. European Carotid Surgery Trialists Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet.1998;351:1379-1387.
8. https://my.clevelandclinic.org/health/diseases/16845-carotid-artery-disease-carotid-artery-stenosis/diagnosis-and-tests
9. https://radiopaedia.org/articles/carotid-artery-stenosis
10. Fuster V, Dyken ML, Vokonas PS, et al. Aspirin as a therapeutic agent in cardiovascular disease. Special Writing Group. Circulation.1993;87:659-675.
11. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ. 1994;308:81-106.
12. Dyken ML, Barnett HJ, Easton JD, et al. Low-dose aspirin and stroke. "It ain't necessarily so." Stroke. 1992;23:1395-1399.
13. Taylor DW, Barnett HJ, Haynes RB, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy:a randomised controlled trial. ASA and Carotid Endarterectomy(ACE) Trial Collaborators. Lancet. 1999;353:2179-2184.
14. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet. 1989;1:1215-1220.
15. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. N Engl J Med. 1989;321:501-507.
16. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE).Lancet. 1996;348:1329-1339.
17. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci. 1996;143:1-13.
18. CaRESS Steering Committee. Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS): phase I clinical trial.J Endovasc Ther. 2003;10:1021-1030.
19. Ringleb PA, Allenberg J, Brückmann H, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy

20. Gurm HS, Yadav JS, Faya P, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. N Engl J Med.2008;358(15):1572-1579.
21. Ansel GM, Hopkins LN, Jaff MR, et al. Safety and effectiveness of the INVATEC MO.MA proximal cerebral protection device during carotid artery stenting: results from the ARMOUR pivotal trial. Catheter Cardiovasc Interv. 2010;76:1-8.
22. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med.2004;351:1493-1501.
23. Mantese VA, Timaran CH, Chiu D, et al. The carotid revascularization endarterectomy versus stenting trial (CREST) stenting versus carotid endarterectomy for carotid disease. Stroke. 2010;41(suppl 10):S31-S34
24. Walker MD, Marler JR, Goldstein M, et al. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS): Endarterectomy for asymptomatic carotid artery stenosis. JAMA. 1995;273:1421-1428.
25. Halliday AW, Thomas D, Mansfield A. The Asymptomatic Carotid Surgery Trial (ACST) rationale and design. Eur J Vasc Surg. 1994;8:703-710.
26. Gorelick PB, Sacco RL, Smith DB, et al. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. JAMA. 1999;281:1112-1120.
27. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2. Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet. 1990;335:827-838.
28. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991;265:3255-3264.
29. Wolf PA, Clagett GP, Easton JD, et al. Preventing ischemic stroke in patients with prior stroke and transient ischemic attack: a statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke. 1999;30:1991-1994.
30. Albers GW, Hart RG, Lutsep HL, et al. AHA Scientific Statement. Supplement to the guidelines for the management of transient ischemic attacks: a statement from the Ad Hoc Committee on Guidelines
31. for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association. Stroke. 1999;30:2502-2511.
32. Gill JS, Zezulka AV, Shipley MJ, et al. Stroke and alcohol consumption.N Engl J Med. 1986;315:1041-1046.

Article topic: Non-Atherosclerotic Carotid Artery Lesions.

Author: Rand Al Kalbani.

Editor: Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Key words: non-atherosclerotic, carotid lesion, dissection, fibromuscular dysplasia, carotid artery aneurysm.

Overview

Non atherosclerotic carotid lesions are uncommon disorder that is more seen in young, aged group, it includes various pathology such as fibromuscular dysplasia, spontaneous carotid artery dissection, extracranial carotid artery aneurysm and radiation stenosis. Recently the incidence started to increase due to better imaging methods including magnetic resonance angiography and computed tomography angiography. The aim of management whether medially, surgically, or endovascular is to preserve efficacy and to decrease the morbidity and mortality rate.[1]

SPONTANEOUS CAROTID ARTERY DISSECTION

Etiology and pathogenesis

It is rare but life-threatening condition, it accounts for 2% of total ischemic strokes, mainly in the age between 35 and 50 years old with no significant difference in gender. In general, it is either caused by neck trauma or spontaneously associated with fibromuscular dysplasia, Marfan's syndrome, cystic medial necrosis, or Ehlers-Danlos syndrome[2], following a violent uncontrolled cough, exercise, or aggressive sudden movement of the head. Dissection arises from the *tunica intima* (the inner layer of the artery) allowing the blood to enter the wall of the artery under the influence of the arterial pressure, forming an intramural hematoma either toward the intima (inward) or toward the adventitia (outward) making a pseudo-aneurysm ([1],[2])

The etiology depends on environmental and genetic factors; some studies say that it is manifested with collagen type III deficiency. Other studies show that elevation in homocysteine increases the incidence of dissection. Also increase in level of proteases matrix metalloproteinase 2 have shown some evidence of dissection. Some vasodilators

abnormalities such as impairment in nitroglycerin may predispose the risk for dissection. Also, it is found that respiratory tract infections are implicated as a trigger ([3])

Clinical presentation and complications

The presence of two symptoms from the classical triad is enough to diagnose spontaneous carotid dissection, including ipsilateral pain in the face, head, and neck, transient ischemic attack or partial Horner's syndrome. 83%of the patients also complain from headache in the frontal or periorbital, or even periauricular region. This pattern is due to the anatomical distribution of the sympathetic fibers of the carotid artery. The internal carotid artery travels with the sympathetic fibers of the eye, and the external carotid artery travels with the sympathetic fibers of the sweat glands of the face. Surprisingly neck pain was only found in 21% of the patients, however transient ischemic attack was found in 60% and Horner's in 50% ([1]).

Doctors should assess for carotid bruits because they are found in 40% of the patients. An important follow through test is oculopneumoplethysmograhpy, accessing the retinal artery pressure ([1]).

Workup and diagnosis

Carotid dissection is seen as a string sign on digital angiography, which is the gold standard image as shown in **figure1**. Usually with irregular stenosis, starting after 2 to 3 cm distal to the carotid bulb and extending but not further from the beginning of the petrous portion of the artery. In less than 10% of the cases we can find double lumen or intimal flap. These radiographical findings may worsen especially in the acute phase within a period of days or even hours.

The long-term re-canalization in patients who had complete occlusion and was treated with anticoagulation is around 47%. Other noninvasive modalities such as magnetic resonance angiography or computed tomography angiography are used as screening methods.

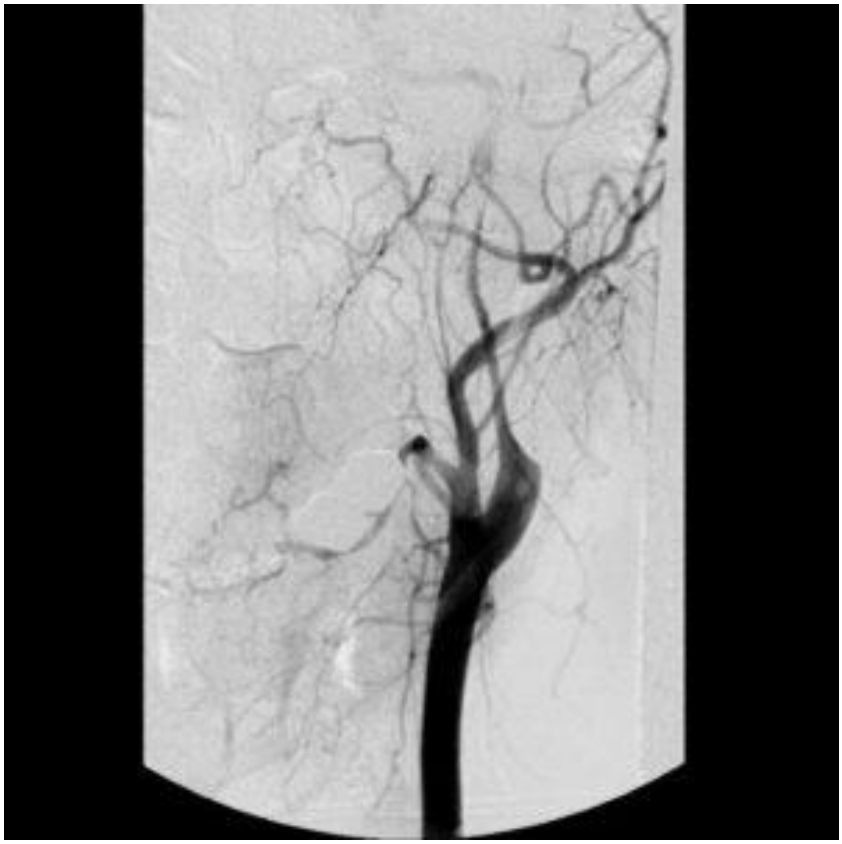


FIGURE 1: Digital angiography string sign of carotid dissection, Case courtesy of Assoc Prof Frank Gaillard.[4]

Treatment

Antithrombotic therapy whether antiplatelet or anticoagulants are the mainstay for the management of carotid dissection. Angioplasty and stenting may be indicated for ischemic symptoms as shown in **figure 2.**

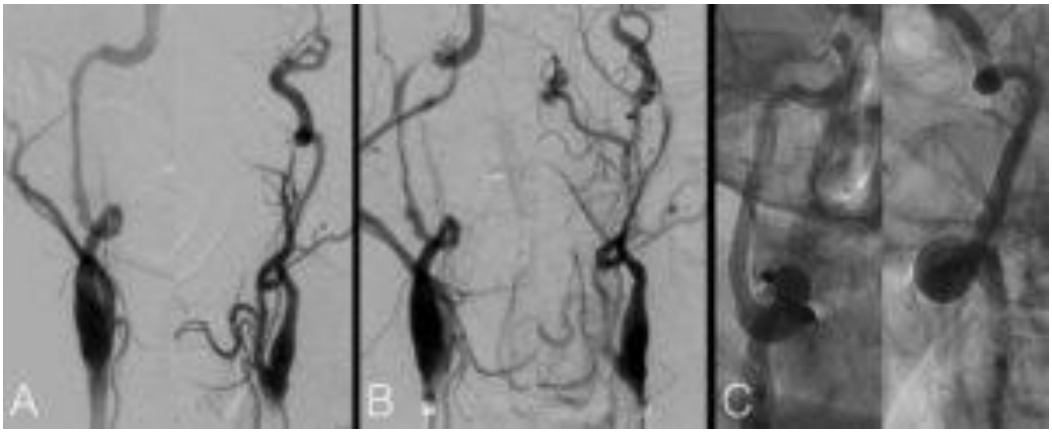


Figure 2: right internal carotid artery digital angiography A) long cervical dissection with 360° loop B) worsened stenosis at the horizontal petrous segment with string sign C) the artery after reconstruction with 3 stents. [5]

In very rare severe cases, direct surgical repair is a choice with patch graft or interposition graft, carotid ligation with or without artery bypass, a superficial temporal artery to middle cerebral artery bypass, or a high-low saphenous vein graft bypass, depending on the need for cerebral blood flow.[1]

Prognosis

The prognosis depends on the severity of the ischemic insult and the extension of the collateral circulation. The morbidity rate is less than 5%. In the first two to three months headache will resolve, 90% of the stenosis will resolve, aneurysms will decrease in size and occlusions will be re-canalized. The risk of recurrent dissection in the first month is 2% then decreases about 1% per year. In rare cases, persistent aneurysms may cause thromboembolic complications years after, but they never rupture.[2]

EXTRACRANIAL CAROTID ARTERY ANEURYSMS

Etiology and pathogenesis

It is a rare condition with incidence less than 1% of total aneurysms, but it is significantly important due to the complications of having neurological thromboembolic events, cranial nerve compressions, or even aneurysm rupture. It is either caused by a trauma such as previous carotid surgery leading to a pseudo-aneurysm, atherosclerosis, fibromuscular dysplasia, or congenital. The most common location is at the bifurcation of the carotid artery followed by middle to distal internal carotid artery.[6] The prevalence of stroke in non-treated patients is 50% and mortality rate around 70% .[7]

Clinical presentation and complications

The patient's presentation varies according to the size and the site of the aneurysm. Large aneurysms present as a pulsatile tender or non-tender mass. Symptomatic patients usually present with neck hematoma or epistaxis, other patients may present with transient ischemic attack due to thromboembolic events caused by the turbulent blood flow.

Workup and diagnosis

It is very essential to diagnose unruptured extracranial carotid artery aneurysm. Ultrasound is the first preferred test to a suspected aneurysm, followed by magnetic resonance angiography for further evaluation to determine the size, shape and location.[8]

Treatment

The management depends on the site, size, shape and cause of the aneurysm. Resection of the aneurysm in an open surgery and grafting is now replaced by endovascular stent grafting due to better outcomes, higher success rate and less morbidity and mortality rate.[1]

If the aneurysm is in the low to mid cervical region, or even fusiform aneurysms, it can be excised directly and then re-anastomosis of the proximal and distal artery as shown in **Figure 4**. If the primary re-anastomosis is not suitable, a Dacron or saphenous vein graft can be used to reconstruct the carotid artery. During the procedure, temporarily clipping of the carotid artery is done with electroencephalogram monitoring. [1]

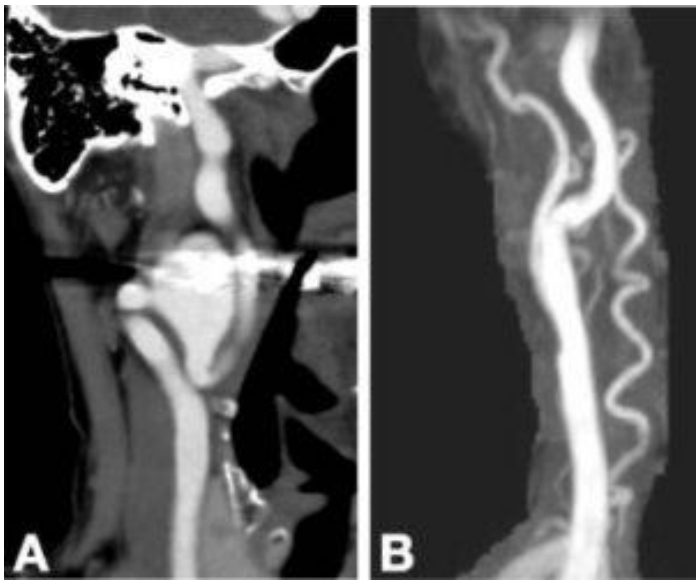


Figure 4: CTA of the right external carotid artery aneurysm A) before surgery B) after resection and reanastomosis of the artery [10]

Direct approach cannot be done if the aneurysm is in the high cervical region; instead, high flow vein bypass is done. Moreover, aneurysms in that area can be caused by Para-pharyngeal infection, so it is highly infectious and stenting in that area can cause chronic implant infection. That is why a carotid occlusion is done to these patients if he passes a balloon test occlusion, if he fails, bypass occlusion with carotid occlusion is the preferred choice. If there is no infection, an endoluminal stent is done[1].

FIBROMUSCULAR DYSPLASIA

Etiology and pathogenesis

It is a unifocal or multifocal, idiopathic, nonatherosclerotic, noninflammatory vascular disease that affects medium to large vessels renal and internal carotid arteries. It is found in women with a ratio of 9:1, and any age group but mainly from 20 to 60 years old.1

Histologically fibromuscular dysplasia presents with three primary pathologies, intimal fibroplasia, medial fibroplasias, and sub-adventitial hyperplasia. Medial fibroplasias are limited to the outer media to the involvement of the entire media.1

The milder form of the disease is characterized by accumulation of collagen and ground substances separating in the disorganized smooth muscle cell, however, in the severe form, the media itself is profoundly disorganized with fibroblast and collagen replacing the smooth muscle[1]

The etiology of fibromuscular dysplasia is unknown, although various hormonal (progesterone and estrogen) and mechanical factors have been suggested.

Clinical presentation and complications

The majority of cases are asymptomatic, patients could also complain from headache, tinnitus, vertigo, lightheadedness and syncope. 2/3 of the patients have carotid bruit, and 18% to 56% have cerebrovascular symptoms due to stenosis or occlusion in the carotid arteries.[1]

Fibromuscular dysplasia can cause hypertension (renal artery fibromuscular dysplasia), spontaneous carotid artery dissection, aneurysm formation, carotid cavernous fistula, thromboembolism, subarachnoid hemorrhage, stroke or even mesenteric ischemia. ([11],[1])

Workup and diagnosis

Fibromuscular dysplasia is usually found incidentally when angiography is done for other reasons. In 80% of patients, the string of beads is found on angiography. A multiple irregular spaced constriction with normal or ectatic intervening segments.[1] As shown in **Figure 5.**

Figure 5: carotid angiogram showing the string of beads in FMD [1]

The second presentation is smooth, concentric tubular stenosis. Other presentation called atypical fibromuscular dysplasia, involving one wall of the affected segment, creating smooth out pouching of the artery. Duplex ultrasound of the carotid arteries is less sensitive technique, it may demonstrate irregular pattern of stenosis. [1]

Treatment

Management depends on the patient's presentation. Medical or surgical treatment should be reserved for patients who have symptoms of cerebral ischemia. Antiplatelet, antithrombotic and antihypertensive drugs are the main treatment for carotid fibromuscular dysplasia. Vascular intervention is rarely performed since it is non athereosclerotic.[12]

RADIATION STENOSIS

Etiology and pathogenesis

Radiation is abundantly used to treat many vascular pathologies, such as arteriovenous malformation, arteriovenous fistulas, cavernous malformations, and vascular tumors. On the other hand, radiation to the normal vessel can induce variable side effects depending on the arterial size and radiation dose. It was observed that damaged endothelial cells by radiation do not function well as a barrier to plasma lipoprotein

infiltration in the vessel wall. As a result, we will have lysosomal activation and cellular proliferation within the vessel wall, resulting in intimal plaque formation. With the continuous radiation in the treatment of neck and mediastinal malignancies, reports of radiation induced extracranial carotid stenosis became more prevalent. External carotid stenosis from radiation is more challenging due to the involvement of extensive segments of the carotid artery and because it is associated with fibrosis of the arterial wall and the normal tissue, which makes endarterectomy more difficult.[1]

Clinical evaluation

Imaging studies are done for patients who developed symptoms of cerebral ischemia or emboli after radiation to the head, neck, or mediastinum. Although radiation changes in large arteries look similar to the atherosclerotic changes seen in the carotid bulb, the spectrum of radiation stenosis is more variable. For example, the arterial changes associated with radiation stenosis can occur in places that cannot be affected by atherosclerosis. Moreover, radiation stenosis can severely affect the surrounding tissue. Lastly, the damaged carotid arterial wall can make sever and more dangerous cardiac endarterectomy than the usual one. A carotid duplex scan gives information about most of the cervical carotid artery, but not a viable choice for the evaluation of the proximal cervical carotid artery and the distal cervical internal carotid artery. For a complete view of the arterial origins of high cervical segments, magnetic resonance angiography is done but may not be obtainable in some patients. So cervical and cerebral angiography remains the "gold standard" for radiation stenosis.[1]

Treatment

As said before dissection of plaques caused by radiation stenosis is more difficult because of the adherence to the intima. So as a primary treatment for radiation stenosis is carotid angioplasty stenting. It is used due to association of stenosis with soft tissue fibrosis, operating through an area of a previous myocutaneous flap, and more proximal arterial involvement.[1]

External links

https://www.neurosurgicalatlas.com/volumes/cerebrovascular-surgery/aneurysms/internal-carotid-artery-bifurcation-aneurysm

https://www.neurosurgicalatlas.com/volumes/cerebrovascular-surgery/revascularization/carotid-endarterectomy

References

1. Kliot, M., Magistretti, P. J., Friedlander, R. M. & Haglund, M. M. *Introduction and General Neurosurgery Oncology Pediatric*
2. Features, P., The, I. O. F. & Features, E. S Pontaneous D Issection of the. *English J.***344**, 898–906 (2007).
3. Patel, R. R. *et al.* Cervical carotid artery dissection: Current review of diagnosis and treatment. *Cardiol. Rev.***20**, 145–152 (2012).
4. Dr Henry Knipe and Assoc Prof Frank Gaillard. Internal carotid artery dissection.
5. Asif, K. S. *et al.* Endovascular reconstruction for progressively worsening carotid artery dissection. *J. Neurointerv. Surg.***7**, 32–39 (2015).
6. Sharma, R. K., Asiri, A. M., Yamada, Y., Kawase, T. & Kato, Y. Extracranial Internal Carotid Artery Aneurysm - Challenges in the Management: A Case Report and Review Literature. *Asian J. Neurosurg.***14**, 970–974 (2019).
7. Ni, L. *et al.* Endovascular stenting for extracranial carotid artery aneurysms. *Medicine (Baltimore).***95**, e5442 (2016).
8. Sosa, P. A., Matar, P. & Gross, I. T. Extracranial Internal Carotid Aneurysm in a 10-Year-Old Boy Diagnosed via Ultrasound. *Pediatr. Emerg. Care***35**, e49–e52 (2019).
9. Gaillard, C. courtesy of A. P. F. internal carotid aretry.
10. Yamamoto, S. *et al.* Surgical and Endovascular Treatments of Extracranial Carotid Artery Aneurysms—Report of Six Cases. *J. Stroke Cerebrovasc. Dis.***26**, 1481–1486 (2017).
11. Georges, A. & Persu, A. Genomics of Fibromuscular Dysplasia. 1–13 (2018) doi:10.3390/ijms19051526.
12. Ko, M. *et al.* Diagnosis and management of fibromuscular dysplasia and segmental arterial mediolysis in gastroenterology field: A mini-review. *World J. Gastroenterol.***24**, 3637–3649 (2018).

Article topic: Neural Tube Defects.

Author: Rania Sanouri.

Editor: Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Overview

Neural tube defects (NTDs) are birth anomalies attributed to a problem in or failure of closure of the neural tube during embryogenesis. The level of failed closure decides the type and the severity of the neural tube defect. Usually, NTDs are believed to be multifactorial, mainly due to genetic and environmental causes. NTDs are common with a prevalence from 0.5 to 10 per 1,000 pregnancies (1).

Epidemiology and risk factors

Since many cases of NTDs end up as spontaneous abortions or legal terminations, data about prevalence is affected (1). Many cases are non-syndromic, other NTDs are due to chromosomal aneuploidy including trisomy 13 & trisomy 18, which account for less than 10%. The prevalence of NTDs in miscarriage & stillbirths is higher than in term pregnancies. It also has ethnic and regional variations, for instance, the incidence of NTDs in Mexico is 3.2 in 2000 births, which is higher than in the United States. Moreover, regions in China have 20 times higher prevalence than in the US (2).

Regarding genetic predisposition, a history of pregnancy with an NTD-affected fetus will have a recurrence risk of 3% in the subsequent pregnancy and 10% if after conceiving a second NTD embryo. In twins, the NTDs' concordance rates among monozygotic twins are7.7%, which is higher than the rate for dizygotic twins (4.4%). For some types of NTDs, there is gender predominance; however, no conclusive evidence has been identified (2).

Many genetic and non-genetic factors are involved in the abnormal closure of the neural tube. One hypothesis called "multifactorial threshold model" assumes that only in synergism can these factors cause failure of closing the neural tube and production of abnormal phenotype. This excludes the ability of one factor to produce NTD and cause disruption to embryogenesis (2).

Non-genetic factors include those from the environment ex: air pollution, maternal factors, diseases, nutrition, exposure to occupational chemicals or physical agents and substance abuse (2).

Classification

According to Lemire classification, neural tube defects are classified into two main defects: neurulation & post-neurulation defects. Neurulation defects include those that occur due to failed closure of the neural tube and thus are open lesions. Examples: Craniorachischisis, anencephaly AKA “exencephaly” and meningomyelocele (myelomeningocele (MM) and myelocele). Whereas post-neurulation defects result in closed, skin-covered lesions sometimes referred to as migration abnormalities, which could be cranial or spinal defects (3).

Post-neurulation cranial defects include microcephaly, hydranencephaly (loss of most of cerebral hemispheres), holoprosencephaly, lissencephaly, porencephaly, agenesis of corpus callosum, cerebellar hypoplasia “Dandy-Walker syndrome” and megalencephaly (3). Post-neurulation spinal defects include: diastematomyelia, diplomyelia and syringomyelia (3).

Embryonic Basis of NTDs: Neural Tube Closure

The knowledge about principles of neural tube defects is taken from experimental models mainly mammals and amphibians because it is difficult to get access to neurulation staging from human embryos (1). The neural tube closure process is complex and involves many events occurring at the cellular level such as convergent extension, apical constriction and interkinetic nuclear migration. In addition, there are many molecular processes including the non-canonical Wnt/planar cell polarity pathway, Shh/BMP signalling and Grhl2/3, Pax3, Cdx2 and Zic2 transcription factors (4). The primary neural tube closure is the result of folding and fusion of the neuroepithelium (1). Other origins like non-neural ectoderm (NNE), mesoderm and notochord have been implicated in regulating the neural tubeclosure (NTC). Any failed changes of neurulation morphology will lead to disturbances in NTC, generating neural tube defects which are among the commonest human birth defects. Understanding of the mechanisms of NTC may aid in the development of methods for predicting and preventing NTDs (4).

Neurulation

Neurulation, which occurs at the 3rd week of embryonic life, is the first step in neural tube development. It involves thickening of the ectoderm from node of Hensen caudally reaching the prochordal plate rostrally. Studies done on xenopus embryos, concluded that ectoderm is made by default to have a neural fate that is usually inhibited by BMPs

(Bone morphogenetic proteins). However, in higher vertebrates, this process is more complex and involves other factors that play a role in inhibition like: FGF (fibroblast growth factors), β-catenin and possibly calcium transient (5).

Neurulation has two subtypes related to the stages of closure:

1. **Primary Neurulation:**

Neural tube formation involves bending of the neuroepithelium at the midline to generate two neural folds that will elevate and fuse (primary neurulation) (1). The formation of the neural groove in the midline results from the different rates of cell proliferation and changes in cell shape and movement in the neural plate. Cell-shaping processes including (apicobasal elongation, apical narrowing, and basal expansion), cell movement and adhesion, which are superimposed by the forces from mesenchyme and the surrounding surface ectoderm, will elevate and converge the neural folds along the dorsal midline and fuse with each other to form the neural tube. Surface ectoderm at the edges of the neural folds will fuse as well. Neural crest-derived ectomesenchyme in the cranial region and in the trunk will later spread around the neural tube under the surface ectoderm and becomes the primordia of the meninges, axial skeleton, and muscles (5).

Neural tube closure is discontinuous with distinct sites of initiation located at characteristic axial levels in both humans and mice. Requirements for closure depend on certain morphological and molecular basis and differ along the body axis. Therefore, NTDs occur due to failure of initiation points or disruption of progression of closure between these sites **(Figure 1)** (1).

Closure of the NT first begins on day 8 at the level of the hindbrain/cervical region during embryological life of mice (closure 1) (Figure 1a), and failure of this event usually leads to craniorachischisis. The next day, closure 2 usually takes place at the caudal forebrain. Once contact and fusion are established between the tips of the neural folds, closure spreads bidirectionally from the sites of closures 1 and 2 in a caudal direction from the rostral end of the neural tube (closure 3). The neuropores (open regions of neural folds) gradually will contract to complete the closure process of both the anterior neuropore (between closures 2 and 3) on embryonic day 9 and the hindbrain neuropore (between closures 1 and 2) later. In humans, however, Cclosure 1 occurs at 21 days of fertilization and the entire process of closure completes by 28 days post fertilization (1).

Cranial neural tube defects (like anencephaly) result from failure of closure 2, or incomplete fusion between closures 1 and 2, which closes the midbrain and the hindbrain. If progression from the anterior end of the neural plate (closure 3) fails, this causes a split face with forebrain anencephaly (1).

Neurulation of the spinal part of the NT progresses caudally while the embryo continues to grow. Primary neurulation completes with final closure of the posterior neuropore on day 10. If the progression of closure fails, a persistent opening of the posterior neuropore results in spina bifida, and the size of the lesion directly correlates to the axial level at which closure stops (1).

2. Secondary Neurulation

Secondary neurulation is the formation of the NT in the lower regions of sacrum and coccyges without neural fold closure (4). This neurulation process is mainly about condensation of specific type of cells known as tail-bud derived cells that form a type of epithelium which closes the neural tube (2). Disruptions in this transitional process will mostly cause closed or skin-covered lesions associated with tethering of the cord and ectopic lipomas **(Figure 1)**.

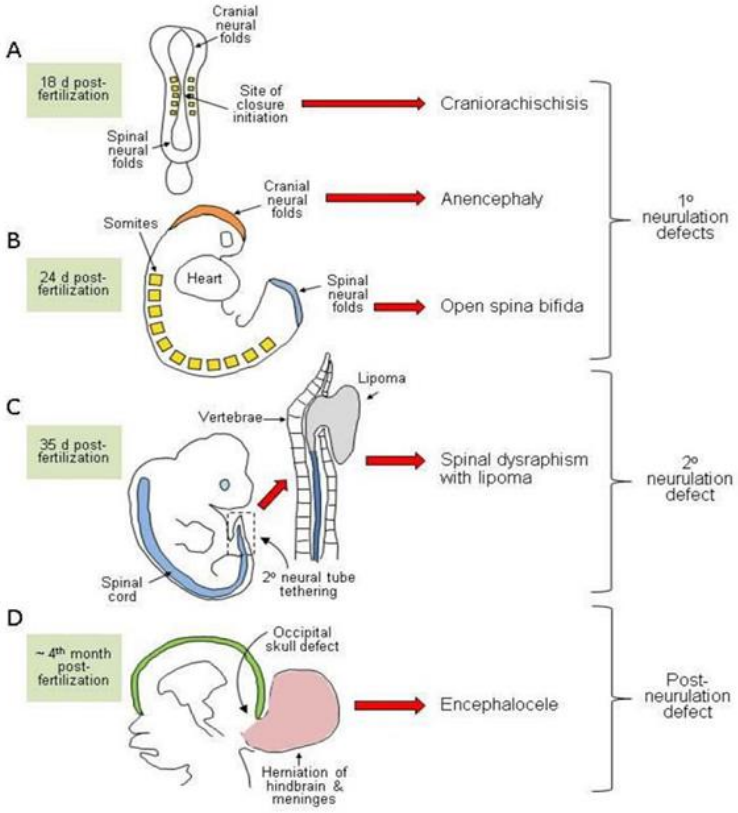


Figure 1: Diagrammatic representation of the developmental origin of malformations broadly classified as neural tube defects in humans (1)

Etiology & Pathogenesis

Development of the neural tube is a multi-step process controlled by genetic and environmental factors. It involves gene–gene, gene–environment and gene–nutrient

interactions. Despite many years of research, the exact cause of NTD remains not fully understood. Nowadays, it is largely agreed that most NTD cases are of multifactorial origin, having a significant genetic component to their etiology that interacts with several environmental risk factors (1).

Genetic

Genetics of NTDs is still not fully understood & very complicated. Single gene disorders like: Waardenburg syndrome, Fraser syndrome & Meckel-Gruber syndrome were found to be associated with NTDs. Moreover, chromosomal anomalies including autosomal trisomy have higher incidence of spina bifida. Other risk factors include monozygotic twinning and consanguinity (5).

Environmental

Multitude of environmental risk factors are related to congenital neural defects including physical agents such as radiation, hyperthermia and stress, as well as drugs (e.g. thalidomide, folate antagonists and antiepileptics and hypervitaminosis A), alcohol, organic mercury, lead, maternal infections (e.g. rubella, syphilis, cytomegalovirus, Toxoplasma gondii), and maternal metabolic conditions (e.g. phenylketonuria, diabetes mellitus). Exposure to noxious agents such as organic solvents, anesthetics, pesticides, and paints has been reported to be related to an increased risk of NTD (5).

Bad maternal health status has been attributed to enhance the risk for NTD in the offspring. The antenatal screening study should include women with spontaneous pregnancy loss, known to be associated with a high incidence of NTD. It is important to point out that contrary to frequent claims, CVS anomalies (not NTDs) are more common in infants of diabetic mothers (5).

Nutritional factors and Folate

Folate one-carbon metabolism **(Figure 2)** comprises complex reactions that mediate transfer of one-carbon groups for several biosynthetic processes. It is required for nucleotide biosynthesis and methylation reactions that occur in neural tube closure. Abnormal thymidylate and purine biosynthesis have been identified in mouse NTD models and some NTD cases. Deficient methylation may also be implicated in NTDs (1).

Given that lower socioeconomic status and increased risk of birth defects are linked, there is possibility that nutritional factors are also related to NTDs. It was found that mothers of NTD fetuses had lower levels of vitamin B9 (folate) in their serum, necessitating trials of folic acid-containing supplements to prevent NTD recurrence. A multi-center randomized controlled trial confirmed that maternal folic acid

supplementation (at 4 mg per day) significantly reduces the recurrence risk, and other clinical trials proved evidence for reduction of occurrence risk as well (1).

Data have shown an inverse relationship between blood folate concentration and risk of an affected pregnancy. Folate levels below the normal range may contribute to NTD development in genetically susceptible individuals. For example: gene- environment interaction was studied in mice to show that folate deficiency does not cause NTDs unless combined with a mutation of a predisposing gene, such as Pax3 gene (1).

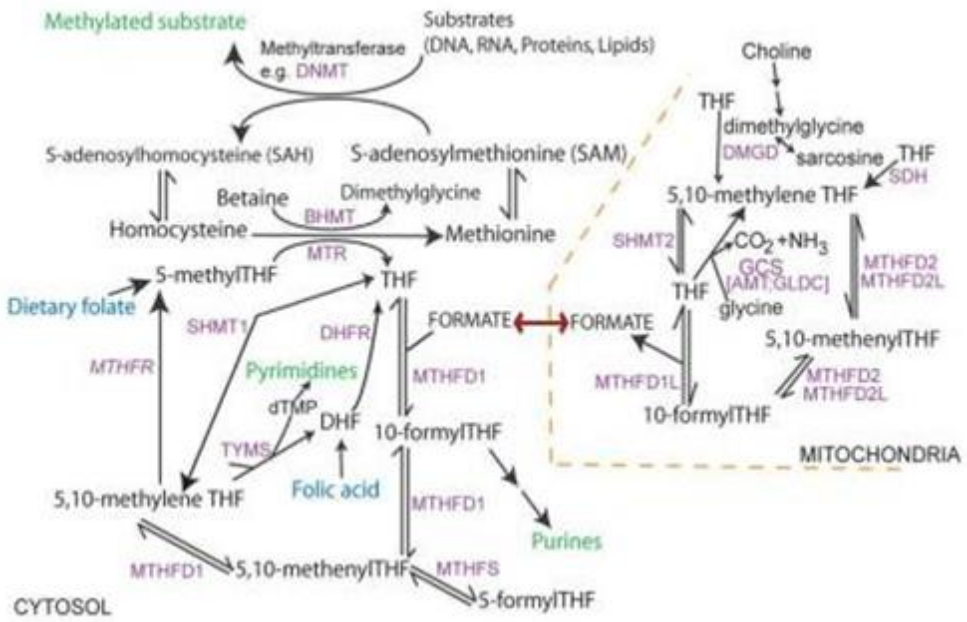


Figure 2: Overview of folate one-carbon metabolism (1).

Pathogenetic Mechanisms of NTD

NTD are often thought to result only from a primary failure of the neural tube closure. however, there is now clinical and experimental explanation to support secondary reopening of an already closed NT, causing NTD. Human embryo studies indicate that post-closure lesions are late in onset. NTD affect not only regions of the neural tube but other non-neural organs as well. Myelomeningoceles are virtually always associated with Chiari II malformations (**Figure 3**) (5). The developmental interruption of neurulation NTD with other anomalies more than isolated NTD(5).

A study done by Seller and Kalousekin 1986 compared the frequency and pattern of isolated NTD and those of NTD associated with other abnormalities. They note that significant bunch of developmental defects are associated with total craniorachischisis and upper thoracic spina bifida, less frequently with anencephaly and lumbosacral spina bifida and never with sacral spina bifida (5). This definitive pattern implies a connection between the mechanisms by which NTD and associated anomalies develop (5).

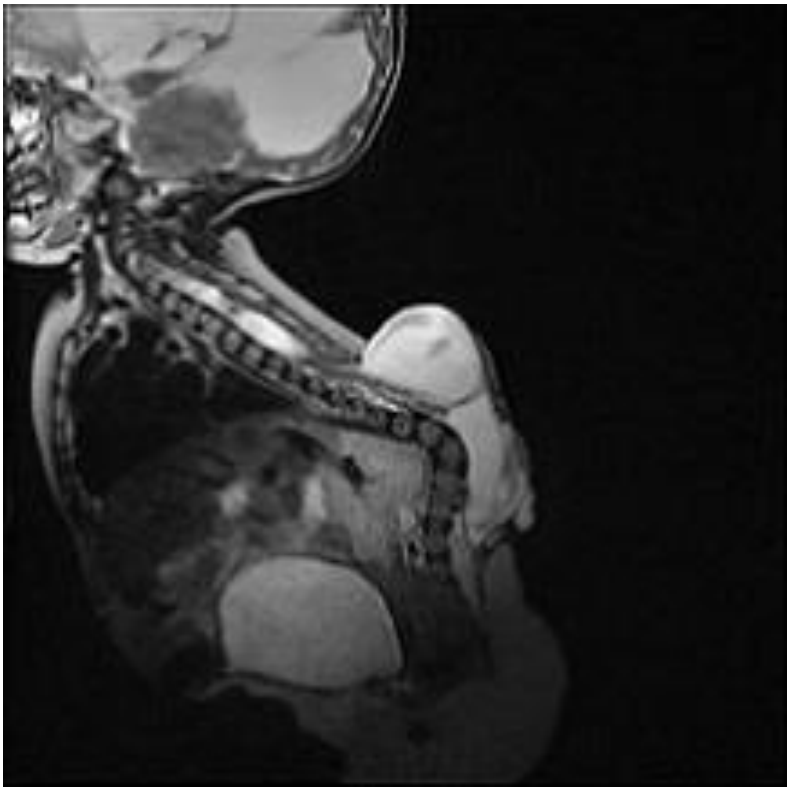


Figure 3: Myelomeningocele in Chiari II malformation, Case courtesy of Dr Arthur Daire (8).

Clinical Presentation & Complications

In general, NTDs share very similar pathogenic features even though they originate differently. Open NTDs result from failure of closure at the site of initiation or incomplete closure after initiation was successful (Figure 1). NTDs can be recognized during or immediately after neurulation because neural folds will be kept open. However, at later stages, the morphological appearance changes considerably due to degeneration. In cranial NTDs, opened neural folds bulge from the developing brain, known as exencephaly. In anencephaly, the skull vault fails to form, leaving the exposed neural tissue liable for degeneration. Both anencephaly and craniorachischisis are lethal at time of birth or shortly after(1).

In the spinal region, opening in the neural folds prevents the sclerotome-derived vertebral arches from covering the neuroepithelium, leaving an opening in the vertebral column known as spina bifida. The neural tissues may be found inside their meningeal sac and can extrude through the opened vertebrae (myelomeningocele; spina bifida cystica) or directly to the amniotic fluid known as myelocele. Babies having with spina bifida need the proper medical care but will suffer neurological impairment and other conditions including hydrocephalus, vertebral abnormalities as well as genitourinary and gastrointestinal disorders (1).

Diagnosis and Maternal-Fetal Surgery

NTDs can be discovered during early prenatal period by ultrasound. Postnatal management for babies born with open spina bifida usually requires surgery to close and cover the lesion, in addition to other following surgeries to alleviate tethering of the spinal cord, treat hydrocephalus, and/or deal with orthopedic and urological problems.

New techniques to provide in-utero fetal surgery for spina bifida aim to limit the possible secondary damage that may result due to exposure of nervous tissue to the surrounding amniotic fluid, and also to improve overall neurological outcomes compared to conventional postnatal repair (1).

Disorders of the Closed Neural Tube

Other conditions which include anomalies of the closed brain or spinal cord and are considered as NTDs **(Figure 1)** involve other less common group of closed spinal NTDs where vertebral arches are malformed but still covered by skin. Examples include spina bifida occulta and spinal dysraphism. The more severe subtypes are associated with various abnormalities of the spinal cordlike lipomas (Figure 1c), and anorectal abnormalities. The embryonic origin of closed spina bifida is presumed to have abnormalities of secondary neurulation.

In encephalocele **(Figure 1d)**, abnormal development of the skull allows herniation of the closed neural tube through the affected bony region, the same applies to meningocele (a closed spina bifida in which the herniated defect consists of meninges extruding through the bony vertebra) (1).

Prevention

NTDs are known to have effective preventive methods available nowadays. Studies have shown the relation and importance of vitamin intake during pregnancy with respect to NTD outcome. One study conducted by the UK Medical council proved that daily 4 mg folic acid supplementation can reduce NTD risk by three times. In addition to many other non-randomized trials, this concludes that folic acid supplementation during pregnancy in a dose of 0.4–5 mg per day can prevent NTD births. Molecular mechanisms & cellular reactions by how folate prevent NTDs are still not completely understood. Maternal folic acid peri-conceptional supplementation strategies have been implemented. However, epidemiological studies have shown that not all NTDs can be prevented and a sub-group of folic acid-resistant NTDs still occur. Experiments done on animal's support inositol supplementation in decreasing the recurrence of NTDs, and it can be used for non-folate responsive NTDs (2).

Data from a trial of pre-conceptional vitamin supplementation for the prevention of neural tube defects suggested that the risk of recurrence of neural tube defect is influenced by the number of previous neural tube defects, area of residency, immediately prior miscarriage, and the inter-pregnancy interval. Also, the study concluded that vitamin supplementation was behind the considerable difference in rates of NTDs between supplemented and non-supplemented mothers (6).

Diagnosis & Treatment

Prenatal detection of neural tube defects

Generally, two techniques are used for screening: biochemical testing of maternal blood for alpha-fetoprotein (AFP) and the use of 2D ultrasound (7).

Alpha fetoprotein (AFP)

Screening of the maternal serum AFP, a glycoprotein secreted by the fetal liver and yolk sac, is usually reserved for open NTDs. However, increased AFP is not diagnostic for open NTD, as other anomalies (omphalocele, gastroschisis and congenital nephrosis can have raised AFP levels as well) (7).

High maternal serum AFP between 15 & 20 weeks of gestation carries a high relative risk for NTDs; 34% of all major congenital defects are linked to abnormal values of AFP. In spina bifida, the sensitivity of maternal AFP is 91%. Overestimation of the gestational age may misinterpret an elevated AFP as normal, or a normal AFP as elevated in underestimated gestational age. Closed lumbosacral spinal defects (20% of spina bifida patients), may be missed by AFP screening, and on ultrasound as well (3).

Ultrasound

The significance of ultrasonography is that it can estimate the gestational age accurately, detect around 95% of spina bifida cases prenatally, and discriminate NTDs from non-neurological causes of increased AFP (e.g., omphalocele) (3). Rates of NTDs discovered by ultrasound are affected by the gestational age and the type of NTD. Studies done during first trimester can detect up to 90% cases of anencephaly and 80% of encephalocele. However, spina bifida is best detected during the second trimester (around 95% of cases). An important part of screening is to look for any additional malformations that may accompany NTD (7). Imaging techniques for diagnosing NTDs include:

2D ultrasound

Anencephaly

Anencephaly, or exencephaly, **(Figure 4)** should be diagnosed after 12 weeks of gestation, as the skull vault would be clearly visualised. Ultrasound findings at the 1st trimester include:

- Absent head contour and exposed neural tissue "lobulated appearance."
- Decreased crown-rump length.
- Absent calvarium. **(Figure 5)**

Absence of the skull and neural tissue will cause disrupted fetal swallow and results in polyhydramnios detected at the 2nd or 3rd trimester (7).

Cephalocele

Cephaloceles are mostly visualized as herniated meninges (meningocele) or brain tissue (encephalocele) through a skull defect. Cephaloceles are usually associated with microcephaly, Dandy-walker malformation, ventriculomegaly, cardiac defects and facial clefts; 75% of cephaloceles herniate in the occipital bone (7).

Spina bifida

The detection rate of open spina bifida cases usually reaches up to 100%, as they can be easily recognized by two main signs: the "lemon" and the "banana" signs. Lemon sign reflects the skull shape in transverse plane. It can be seen as early as 13 weeks of gestation and is present in almost all cases of between 16 and 24 weeks of gestation **(Figure 6)**. However, the lemon sign is not too specific for NTDs, as around 1% of normal fetuses can have a similar concavity (7).

The banana sign describes the shape and reflects the traction of the cerebellum, correlated to the leakage of spinal fluid from the open spinal lesion. Fetal MRI can also show spinal/vertebral dysraphism with fluid-filled sac of meninges extruding at the back.

3D ultrasound

3D ultrasound gives an exceptional view of spinal lesions for diagnosing NTDs. One review article summed up the significance of 3D ultrasound as follows:

- Complete 3D visualization of the spine and other structures from other planes.
- Data from ultrasound can be reviewed after the patient has left the room.
- Provides multitude of algorithms for observing different features of the same structure.
- Multiple planes can be displayed at the same time.

- Ability to transmit data over networks for consultation in other centers.
- The ability to use software for interactive educational tools (7).

Amniocentesis

In cases of pregnant ladies with history of myelomeningocele, prenatal amniocentesis is recommended to exclude spinal anomalies not seen by ultrasound, and to provide the best postpartum care in case of MM diagnosis. Increased AFP in the amniotic fluid peaks around 15 weeks of pregnancy in cases of open NTDs. Amniocentesis is a risky procedure carrying 6% chance of fetal loss (3).

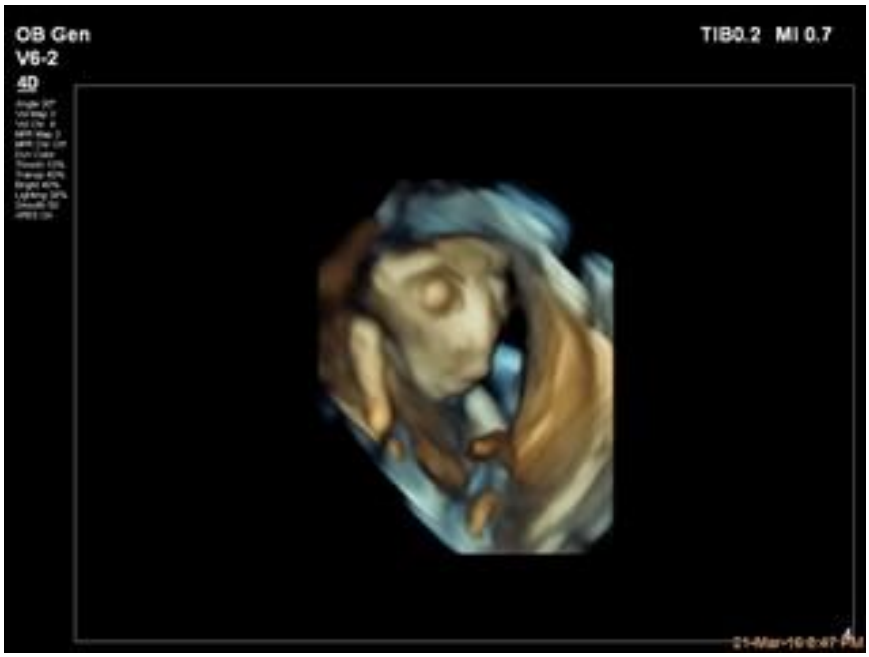


Figure 4: 3D image of anencephaly, Case courtesy of Dr Islam Mohamed El Gezeiry (9)

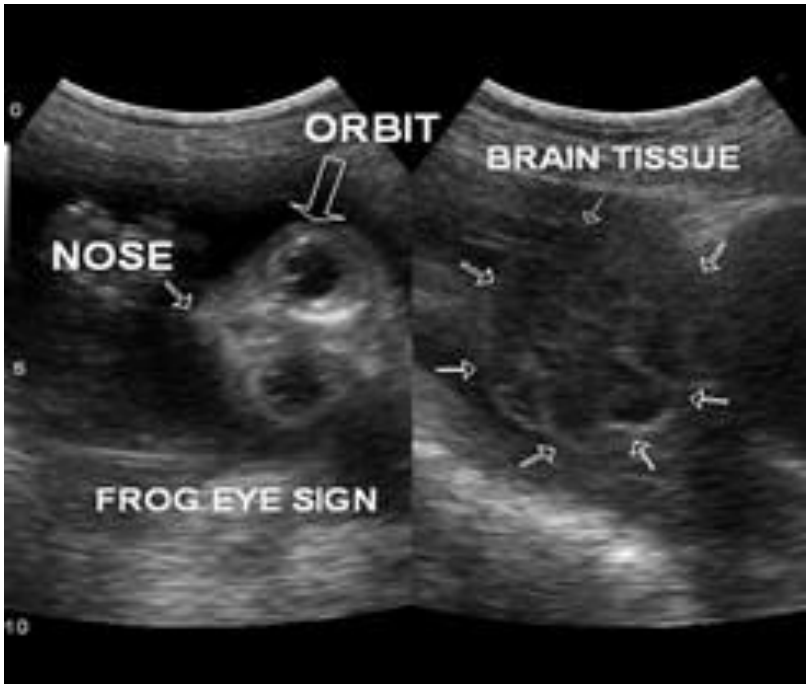


Figure 5: Abscense of bony calvarium, Case courtesy of Dr Mohd Imran (10)

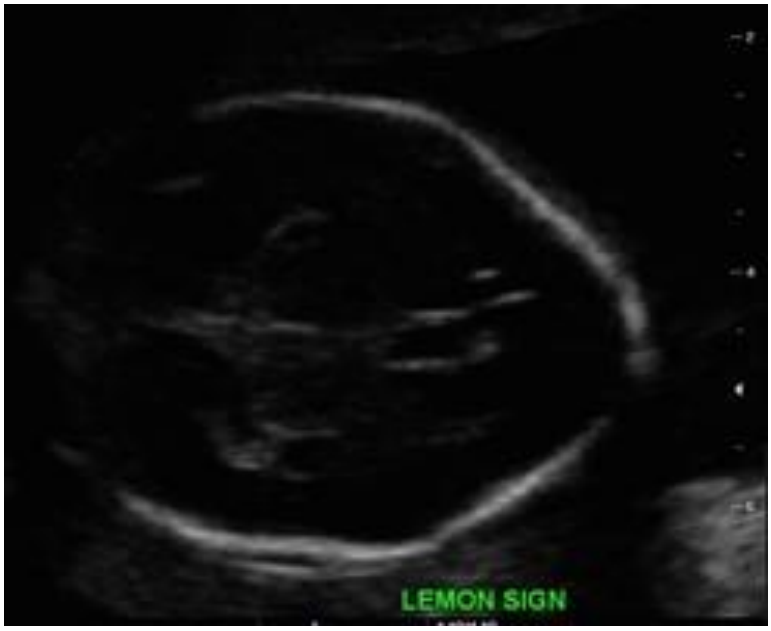


Figure 6: Lemon sign, Case courtesy of Dr Praveen Jha (11)

Diagnosis & Prognosis

1. Craniorachischisis

A disorganized mass of cerebral tissue with cervical hyperextension may be observed by ultrasound. Other differential diagnoses for craniorachischisis include nuchal tumors (e.g., lymphangiomas), Klippel–Feil syndrome and Jarcho–Levin syndrome, also known as “spondylocostal dysostosis” (2).

Craniorachischisis is a fatal condition with no cure or surgical management and usually death of newborns is inevitable (2).

2. Anencephaly

It is very crucial to distinguish between anencephaly mentioned above and amniotic band-related head destruction, also characterized by lost cranial vault, as anencephaly tends to reoccur in subsequent pregnancies unlike the other sporadic entity (2).Anencephalic infants often have no other malformations, plus the cranial defect is symmetrical in contrast to that in the cases of amniotic bands syndrome.

Anencephaly is another lethal condition commonly detected during early gestation and legally terminated. However, minority of cases that progress to term die within few days after birth (2).

3. Myelomeningocele (MM)

Fetal MM repair can reverse the cerebellar displacement. Clubfoot (abnormal internal rotation of the feet) is nearly presented in all cases of MM because of prolonged decrease in leg movements during pregnancy.

Prognosis: Myelomeningocele or myelocele cases have good survival if they were not associated with other serious defects. The neurological impairment and clinical deficits correlate with the level of the lesion, those usually include Bladder dysfunction, fecal incontinence, and sexual dysfunction (2).

Results of management of MM Study trial (MOMS) declared that in utero surgical intervention before 26 weeks of gestation can conserve neurologic function in some cases. However, prenatal surgery is very risky and can cause prenatal delivery or premature rupture of membranes (PROM). Cases that come with hydrocephalus can lead to intellectual disability, still it is quite uncommon (25%) (2).

MM surgical repair should be started within the first 72 hours after birth. Cardiopulmonary and genitourinary systems assessments should be undertaken, and a cranial ultrasonography should be performed later (to check the size of ventricular system). Any delay after that can increase morbidity & mortality. If closure of a MM was delayed after 72 hours, cultures from the neural placode should be taken to exclude any infection. If cultures return positive, an external ventricular drain should be placed, and appropriate antibiotics administered until the infection clears (12).

4. Encephaloceles

Encephaloceles have an annual incidence of 1 in 10,000 born babies in the US. The cystic mass protruding through the defect can be detected by ultrasound. Encephaloceles can be in any location of the cranial vault (anterior, parietal, or occipital). The occipital is the most common location and can be seen in Chiari II malformation. however, Chiari II malformation can have protrusion from the 1st cervical vertebra or herniation of the cerebellum with hydrocephalus. Other anomalies include Microcephaly & ventriculomegaly (2).

Differential diagnosis for encephalocele may include craniofacial masses including: (hemangiomas, nasolacrimal duct cysts, neuralgia heterotopia, lymphangiomas and lipomas (2).

Overall, the prognosis varies depending on the content of the mass and its location. The more the mass is located rostrally, the better the outcome. Other factors that play a role in the prognosis include hydrocephalus and the degree of brain involvement. Traction of some parts of the brain caused by the herniation can lead to different levels of intellectual disabilities, epilepsy and motor and sensory impairment. The management of encephaloceles is only surgical repair (2).

5. Spina bifida Occulta

Spina bifida occulta are covered defects that usually involve the lower lumbar and sacral regions and result due to incomplete vertebral arches (2).

Gross dysmorphology shows cutaneous marks like: Nevi, subcutaneous lipomas, hair tufts, hemangiomas, depigmentation, and dermal sinus tract. These could be the only signs of a spina bifida occulta. Spina bifida occulta can come with other skeletal defects such as scoliosis, asymmetrical gluteal cleft, and leg length discrepancy (2).

The prenatal diagnosis is challenging, since its not associated with secondary cranial anomalies. The most common detectable form in utero is the closed spina bifida associated with intradural lipoma. Lipomas can appear very similar to meningoceles on ultrasound (2).

High resolution ultrasound can be used before ossification of the vertebral body takes place (before 6th months), yet its sensitivity is still low, especially in cases of a subcutaneous mass (2). The more preferred diagnostic tool is magnetic resonance, which usually requires sedation and can be costly (2).

Spina bifida occulta is a less severe spectrum of spinal dysraphism often detected later in life when the neurological symptoms begin to show up due to cord traction because spinal cord growth used to be much slower than the spinal column during intrauterine life. However, only after delivery can the distal part of the spinal cord reach its normal level and become more liable for injury. In cases of thickening of filum terminale, increased physical activity or lumbar trauma, the presentation may be earlier in childhood. Symptomatic patients with neurological progression will require neurosurgical treatment.

6. Meningocele

Macroscopically resembles myelomeningocele, thus can be difficult to distinguish between them by ultrasound prenatally. Through the location of a neural placode, however, we can tell the difference macroscopically (2). Neural placodes are focal thickenings giving rise to various cells. For example, cranial neural placodes (thickenings in the head of an embryo) can give rise to neurons of a cranial nerve sensory ganglia and other sensory organs (12).

When the placode is out of the the canal and through the vertebra, and because there is expansion of the subarachnoid space, this will create a defect to the cutaneous tissue, and results in a myelomeningocele. On the other hand, the subarachnoid space is not expanding in a case of a myelocele, plus the placode is kept in or deep to the cutaneous surface (2).

The herniated mass is often covered by skin with different degrees of dysplasia, also the lesion is usually pedunculated and easily compressed with transillumination (2).

Prenatal diagnosis by ultrasound where spinal dysraphism may be seen with an associated cystic mass. The characteristics of the cystic mass are comparable with that of the myelomeningocele, although they lack septa in the herniated mass, and the cranial anatomy is unremarkable (2).

Meningocele cases usually have no lower limb deformities or sphincter dysfunction with preserved neurological function on exam. The treatment of meningocele involves surgical correction (2).

References

1. Greene, N. D. E., & Copp, A. J.. Neural tube defects. Annual Review of Neuroscience, 2014; 37, 221–242. https://doi.org/10.1146/annurev-neuro-062012-170354
2. Avagliano, L., Massa, V., George, T. M., Qureshy, S., Bulfamante, G. Pietro, &Finnell, R. H.. Overview on neural tube defects: From development to physical characteristics. Birth Defects Research, 2019; 111(19), 1455–1467. https://doi.org/10.1002/bdr2.1380
3. Greenberg, Mark S. Handbook of neurosurgery. New York: Thieme Publishers New York. 2020.
4. Nikolopoulou, E., Galea, G. L., Rolo, A., Greene, N. D., &Copp, A. J.. Neural tube closure: cellular, molecular and biomechanical mechanisms. Development (Cambridge, England), 2017;144(4), 552–566. https://doi.org/10.1242/dev.145904
5. Padmanabhan, R.. Etiology, pathogenesis and prevention of neural tube defects. *Congenital Anomalies*, 2006;*46*(2), 55–67. https://doi.org/10.1111/j.1741-4520.2006.00104.x
6. Wild, J., Read, A. P., Sheppard, S., Seller, M. J., Smithells, R. W., Nevin, N. C., Schorah, C. J., Fielding, D. W., Walker, S., & Harris, R.. Recurrent neural tube defects, risk factors and vitamins. Archives of Disease in Childhood, 1986;61(5), 440–444. https://doi.org/10.1136/adc.61.5.440
7. Cameron, M., & Moran, P..Prenatal screening and diagnosis of neural tube defects. Prenatal Diagnosis, 2009;29(4), 402–411. https://doi.org/https://doi.org/10.1002/pd.2250
8. (n.d.). *Myelomeningocele in chiari II malformation*.
9. (n.d.). *anencephaly*.
10. (n.d.). *acrania-exencephaly-sequence*.
11. (n.d.). *Lemon sign seen in spina bifida*.
12. Winn, H. *Youmans and Winn neurological surgery* (H. R. Winn (ed.); 7th editio). Elsevier. 2017.

Article Topic: Chiari Type I Malformation.

Author: Marah Bassam Akhdar.

Editor: Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Keywords: Chiari Type I Malformation, Tonsillar Ectopia, Hydrocephalus, Neural Tube Defect, Posterior Fossa Anomalies.

Congenital Malformations & Perinatal Brain Injury

Central Nervous System Malformations giving rise to mental retardation, cerebral palsy, neural tube defects and posterior fossa anomalies have an incidence rate of 1%-2%. Perinatal insults, brain injuries, genetic, and environmental factors interfering with normal central nervous system development could result in various birth defects [1].

Posterior Fossa Anomalies

The most common manifestations of posterior fossa anomalies include the displacement or partial/complete agenesis of portions of the cerebellum [1]. One of these anomalies is Chiari Type I Malformation.

Introduction

Among Chiari Malformations, Chiari Type I Malformation is the least severe and most common variant on the spectrum. It manifests itself during late childhood and adulthood [2]. Chiari Type I Malformation is characterized by tonsillar ectopia which is the caudal descent of cerebellar tonsils below the level of the foramen magnum. The clinical syndrome is produced due to the impaction of the foramen magnum, cervicomedullary junction compression by tonsillar ectopia and cerebrospinal fluid flow interruption [3].

The definition of Chiari Type I Malformation is highly controversial as there is no universally accepted definition among scientists. The Chiari Type I Malformation shows incongruity in radiological findings [4]. As a result, some authors have proposed to term Chiari Type I Malformation as ‘Chiari Syndrome’ and denote ‘Chiari Malformation’ for types II-IV. The alternative term would clearly point out the distinct etiology, pathophysiology, radiology, and clinical features of Chiari Type I [5].

History

The Austrian pathologist Hans Chiari described Chiari Type I Malformation as the herniation of cerebellar tonsils passing through the foramen magnum [6].

This description often involved further anatomical variations of the skull and central nervous system [6,7]. Various theories were proposed to justify the underlying mechanism for hindbrain herniation [8]. The nomenclature of Hans Chiari described asymmetrical tonsillar ectopia; however, it lacked a quantifiable amount of tissue herniation [9]. In 1985, Aboulezz et al. proposed that cerebellar herniation could be up to 3 mm below the foramen magnum [10]. Later, Barkovich et al. posited that a 3mm herniation is the minimal cut off for Chiari Type I [11], although an inferior cutoff of 5mm herniation is widely accepted [12].

Etiology

Although the genetics of Chiari Type I Malformation still needs further confirmation [13], a familial aggregation analysis suggests genetic basis for the disease [14, 15]. Recent studies have proposed links to chromosomes 2, 9, 14 and 15 [14, 16, 17]. There is a hypothesis that Chiari Type I originated as a paraxial mesoderm disorder resulting in the formation of a small posterior fossa. The formation of a hypoplastic posterior fossa causes cerebellar compression, cerebellar tonsillar herniation, and foramen magnum impaction. This hypothesis is consistent with suggested associations of Chiari Type I Malformation and other congenital mesodermal connective tissue disorders: for example, Ehlers- Danlos Syndrome [18].

Moreover, secondary conditions including craniocerebral disproportion, craniosynostosis, secondary neurulation abnormalities, platybasia, and bone metabolic disorders could be a leading cause of Chiari Type I Malformation. A pressure build-up due to hydrocephalus or tumor growth could also result in Chiari Type I Malformation. This type of malformation could be iatrogenic due to lumboperitoneal shunt used for idiopathic intracranial hypertension treatment [19]. Chiari Type I may be rarely but possibly caused by an injury. Another possibility for the etiology of Chiari Type I could be a tethered cord at the sacrum. A caudal traction could pull on the bone marrow and brainstem structures causing the descent of cerebellar tonsils and in turn Chiari Type I Malformation [20].

Epidemiology

Chiari Type I Malformation is the most common type of Chiari Malformations. The prevalence of Chiari Type I Malformation is approximately 1in 1000 births. Among

adults a female predominance of 3:1 has been established in comparison to children where the disease does not appear to be related to sex [21].

It has also been observed that differences in the prevalence of Chiari Type I Malformation in various ethnicities may be due to ethnic variations in posterior fossa size and cerebrospinal fluid flow [22, 23, 24].

It is also remarkable to mention that the epidemiological data is underestimated due to late manifestation of the disease and high rates of asymptomatic patients [2].

Pathogenesis/Pathophysiology

The classification of Chiari Malformations is based upon the morphology. Chiari Type I Malformation presents with >5 mm caudal descent of the cerebellar tonsils below the foramen magnum [25].

Generally, the pathogenesis leading to Chiari Type I Malformation can be categorized into four groups: (1) Structural anomalies of the skull base, (2) abnormal segmentation of cervical vertebral bodies, (3) overcrowding due to small posterior fossa and/or cranial vault, and (4) presence of excessive tissue in the posterior fossa or cranial vault [26].

Chiari Type I Malformation causes cerebrospinal fluid outflow obstruction and neurological dysfunction by direct compression of neural tissue at the craniovertebral junction. Obstruction of cerebrospinal fluid outflow could lead to progressive formation of secondary hydrocephalus or syringomyelia which is found in around 65-75% of Chiari Type I Malformation cases [27].

Tonsillar ectopia is regarded as an incidental neuroradiological finding, meaning that not all cases of Chiari Malformation Type I detected on imaging are symptomatic. Additionally, the severity of the disease does not correlate with the degree of herniation as cases with prominent herniation could also be asymptomatic [28, 29]. As previously mentioned, the manifestation usually presents in adulthood in the third-fifth decades of age [30, 31].

Chiari Malformation Type I presents in all ethnicities, with slight female predominance in adults which is believed to be due to hormonal status or genetic variants affecting disease susceptibility and progression. There is no sex predominance of the disease in pediatric cases suggesting a different etiology between adults and pediatrics [30, 32, 33].

The genetics of Chiari Type I Malformation are thought to be multigenic that involve genes that influence the morphology of cranial base and craniocervical junction, cerebellar size, cerebrospinal fluid production, and absorption. Recent studies suggest the whole exome sequencing on large cohorts of Chiari Type I Malformation patients

has great potential to improve the understanding of Chiari Type I Malformation pathogenesis [34].

Chiari Type I Malformation patients are mostly asymptomatic; nonetheless, the main symptom to manifest in both adults and children is pain or tussive headache in the occipital/cervical region [35]. Headaches in Chiari Type I Malformation could be exacerbated with Valsalva maneuver as a result of small foramen magnum. Clinical features may include syncopal episodes and sinus bradycardia due to autonomic dysfunction, swallowing alterations and vomiting due to glossopharyngeal and vagus nerves involvement resulting in an absent gag reflex, balance difficulties resulting in unsteady gait, hand coordination difficulties, tingling and numbness in extremities due to sensorial manifestations, dizziness, tinnitus, progressive muscular weakness in the arms and legs, and stiffness in the back, shoulders, arms, or legs, acute paraparesis, etc. [35,36,37,38,39,40,41].

Prognosis

For most patients, the prognosis is good. However, thorough, and proper investigations should be performed to decide the proper treatment approach (medical/ surgical). 73% of patients show favorable surgical outcomes in less than one year post surgery. In addition, 79% improve at the one to three years follow-up postoperatively [2,42].

Management

Management options for Chiari Type I Malformation are rather empirical due to the lack of clear agreement upon a precise algorithm. Medical and surgical approaches have provided a degree of relief for symptomatic patients of Chiari Type I Malformation [2].

Symptomatic patients that present with headaches or neck pain could be prescribed with physical support collars, muscle relaxants, and non-steroidal anti-inflammatory drugs (NSAIDS) to relief the pain. Nonetheless, less common symptoms including gait disturbance are minimally affected by the above-mentioned options. Recent proposals have suggested meditation or yoga therapy as forms to address the pain [2].

Chiari Type I Malformation patients who present with severe symptoms as well as confirmed cerebellar ectopia on imaging and cerebrospinal fluid (CSF) obstruction on cine MRI are typically offered surgical interventions. Posterior Fossa Decompression (PFD) is the most adopted neurosurgical approach that focuses on decompressing the cervicomedullary junction thus restoring cerebrospinal fluid (CSF) flow. The surgery involves a suboccipital craniectomy and laminectomy at the level of C1 posterior arch [43]. In some cases, duraplasty during Posterior Fossa Decompression (PFDD) is

performed. The latter is determined intraoperatively using cine MRI [46]. Posterior Fossa Decompression (PFD) is performed in 99% of the literature [44].

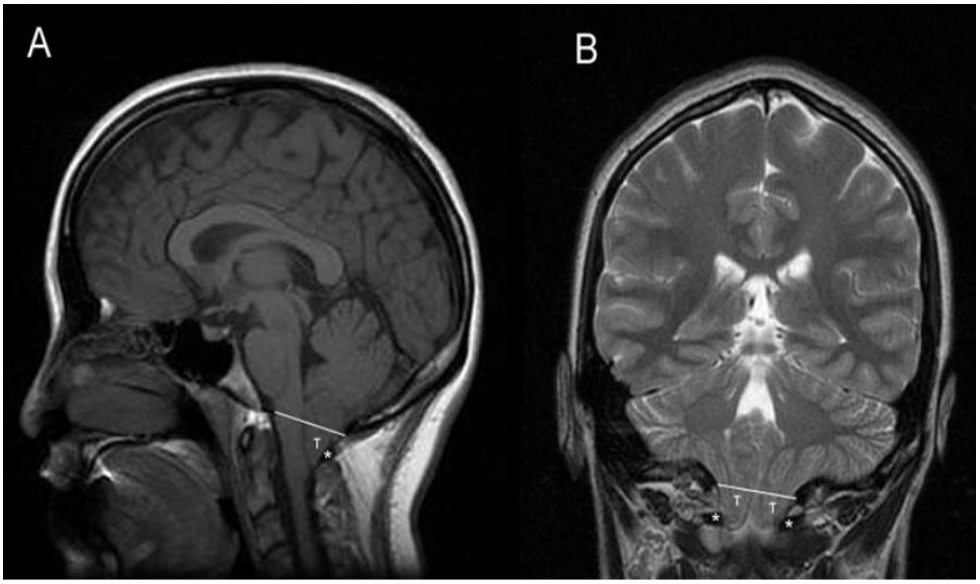
To address Chiari Type I Malformation with syringomyelia, surgeons perform a sub meningeal cerebellar tonsillar herniation resection and cisterna magna reconstruction without craniectomy [45]. Several studies have proposed the syringomyelia decompression by distal drainage using a syringosubarachnoid shunt [47]. The latter are considered minimally invasive approaches to manage Chiari Type I with syringomyelia.

Latest Advancements in Management

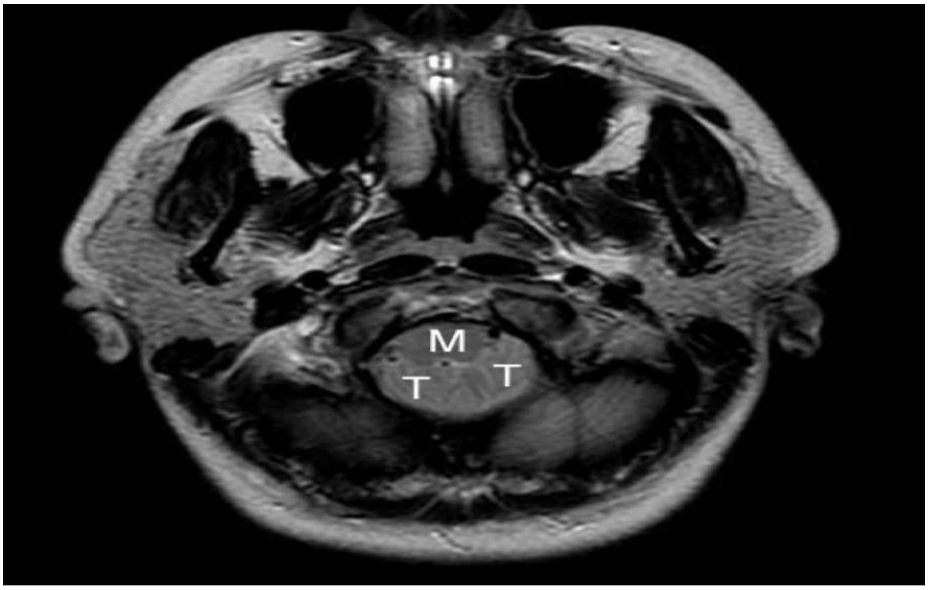
Numerous research studies are being conducted to find the most efficacious Chiari Type I Malformation management strategies.

Recent studies revealed that performing Posterior Fossa Decompression (PFD) without duraplasty does not achieve the needed outcomes. Today, the most favorable approach is Posterior Fossa Decompression with Duraplasty (PFDD). Additionally, some studies do not recommend tonsillar resection due to elevated risk of side effects. Other studies show that using a shunt increases the size of cavities [48].

Further investigations should be performed to establish a unified algorithm for the management of Chiari Type I Malformation.

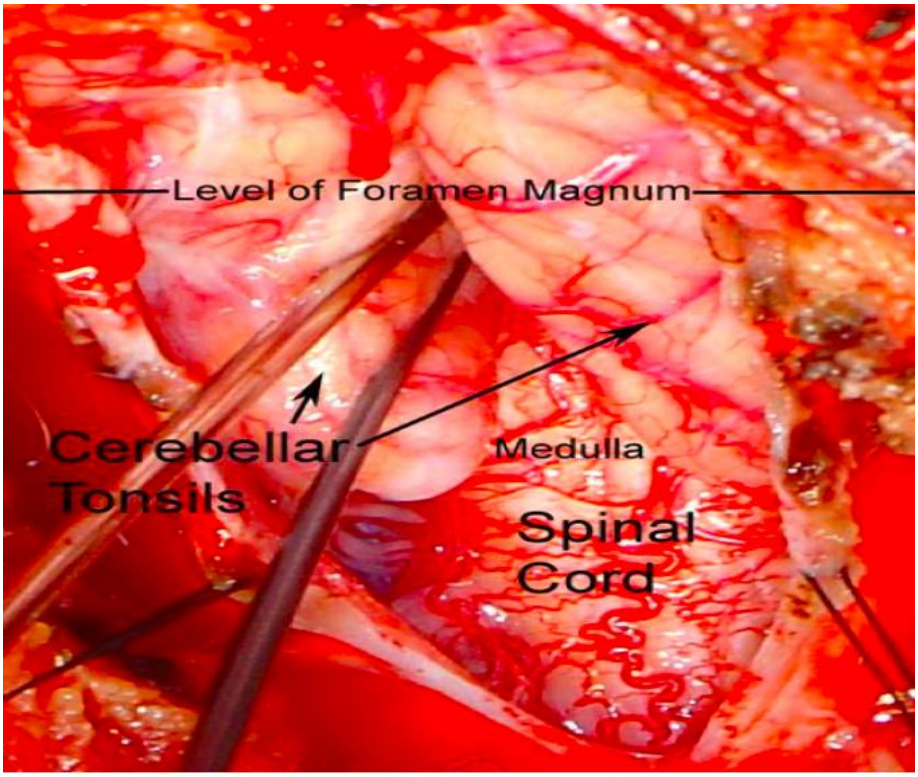


Sagittal and coronal MRI images of Chiari type I malformation. Note descent of cerebellar tonsils (T) below the level of foramen magnum (white line) down to the level of C1 posterior arch (asterisk).
Peyman Pakzaban, MD. "Chiari Malformation." *Practice Essentials, Problem, Epidemiology*, Medscape, 10 Nov. 2019, emedicine.medscape.com/article/1483583-overview#a9.



Axial MRI image at the level of foramen magnum in Chiari type I malformation. Note crowding of foramen magnum by the ectopic cerebellar tonsils (T) and the medulla (M). Also note the absence of cerebrospinal fluid.

Peyman Pakzaban, MD. "Chiari Malformation." *Practice Essentials, Problem, Epidemiology*, Medscape, 10 Nov. 2019, emedicine.medscape.com/article/1483583-overview#a9.



Intraoperative photograph of Chiari type 1 malformation showing descent of cerebellar tonsils well below the level of foramen magnum.

Peyman Pakzaban, MD. "Chiari Malformation." *Practice Essentials, Problem, Epidemiology*, Medscape, 10 Nov. 2019, emedicine.medscape.com/article/1483583-overview#a9.

References

1. Kumar, Vinay, Abul K. Abbas, Jon C. Aster, and James A. Perkins. *Robbins Basic Pathology*. Tenth edition. Philadelphia: Elsevier, 2018.
2. Kular S, Cascella M. Chiari I Malformation. [Updated 2020 Jul 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554609/
3. Peyman Pakzaban, MD. "Chiari Malformation." *Practice Essentials, Problem, Epidemiology*, Medscape, 10 Nov. 2019, emedicine.medscape.com/article/1483583-overview#a1.
4. Muzumdar D. Chiari 1 malformation: Revisited. J Pediatr Neurosci. 2019 Oct-Dec; 14(4):179.
5. Frič R, Eide PK. Chiari type 1-a malformation or a syndrome? A critical review. Acta Neurochir (Wien). 2020 Jul;162(7):1513-1525.
6. Tubbs RS, Iskandar BJ, Bartolucci AA, Oakes WJ (2004) A critical analysis of the Chiari 1.5 malformation. J Neurosurg 101:179–183
7. Cesmebasi A, Loukas M, Hogan E, Kralovic S, Tubbs RS, CohenGadol AA (2015) The Chiari malformations: a review with emphasis on anatomical traits. Clin Anat 28:184–194
8. Tubbs RS, Griessenauer CJ, Hendrix P, Oakes P, Loukas M, Chern JJ, Rozzelle CJ, Oakes WJ (2015) Relationship between pharyngitis and peri-odontoid pannus: a new etiology for some Chiari I malformations? Clin Anat 28:602–607
9. Chiari H (1891) Ueber Veranderungen des Kleinhirnsinfolge von Hydrocephalie des Grosshirns. Med Wochenschr 17:1172–1175
10. Aboulezz AO, Sartor K, Geyer CA (1985) Position of cerebellar tonsils in the normal population and in patients with Chiari malformation: a quantitative approach with MRimaging. J Comput Assist Tomogr 9:1033–1036
11. Barkovich AJ, Wippold FJ, Sherman JL, Citrin CM (1986) Significance of cerebellar tonsillar position on MR. AJNR Am J Neuroradiol 7:795– 799
12. Smith BW, Strahle J, Bapuraj R, Muraszko KM, Garton HJL, Maher CO (2013) Distribution of cerebellar tonsil position: implication in understanding Chiari malformation. J Neurosurg 119: 812–819
13. Capra V, Iacomino M, Accogli A, Pavanello M, Zara F, Cama A, De Marco P. Chiari malformation type I: what information from the genetics? Childs Nerv Syst. 2019 Oct;35(10):1665-1671.
14. Speer MC, George TM, Enterline DS, Franklin A, Wolpert CM, Milhorat TH. A genetic hypothesis for Chiari I malformation with or without syringomyelia. *Neurosurg Focus*. 2000 Mar 15. 8(3):E12.
15. Abbott D, Brockmeyer D, Neklason DW, Teerlink C, Cannon-Albright LA. Population-based description of familial clustering of Chiari malformation Type I. *J Neurosurg*. 2017 Feb 3. 1-6.
16. Boyles AL, Enterline DS, Hammock PH, Siegel DG, Slifer SH, Mehltretter L, et al. Phenotypic definition of Chiari type I malformation coupled with high-density SNP genome screen shows significant evidence for linkage to regions on chromosomes 9 and 15. *Am J Med Genet A*. 2006 Dec 15. 140(24):2776-85.
17. Abbott D, Brockmeyer D, Neklason DW, Teerlink C, Cannon-Albright LA. Population-based description of familial clustering of Chiari malformation Type I. J Neurosurg. 2018 Feb;128(2):460-465.
18. Milhorat TH, Bolognese PA, Nishikawa M, McDonnell NB, Francomano CA. Syndrome of occipitoatlantoaxial hypermobility, cranial settling, and chiari malformation type I in patients with hereditary disorders of connective tissue. *J Neurosurg Spine*. 2007 Dec. 7(6):601-9.
19. Hentati A, Badri M, Bahri K, Zammel I. Acquired Chiari I malformation due to lumboperitoneal shunt: A case report and review of literature. Surg Neurol Int. 2019;10:78.
20. Yan H, Han X, Jin M, Liu Z, Xie D, Sha S, Qiu Y, Zhu Z. Morphometric features of posterior cranial fossa are different between Chiari I malformation with and without syringomyelia. Eur Spine J. 2016 Jul;25(7):2202-9.
21. Langridge B, Phillips E, Choi D. Chiari Malformation Type 1: A Systematic Review of Natural History and Conservative Management. World Neurosurg. 2017 Aug;104:213-219.
22. Tubbs RS, McGirt MJ, Oakes WJ. Surgical experience in 130 pediatric patients with Chiari I malformations. J Neurosurg 2003;99(2):291–296
23. Haughton VM, Korosec FR, Medow JE, Dolar MT, Iskandar BJ. Peak systolic and diastolic CSF velocity in the foramen magnum in adult patients with Chiari I malformations and in normal control participants. AJNR Am J Neuroradiol 2003;24(2):169–176
24. Brickell KL, Anderson NE, Charleston AJ, Hope JK, Bok AP, Barber PA. Ethnic differences in syringomyelia in New Zealand. J Neurol Neurosurg Psychiatry 2006;77(8):989–991
25. Hidalgo J, Dulebohn S. Arnold Chiari Malformation. 2017 Jun.
26. Garzon-Muvdi, T., Jallo, G., Poretti, A., Ashmawy, R., Huisman, T., & Raybaud, C. (2016). *Chiari Type 1 Deformity in Children: Pathogenetic, Clinical, Neuroimaging, and Management Aspects. Neuropediatrics, 47(05), 293–307.* doi:10.1055/s-0036-1584563
27. Mueller DM, Oro' JJ (2004) Prospective analysis of presenting symptoms among 265 patients with radiographic evidence of Chiari malformation type I with or without syringomyelia. J Am Acad Nurse Pract 16:134– 138
28. Elster AD, Chen MY (1992) Chiari I malformations: clinical and radiologic reappraisal. Radiology 183(2):347–353
29. Meadows J, Kraut M, Guarnieri M, Haroun RI, Carson BS (2000) Asymptomatic Chiari type I malformations identified on magnetic resonance imaging. J Neurosurg 92(6):920–926
30. Milhorat TH, Chou MW, Trinidad EM, Kula RW, Mandell M, Wolpert C, Speer MC (1999) Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. Neurosurgery 44:1005–1017
31. Fernández AA, Guerrero AI, Martínez MI, Vázquez ME, Fernández JB, Chesa i, Octavio E et al (2009) Malformations of the craniocervical junction (Chiari type I and syringomyelia: classification, diagnosis and treatment). BMC Musculoskelet Disord 10(Suppl 1):S1

32. Milhorat TH, Nishikawa M, Kula RW et al (2010) Mechanisms of cerebellar tonsil herniation in patients with Chiari malformations as guide to clinical management (1010). Acta Neurochir 152:1117– 1127
33. Tubbs RS, Beckman J, Naftel RP, Chern JJ, Wellons JC, Rozzelle CJ, Blount JP, Oakes WJ (2011) Institutional experience with 500 cases of surgically treated pediatric Chiari malformation type I. J Neurosurg Pediatr 7:248–256
34. Capra, V., Iacomino, M., Accogli, A., Pavanello, M., Zara, F., Cama, A., & De Marco, P. (2019). *Chiari malformation type I: what information from the genetics? Child's Nervous System.* doi:10.1007/s00381-019- 04322-w
35. Tubbs RS, Beckman J, Naftel RP, Chern JJ, Wellons JC, Rozzelle CJ, Blount JP, Oakes WJ. Institutional experience with 500 cases of surgically treated pediatric Chiari malformation Type I. J Neurosurg Pediatr. 2011 Mar;7(3):248-56.
36. Weig SG, Buckthal PE, Choi SK, Zellem RT. Recurrent syncope as the presenting symptom of Arnold-Chiari malformation. Neurology. 1991 Oct;41(10):1673-4.
37. Selmi F, Davies KG, Weeks RD. Type I Chiari deformity presenting with profound sinus bradycardia: case report and literature review. Br J Neurosurg. 1995;9(4):543-5.
38. Schneider B, Birthi P, Salles S. Arnold-Chiari 1 malformation type 1 with syringohydromyelia presenting as acute tetraparesis: a case report. J Spinal Cord Med. 2013 Mar;36(2):161-5.
39. Tubbs RS, Doyle S, Conklin M, Oakes WJ. Scoliosis in a child with Chiari I malformation and the absence of syringomyelia: case report and a review of the literature. Childs Nerv Syst. 2006 Oct;22(10):1351-4.
40. Strahle JM, Taiwo R, Averill C, Torner J, Shannon CN, Bonfield CM, Tuite GF, Bethel-Anderson T, Rutlin J, Brockmeyer DL, Wellons JC, Leonard JR, Mangano FT, Johnston JM, Shah MN, Iskandar BJ, Tyler-Kabara EC, Daniels DJ, Jackson EM, Grant GA, Couture DE, Adelson PD, Alden TD, Aldana PR, Anderson RCE, Selden NR, Baird LC, Bierbrauer K, Chern JJ, Whitehead WE, Ellenbogen RG, Fuchs HE, Guillaume DJ, Hankinson TC, Iantosca MR, Oakes WJ, Keating RF, Khan NR, Muhlbauer MS, McComb JG, Menezes AH, Ragheb J, Smith JL, Maher CO, Greene S, Kelly M, O'Neill BR, Krieger MD, Tamber M, Durham SR, Olavarria G, Stone SSD, Kaufman BA, Heuer GG, Bauer DF, Albert G, Greenfield JP, Wait SD, Van Poppel MD, Eskandari R, Mapstone T, Shimony JS, Dacey RG, Smyth MD, Park TS, Limbrick DD. Radiological and clinical predictors of scoliosis in patients with Chiari malformation type I and spinal cord syrinx from the Park-Reeves Syringomyelia Research Consortium. J Neurosurg Pediatr. 2019 Aug 16;:1-8.
41. Dobkin BH. The adult Chiari malformation. Bull Los Angeles Neurol Soc. 1977 Mar;42(1):23-7.
42. Greenberg JK, Yarbrough CK, Radmanesh A, Godzik J, Yu M, Jeffe DB, Smyth MD, Park TS, Piccirillo JF, Limbrick DD. The **Chiari**Severity Index: a preoperative grading system for **Chiarimalformation type** 1. Neurosurgery. 2015 Mar;76(3):279-85; discussion 285.
43. Siasios J, Kapsalaki EZ, Fountas KN. Surgical management of patients with **Chiari**I **malformation**. Int J Pediatr. 2012;2012:640127.
44. Arnautovic A, Splavski B, Boop FA, Arnautovic KI. Pediatric and adult **ChiarimalformationType** I surgical series 1965-2013: a review of demographics, operative treatment, and outcomes. J Neurosurg Pediatr. 2015 Feb;15(2):161-77.
45. Lou Y, Yang J, Wang L, Chen X, Xin X, Liu Y. The clinical efficacy study of treatment to **Chiarimalformationtype** I with syringomyelia under the minimally invasive surgery of resection of Submeningeal cerebellar Tonsillar Herniation and reconstruction of Cisterna magna. Saudi J Biol Sci. 2019 Dec;26(8):1927-1931.
46. Delavari N, Wang AC, Bapuraj JR, Londy F, Muraszko KM, Garton HJL, Maher CO. Intraoperative Phase Contrast MRI Analysis of Cerebrospinal Fluid Velocities During Posterior Fossa Decompression for **Chiari**I **Malformation**. J Magn Reson Imaging. 2020 May;51(5):1463-1470.
47. Amarouche M, Minichini V, Davis H, Giamouriadis A, Bassi S. Syringosubarachnoid shunt: insertion technique. Br J Neurosurg. 2019 Dec 18;:1-4.
48. Zhao JL, Li MH, Wang CL, Meng W. A Systematic Review of Chiari I Malformation: Techniques and Outcomes. World Neurosurg. 2016 Apr;88:7-14. doi: 10.1016/j.wneu.2015.11.087. Epub 2015 Dec 28. PMID: 26732952.

Article topic: Dandy Walker Syndrome.

Author: Ghayda Netham Al-Majali.

Editor: Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Overview

Dandy-Walker syndrome (DWS), or Dandy-Walker malformation (DWM), is a rare congenital brain malformation that occurs during embryonic development of the cerebellum and fourth ventricle. It was first described by Dandy & Blackfan in 1914 and dubbed “Dandy Walker malformation” forty years later by Benda (1). DWS is the most common posterior fossa abnormality characterized by agenesis or hypoplasia of the cerebellar vermis and cystic dilation of the fourth ventricle causing enlargement of the posterior fossa with cerebrospinal fluid and upward displacement of the tentorium and torcula (2)(3). Patients may have hydrocephalus at the time of diagnosis (4).

Embryology

The rhombencephalon (hindbrain) develops into the metencephalon (pons and cerebellum) and myelencephalon (medulla oblongata) around the fifth week of gestation. Development of cerebellum begins in the ninth week, when the cerebellar hemispheres develop from the rhombic lips, subsequently fusing to form the vermis. The choroid plexus of the fourth ventricle as well as the foramina of Luschka and Magendie form around the tenth week of gestation from the rhombic vesicle. Cerebrospinal fluid (CSF) then accumulates within the fourth ventricle, forming this space. Subsequently, the cerebellar lobules develop in an anterior-to-posterior direction and are completely formed by week 18. Because it develops more slowly than the cerebral hemispheres, the cerebellum appears smaller at 20 weeks gestation relative to the large posterior fossa CSF spaces, leading to a potential over-diagnosis of vermian hypoplasia by antenatal ultrasonography (5).

Etiology and Pathogenesis

DWS was believed to be caused by abnormality and atresia of the foramina of Luschka and Magendie, leading to enlargement of the fourth ventricle and vermian hypoplasia.

However, recent evidence indicates that DWS results from developmental abnormalities affecting the roof of the rhombencephalon, leading to variable degrees of vermian hypoplasia and cystic enlargement (6).

Although the majority of cases are rare and not familial (6), some may result from chromosomal aberrations, Mendelian disorders, environmental exposures (such as German measles and congenital rubella which can severely affect early embryonic development), teratogens, or fetal exposure to alcohol (7).

Although DWS is typically sporadic, first-degree relatives have a higher risk of acquiring DWM compared with the general population (7)(8). Rare genetic mutations in a small number of cases have been detected in some genes including FOXC1, FGF17, LAMC1, NID1, ZIC1, and ZIC4 (8).

There are two hypotheses for the etiology of DWM. The first is the arrest of the vermian development and the second is failure of fourth ventricle foramina fenestration resulting in an enlarged Blake's pouch, compressing the vermis (9).

Clinical Presentation and Complications

Many patients of DWS remain clinically asymptomatic for years, while others present with many comorbidities & anomalies which increase the chances of earlier diagnosis (7).

DWS may be isolated or associated with facial malformations (e.g. angiomas, cleft palate, macroglossia, and facial dysmorphia), musculoskeletal malformations, cardiovascular anomalies (e.g. septal defects, patent ductus arteriosus, aortic coarctation, dextrocardia), ocular abnormalities (e.g. coloboma, retinal dysgenesis, microphthalmia) and genitourinary, respiratory or gastrointestinal system abnormalities (6). Central nervous system (CNS) disorders related to DWS include malformations of cortical development, holoprosencephaly, agenesis of the corpus callosum (ACC) and neural tube defects (2). DWS is also associated with other systemic anomalies including genetic aberrations, environmental factors, teratogens, Mendelian disorders, syndromic malformations, congenital infections, and various other comorbidities (9).

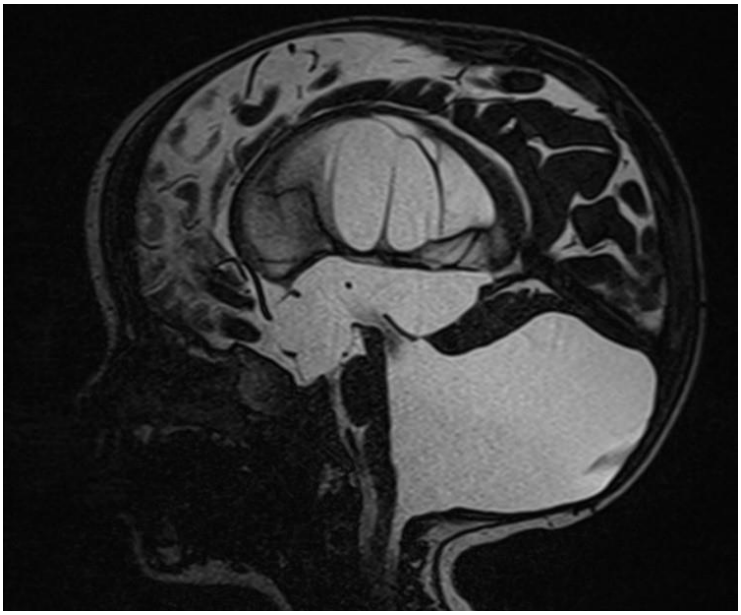


Figure 1: Dandy Walker Malformation; Case courtesy of Dr Mostafa El-Feky (10).

Figure 2: Dandy Walker Syndrome; Partial hypoplasia of the cerebellar hemispheres. Marked expansion and dilation of the ventricles of the brain, reducing the volume of the substance of the brain, hypoplasia of the corpus callosum; Case courtesy of Dr Osadchiy Anton (11).

Differential Diagnosis

Differential diagnoses include posterior fossa abnormalities including retrocerebellar arachnoid cysts, cystic hygroma, Blake's pouch cyst (BPC), mega cisterna magna, and vermian hypoplasia. These may be sometimes associated with hydrocephalus, which can commonly present in an analogous way to DWS (6).

Additionally, several syndromes are correlated with DWS, such as Aase-Smith, cerebro-oculo-muscular syndrome, Coffin-Siris, Cornelia de Lange's syndrome and Aicardi, Fryns syndrome, Klippel-Feil syndrome, Turner's syndrome and Joubert's syndrome which is absence or underdevelopment of the cerebellar vermis (2)(7).

Retrocerebellar arachnoid cysts might be large enough to cause compression of cerebellar hemispheres and fourth ventricle which can produce significant mass effect, and the vermis remains intact. BPC presents as a retrocerebellar fluid collection characterized by posterior ballooning of the superior medullary velum into the cisterna magna, below and posterior to the vermis with communication to the fourth ventricle (2).

The typical finding in mega cisterna magna is enlarged cisterna magna measuring more than 10mm in the axial plane at the level of the transcerebellar diameter. However, fluid collection is located postero-inferior to a normally developed cerebellum with no mass effect on it, normal vermis and normal fourth ventricle (2).

Dandy-Walker variant (DWV) is a term first introduced by Harwood-Nash and Fitz to describe a milder spectrum of DWS-like signs that did not correspond with the classic definition. DWV consists of an inferior cerebellar vermian defect and communication between a normal-sized cisterna magna and fourth ventricle, so it does not fit all Dandy Walker Syndrome criteria for diagnosis (e.g., vermian hypoplasia and cystic dilatation or enlargement of the fourthth ventricle, without enlargement of the posterior fossa) (5).

Dandy Walker Complex (DWC) is another expression describing a continuum of posterior fossa malformations categorized from mild (mega cisterna magna only) to moderate (hypoplasia of vermis, enlarged fourth ventricle) to severe (agenesis of vermis, dilation of posterior fossa cyst and fourth ventricle) (12). So, DWS requires six radiographic features for diagnosis:

1. Large posterior fossa cyst communicating with the 4th ventricle.
2. Absence of a portion of the inferior vermis at different degrees.
3. Hypoplasia, anterior rotation, and upward displacement of the vermis remnant
4. Absence or flattening of the angle of the fastigium (highest point of fourth ventricle).
5. Large posterior fossa with torcular elevation.
6. Anterolateral displacement of normal or hypoplastic cerebellar hemispheres (5).

This wide spectrum of posterior fossa cystic anomalies provides a basis for differential diagnosis in prenatal or postnatal presentations, and these include Dandy Walker Variant, mega cisterna magna, posterior fossa arachnoid cyst, persistent Blake's pouch cyst, fourth ventriculocele, and congenital vermian hypoplasia (5).

Differentiating features

DWS and DWV are difficult to distinguish and may act as a continuum of developmental abnormalities grouped together as Dandy Walker complex (DWC) (1). Retrocerebellar arachnoid cysts and BPC may imitate and mimic DWS, but do not have vermian

agenesis (1). The position of the choroid plexus of the fourth ventricle is normal in arachnoid cysts, absent in DWS, and displaced into the superior cyst wall in BPC (1). An intrathecal enhanced Computed Tomography (CT) scan (which performed after instilling iodinated contrast into a ventricular catheter) would distinguish and identify mega cisterna magna which communicates with the ventricles, while DWS and most (but not all) arachnoid cysts do not (1).

Figure 3: Dandy Walker Variant (DWV); Case courtesy of Dr Aditya Shetty {A cystic area of CSF density is seen in the posterior fossa, with a "keyhole" appearance. This cystic area is in continuation with the 4th ventricle. Vermian hypoplasia is also seen with gross hydrocephalus. The "keyhole connection sign" (white dashes) shows to the abnormal connection of the cistern Magna and the posterior aspect of the 4th ventricle} (13).

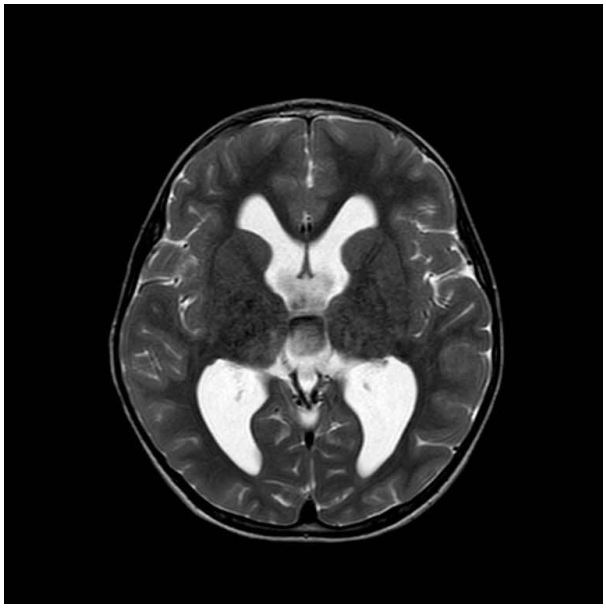


Figure 4: Blake's Pouch Cyst (BPC) – Axial T2; Case courtesy of Dr Sepehr Haghighi; {5-year-old female presented with Headache. The enlarged 4th ventricle is seen freely communicating with infracerebellar posterior fossa cyst. The vermis of cerebellum is upward displaced with no hypoplasia. Normal bidirectional flow of CSF at the cranio-cervical junction and cervical subarachnoid spaces is detected} (14).

Figure 5: Mega Cisterna Magna – Axial T2; Case courtesy of Assoc Prof Frank Gaillard (15).

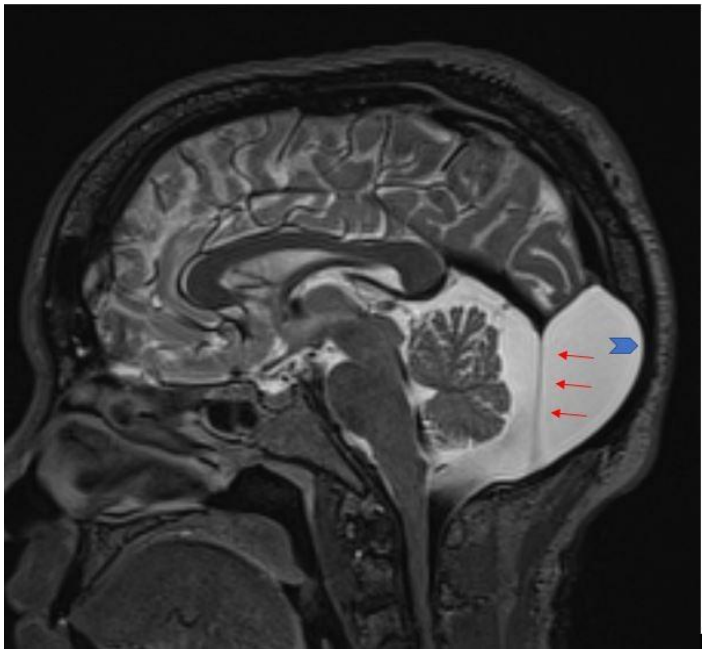


Figure 6: Retro-cerebellar Arachnoid Cyst- sagittal T2; Case courtesy of Dr Amr Farouk. {Annotated image showing the membrane of the arachnoid cyst (red arrows). Remodeling of the skull is also present (blue arrow)} (16).

Epidemiology

DWS and related variants have an incidence of 1 in 35000 live births in the United States (1). It is reported in only 1 in 25000 to 30000 live births which occurs during the embryonic development of the cerebellum and 4th ventricle in Asia (7).

Autosomal recessive inheritance has been determined in a few cases, Male: female ratio is 1:3 and it may be associated with PHACES syndrome, which stands for Posterior fossa malformations, hemangioma, arterial lesions, cardiac abnormalities, and eye

abnormalities (1). These anomalies account for 1 to 4% of Hydrocephalus cases (2). This malformation is found in 4% to 12% of hydrocephalus in infants (17).

Treatment of hydrocephalus with shunting improves mortality (18). Fetal mortality directly correlates with the presence of extra CNS malformations (19). Gestational exposure to rubella, CMV, toxoplasmosis, Warfarin, alcohol, and isotretinoin are thought to be risk factors (1).

Prognosis

Patients with DWS may present different degrees of hydrocephalus (80% of DWS cases have hydrocephalus), which if untreated may lead to severe neurological abnormalities and death (6). 50% of Children with untreated hydrocephalus die before the age of 3 years, and only around 20 to 23% reach adult life or puberty (6). Most patients with untreated hydrocephalus who reach adult life will have motor, visual and auditory deficits (20). The diameter of the fetal lateral ventricle through obstetric ultrasound may have important prognostic value, and as described in a previous study, lateral ventricles measuring between 11-15 mm are associated with a 21% risk of delayed development (6). If the diameter measures more than 15 mm, the risk of delayed development is above 50% (21). Most case series of patients with non-tumoral hydrocephalus may indicate a risk for epilepsy of approximately 30% (20).

Functional outcomes vary due to several factors, which include other structural brain anomalies, extra-CNS manifestations, epilepsy, motor, visual or hearing impairment, and other congenital anomalies (22)(23). Therefore, the prognosis differs widely as there are various levels of severity of the malformation (1). Pediatric neurosurgical literature suggests a 12–50% of mortality rate (24), although this is improving with modern shunting techniques (1). Ataxia, spasticity or alteration in muscle tone, and poor motor control are also common and only 50% have normal IQ (1).

In (10%-20%) of cases with DWS, manifestations, signs and symptoms of the malformation do not appear until late childhood or adulthood. These patients have a different range of features compared to those affected in infancy. These features could include headaches, an unsteady walking gait, facial palsy, increased muscle tone, muscle spasms, and mental and behavioral changes. Very rare that people with DWS have no health problems related to the malformation. Problems related to hydrocephalus or complications of its treatment are the most common cause of death in people with DWS (25).

Treatment and Management

Treatment of DWS is through treating the manifestations and associated comorbidities (6). Most patients present with signs and symptoms from increased intracranial pressure (ICP), most related to hydrocephalus and posterior fossa cyst. For this reason, treatment aims to control intracranial pressure, usually through surgery with a focus on alleviating hydrocephalus and posterior fossa symptoms (2)(4). Treatment may include surgical interventions like ventriculoperitoneal (VP) shunting, or cystoperitoneal (CP) shunting. Other patients may be candidates for endoscopic procedures, including endoscopic third ventriculostomy (ETV) (6).

Ventriculoperitoneal (VP) shunt

A VP shunt is a cerebral shunt that drains excess and accumulated CSF when there is an occlusion in the normal outflow, or decreased absorption of the fluid (26). Accumulated CSF can increase the intracranial pressure resulting in cerebral edema and herniation (26). The shunts drain excess accumulated CSF into the peritoneal cavity, the atrium, or the pleura; thus, appropriately called ventriculoperitoneal, ventriculoatrial, and ventriculopleural shunts (26).

Indication of VP shunt

Disorders typically requiring shunting include:

1. Congenital hydrocephalus after aqueductal stenosis,
2. Tumors leading to CSF blockage of the lateral ventricles, third ventricle, and those in the posterior fossa blocking the cerebral aqueduct or fourth ventricle,
3. Communicating hydrocephalus secondary to meningitis or subarachnoid hemorrhage,
4. Myelomeningocele because the flow of CSF is altered due to hindbrain malformation,
5. Idiopathic intracranial hypertension,
6. Arachnoid cysts,
7. Dandy-Walker syndrome with a cystic deformity of the fourth ventricle, hypoplasia of the cerebellar vermis, and an enlarged posterior fossa (26).

Contraindication of VP shunt

Ventriculoperitoneal shunt is absolutely contraindicated with infection over the entry site, infection of the CSF and allergy to any of the catheter components (27). It is relatively contraindicated in these cases: altered coagulation function, high CSF protein and CSF with blood (26).

Equipment Needed for Surgery

A VP shunt is placed in the operating room under general anesthesia by a neurosurgeon. The equipment needed to perform the procedure include:

1. Shunt system (ventricular catheter, peritoneal catheter, and small, medium or high-pressure valve), specimen tubes for CSF,
2. Drill for the burr hole,
3. Shunt passer
4. Image-guided navigation system only for small ventricles (26).

Preoperative Preparation

Brain magnetic resonance imaging (MRI) or computed tomography (CT) scan is reviewed for the planning of the shunt and proper placement of the proximal catheter. The patient is placed supine, for a parieto-occipital approach, the head is tilted to the contralateral side of the shunt placement. Preoperative antibiotics are given, and the patient is dressed in sterile conditions (26).

The Technique of VP shunt

The Technique of VP shunt is done by shaving the hair away from the head incision site, cleaning the skin with an antiseptic and applying a sterile fenestrated drape over the incision sites (head, neck, chest, and abdomen) (26). Then, making a "U or C" shaped skin incision over the entry point where the burr hole is to be performed for the introduction of the ventricular catheter (28).

If the frontal approach will be used, Kocher's point is used; which is an entry point that is 11 cm superior and posterior from the nasion, 3 cm lateral to midline along the mid pupillary line, and 1-2 cm anterior to the coronal suture; catheter should then be passed to a depth of 5-5.5 cm (28).

If parieto-occipital approach will be used, Keen's point is used; which is approximately 2.5 to 3 cm superior and posterior to the pinna and the catheter should be passed to a depth of 4 to 5 cm or until reaching the trigone of the ipsilateral or the same side lateral ventricle, but sometimes it is aiming toward the frontal horn of the lateral ventricle so Alternatively, Dandy's point can be used which is 3 cm above the inion and 2 cm left or right to the midline (28).

Burr hole is done at the desired entry point and the dura incised, a small entry point in the cortex is coagulated and incised, ventricular catheter is introduced directed into the ventricle and cut to the appropriate pre-measured length, then CSF samples are collected and the ventricular shunt is connected to the valve and secured with a silk tie (26).

An incision in the abdomen is done to access the peritoneal cavity; the site depends on the surgeon's preference and can be done in the upper quadrant, or the midline and Shunt passer is used to pass the peritoneal distal catheter between both incisions (26).

Peritoneal catheter is connected and attached to the valve and secured with a silk tie and after good distal CSF flow at the peritoneal catheter, it is introduced into the peritoneal cavity. Finally, Wounds are closed in anatomical layers (CSF sample is sent to the laboratory for cell count, glucose, protein, gram stain, and culture) (26).

Complication of VP Shunting

Complications include:

1. Infection due to skin flora entering the shunt (usually from Staphylococcus epidermidis),
2. Intracerebral or intraventricular hemorrhage,
3. Malposition,
4. Shunt disconnection or obstruction,
5. Subdural hematomas. (26).
6. Abdominal CSF collections (pseudocyst or CSFoma) (29).

Acute signs and symptoms of malfunction or infection include headache, lethargy, diplopia, nausea, vomiting, seizure, irritability, poor feeding, head enlargement when sutures are open, fever and neck rigidity (26).

Clinical Significance, Evaluation and Outcome

Tapping a shunt is performed for both diagnostic and therapeutic reasons, and VP shunt is considered one of the advances that has a high impact on neurosurgical patient care (26).

Shunt X-rays are done to evaluate the integrity of the system and CT scan or MRI is done to evaluate the size of the ventricles (26). VP shunt can be lifesaving, but the eventual outcome depends on the reason why the shunt was inserted (26).For benign or mild disorders, most patients have a good outcome, but for malignant tumors the outcome is usually poor; often patients die from other causes unrelated to the shunt (26).The complication rates of VP shunts range from 2-20%. In addition, shunt revision is required in about 5-10% of neonates and pediatrics (30).

Updated Research Regarding Management/ Treatment

Treatment options for Dandy-Walker malformation – Retrospective Study – Published in Nov/2006 in the journal of neurosurgery (JNS) DOI: 10.3171/ped.2006.105.5.348

The study aimed to evaluate the effectiveness of various treatment options available for children with DWM and the role of endoscopic procedures (ETV) in the treatment of this syndrome (31) by retrospective review of 72 children who underwent surgical treatment for DWS during a sixteen-year period. All patients underwent CT scanning, and 26 underwent MRI. The initial surgical treatment included (VP) shunt insertion in 21 patients, (CP) shunt insertion in 24 patients, and (combined VP and CP shunt) insertion in 3 patients, and 21 patients underwent endoscopic interventions (ETV alone in 16 patients, ETV with aqueductal stent placement in 3 patients, and ETV with fenestration of the obstructing membrane in 2 patients). Also, 3 patients underwent membrane excision via a posterior fossa craniectomy (31).

In the 26 patients who had undergone preoperative MRI, aqueductal patency was noted in 23 patients versus aqueductal obstruction in 3 patients. These three patients underwent insertion of a stent from the third ventricle to the posterior fossa cyst in addition to the ETV surgical procedure. During the follow-up period, 12 patients with a CP shunt and 4 patients with a VP shunt experienced shunt malfunctions and complications that required revision. Four patients with a CP shunt also required placement or insertion of a VP shunt. In addition, five of the 21 ETVs failed, requiring VP shunt placement (31).

A reduction in the size of ventricle was noted on postoperative images occurred more frequently in patients with VP shunt, whereas a decrease in cyst size was more obvious in patients with CP shunt. Successful ETV resulted in a slight decrease in ventricle size and varying degrees or levels of reduction in cyst size (31). Therefore, it was concluded that ETV may be considered an acceptable alternative in children with DWS (31).

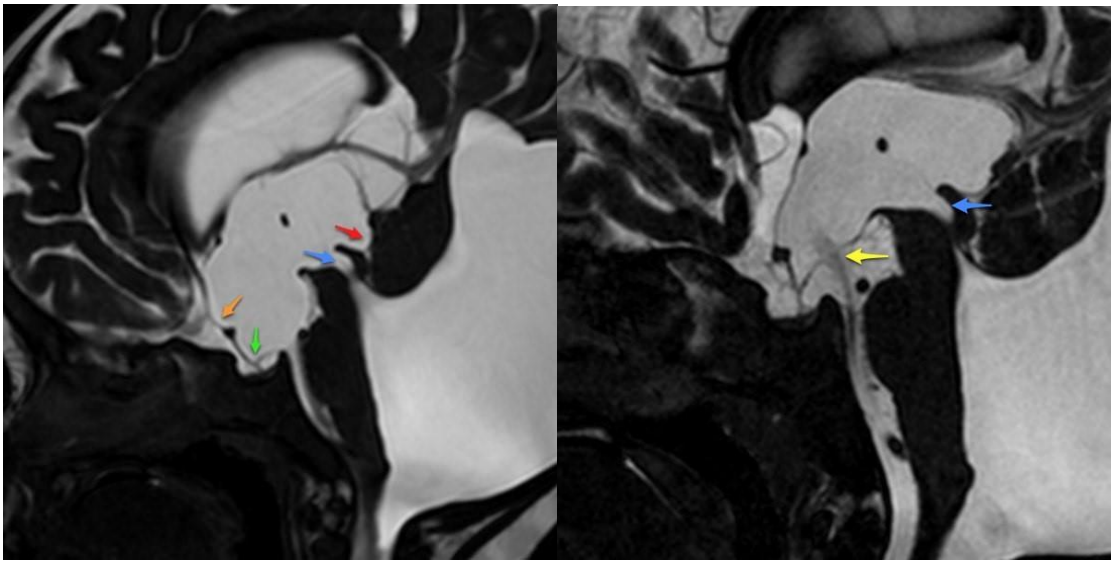


Figure 7: (A); pre ventriculostomy, (B); post ventriculostomy. { Endoscopy Third Ventriculostomy; Case courtesy of Assoc Prof Frank Gaillard} (32).

External links

Ventriculo peritoneal shunting: (33)

- https://www.neurosurgicalatlas.com/volumes/csf-diversion-procedures/ventriculo-peritoneal-shunt
- https://www.youtube.com/watch?v=ZSV1LauJlYk
- https://www.youtube.com/watch?v=vbwonC23oro
- https://www.youtube.com/watch?v=SDsBr6sXkH4

Endoscopic Third Ventriculostomy: (34)

- https://www.neurosurgicalatlas.com/volumes/csf-diversion-procedures/endoscopic-third-ventriculostomy
- https://www.youtube.com/watch?v=18J1hpG7G7U

References

1. (n.d.). Greenberg Hand Book of Neurosurgery 9th edition. https://drive.google.com/file/d/1wAafClkU7YYXvEZZjMegPMNxxsvHngkD/view?fbclid=IwAR0xOhy9O8rjmg_BTAZhGmYsomK9DiSnF-JqHFN3dYYkGBTep_JUdZX712w
2. Correa, G. G., Amaral, L. F., & Vedolin, L. M. (2011). Neuroimaging of Dandy-Walker malformation: new concepts. *Topics in Magnetic Resonance Imaging : TMRI*, *22*(6), 303–312. https://doi.org/10.1097/RMR.0b013e3182a2ca77
3. Jurcă, M. C., Kozma, K., Petcheşi, C. D., Bembea, M., Pop, O. L., MuŢiu, G., Coroi, M. C., Jurcă, A. D., & Dobjanschi, L. (2017). Anatomic variants in Dandy-Walker complex. Romanian Journal of Morphology and Embryology = Revue Roumaine de Morphologie et Embryologie, 58(3), 1051–1055.
4. Kumar, R., Jain, M. K., & Chhabra, D. K. (2001). Dandy-Walker syndrome: different modalities of treatment and outcome in 42 cases. Child's Nervous System : ChNS : Official Journal of the International Society for Pediatric Neurosurgery, 17(6), 348–352. https://doi.org/10.1007/s003810000425
5. Surgery, youmans and winn neurological. (n.d.). Youmans and Winn Neurological Surgery 7. https://drive.google.com/file/d/1hDvJTMdpuZAMXXgiW1SOECjU5Pizzpr7/view?fbclid=IwAR365UiQNEPZsNewUoS4vh8rrohzv0GfoRAdvRRAIiUuzBQ3_xgiIpf4RjI
6. Zamora, E. A., & Ahmad, T. (2020). Dandy Walker Malformation.
7. Stambolliu, E., Ioakeim-Ioannidou, M., Kontokostas, K., Dakoutrou, M., & Kousoulis, A. A. (2017). The Most Common Comorbidities in Dandy-Walker Syndrome Patients: A Systematic Review of Case Reports. Journal of Child Neurology, 32(10), 886–902. https://doi.org/10.1177/0883073817712589
8. Bosemani, T., Orman, G., Boltshauser, E., Tekes, A., Huisman, T. A. G. M., & Poretti, A. (2015). Congenital abnormalities of the posterior fossa. Radiographics : A Review Publication of the Radiological Society of North America, Inc, 35(1), 200–220. https://doi.org/10.1148/rg.351140038
9. Robinson, A. J. (2014). Inferior vermian hypoplasia--preconception, misconception. In Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology (Vol. 43, Issue 2, pp. 123–136). https://doi.org/10.1002/uog.13296
10. (n.d.-a). Dandy Walker Malformation. https://radiopaedia.org/articles/dandy-walker-malformation-1?lang=us
11. (n.d.-b). Dandy Walker Syndrome. https://radiopaedia.org/cases/dandywalker-syndrome?lang=us
12. Harper, T., Fordham, L. A., & Wolfe, H. M. (2007). The fetal dandy walker complex: associated anomalies, perinatal outcome and postnatal imaging. Fetal Diagnosis and Therapy, 22(4), 277–281. https://doi.org/10.1159/000100790
13. (n.d.-c). Dandy Walker Varient. https://radiopaedia.org/cases/dandy-walker-variant-8?lang=us
14. (2020). Blake's Pouch Cyst. https://radiopaedia.org/cases/blakes-pouch-cyst-8?lang=us
15. (n.d.-e). Mega Cisterna Magna. https://radiopaedia.org/articles/mega-cisterna-magna-1?lang=us
16. (n.d.-f). retrocerebellar arachnoid cyst. https://radiopaedia.org/cases/retro-cerebellar-arachnoid-cyst?lang=us
17. Monteagudo, A. (2020). Dandy-Walker Malformation. American Journal of Obstetrics and Gynecology, 223(6), B38–B41. https://doi.org/10.1016/j.ajog.2020.08.184
18. Bokhari, I., Rehman, L., Hassan, S., & Hashim, M. S. (2015). Dandy-Walker Malformation: A Clinical and Surgical Outcome Analysis. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP, 25(6), 431–433.
19. Nyberg, D. A., Cyr, D. R., Mack, L. A., Fitzsimmons, J., Hickok, D., & Mahony, B. S. (1988). The Dandy-Walker malformation prenatal sonographic diagnosis and its clinical Journal of Ultrasound in Medicine : Official Journal of the American Institute of Ultrasound in Medicine, 7(2), 65–71.https://doi.org/10.7863/jum.1988.7.2.65
20. Chumas, P., Tyagi, A., & Livingston, J. (2001). Hydrocephalus--what's new? Archives of Disease in Childhood. Fetal and Neonatal Edition, 85(3), F149-54. https://doi.org/10.1136/fn.85.3.f149
21. Yashon, D., Jane, J. A., & Sugar, O. (1965). The course of severe untreated infantile hydrocephalus. Prognostic significance of the cerebral mantle. Journal of Neurosurgery, 23(5), 509–516. https://doi.org/10.3171/jns.1965.23.5.0509
22. Donders, J., Canady, A. I., & Rourke, B. P. (1990). Psychometric intelligence after infantile hydrocephalus. A critical review and Child's Nervous System : ChNS : Official Journal of the International Society for Pediatric Neurosurgery, 6(3), 148–154. https://doi.org/10.1007/BF00308492
23. Dennis, M., Fitz, C. R., Netley, C. T., Sugar, J., Harwood-Nash, D. C., Hendrick, E. B., Hoffman, H. J., & Humphreys, R. P. (1981). The intelligence of hydrocephalic children. Archives of Neurology, 38(10), 607–615. https://doi.org/10.1001/archneur.1981.00510100035004
24. Treviño Alanís, M. G., González Cantú, N., Montes Cruz, J. V, García Flores, J. B., Martínez Menchaca, H. R., & Rivera Silva, G. (2014). [Dandy Walker malformation]. Archivos argentinos de pediatria, 112(1), 103–104. https://doi.org/10.5546/aap.2014.103
25. (n.d.). Dandy Walker Malformation. https://medlineplus.gov/genetics/condition/dandy-walker-malformation/#:~:text=Dandy-Walker malformation affects brain,be observed with medical imaging.
26. Fowler, J. B., De Jesus, O., & Mesfin, F. B. (2020). Ventriculoperitoneal Shunt.
27. Jimenez, D. F., Keating, R., & Goodrich, J. T. (1994). Silicone allergy in ventriculoperitoneal shunts. Child's Nervous System : ChNS : Official Journal of the International Society for Pediatric Neurosurgery, 10(1), 59–63.https://doi.org/10.1007/BF00313586

28. Morone, P. J., Dewan, M. C., Zuckerman, S. L., Tubbs, R. S., & Singer, R. J. (2020). Craniometrics and Ventricular Access: A Review of Kocher's, Kaufman's, Paine's, Menovksy's, Tubbs', Keen's, Frazier's, Dandy's, and Sanchez's Points. Operative Neurosurgery (Hagerstown, Md.), 18(5), 461–469. https://doi.org/10.1093/ons/opz194
29. Kashyap, S., Ghanchi, H., Minasian, T., Dong, F., & Miulli, D. (2017). Abdominal pseudocyst as a complication of ventriculoperitoneal shunt placement: Review of the literature and a proposed algorithm for treatment using 4 illustrative cases. In Surgical neurology international (Vol. 8, p. 78). https://doi.org/10.4103/2152-7806.206007
30. Junaid, M., Ahmed, M., & Rashid, M. U. (2018). An experience with ventriculoperitoneal shunting at keen's point for hydrocephalus. Pakistan Journal of Medical Sciences, 34(3), 691–695. https://doi.org/10.12669/pjms.343.14081
31. Mohanty, A., Biswas, A., Satish, S., Praharaj, S. S., & Sastry, K. V. R. (2006). Treatment options for Dandy-Walker malformation. Journal of Neurosurgery, 105(5 Suppl), 348–356. https://doi.org/10.3171/ped.2006.105.5.348
32. (n.d.-d). Endoscopy Third Ventriculostomy. https://radiopaedia.org/articles/third-ventriculostomy?lang=us
33. (n.d.-b). Ventriculo-Peritoneal Shunting. https://www.neurosurgicalatlas.com/volumes/csf-diversion-procedures/ventriculo-peritoneal-shunt#section1
34. (n.d.-a). Endoscopic third ventriculostomy. https://www.neurosurgicalatlas.com/volumes/csf-diversion-procedures/endoscopic-third-ventriculostomy

Article topic: Low grade glioma.

Author: Shoroug Naser Al Hamdan.

Editing: Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Keywords: Low grade glioma, grade II brain tumor.

Definition

The term low-grade glioma (LGG) refers to tumors classified by the World Health Organization (WHO) as grades I and grade II, including oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas [1].

WHO grade I LGGs are truly benign tumors that can be treated with surgical removal. On the other hand, WHO grade II LGGs are diffuse and infiltrative intracerebral lesions rarely curable, [2] they are slowly progressing conditions that have the susceptibility for malignant transformation and invariably progress to a high-grade glioma [2][3]. Low grade glioma is the most common benign brain tumors in children.

Epidemiology

The predicted incidence of grade II astrocytomas, oligodendrogliomas and mixed gliomas in the United States is 51%, 25%, and 20%, respectively, per 100,000 per year. [5] The Low-grade gliomas occur more than twice as frequently in whites as in blacks. The peak incidence for astrocytomas is between 30 and 40 years of age, the peak incidence for oligodendrogliomas is slightly older (40 to 45 years of age) [5]. Low-grade gliomas are slightly more common in males [4].

The risk factors for the development of low-grade gliomas are poorly understood. The only recognized environmental risk factor is distant history of ionizing radiation, such as in long-term survivors of childhood leukemia.[4] A history of allergies or asthma is protective against gliomas, suggesting a role for immune surveillance [4]. Well-defined inherited tumor predisposition syndromes (neurofibromatosis type 1, Li-Fraumeni cancer syndrome, Lynch syndrome, Ollier disease, Maffucci syndrome, and melanoma neural system tumor syndrome) account for a minimal proportion of cases, but the 5% to 10% of patients with glioma with a positive family history for glioma and studies demonstrating a twofold glioma risk in first-degree relatives of patients with glioma pointing to other complex hereditary factors [4].

Clinical features

Patients with low grade gliomas are usually younger than that for anaplastic gliomas or glioblastomas [4]. Although it is possible to see a newly diagnosed patient older than 60 years of age, the typical patient ranges in age from the late twenties to the mid forties [4]. Most patients present with seizures, sometimes generalized tonic-clonic, but commonly with a history of unrecognized partial seizures for several months or more [4]. Seizures are especially common with oligodendroglial histology, perhaps because oligodendrogliomas tend to invade the cortex [4].

It is uncommon for low-grade gliomas to present with fixed focal deficits, they tend to infiltrate rather than compress or destroy eloquent brain parenchyma [4]. Neuroimaging is typically critical for diagnosis of low-grade glioma [4]. More than 95% of these tumors are supratentorial. [6] Harshly equally split between frontal and temporal locations with very few occipital lobe tumors [4]. On CT, tumors in general show low attenuation [4]. Approximately 20% of low-grade gliomas establish calcification on CT, particularly oligodendrogliomas.[4] One-fourth of low-grade gliomas have several contrast enhancements on CT. [4]

This is usually patchy as opposed to ring enhancing [4]. The epicenter of low-grade gliomas in general is in the white matter, but tumors with an oligodendroglial component tend to infiltrate and sometimes expand to the cortex [4]. MRI delineates tumors more clearly than CT, it usually shows low-grade gliomas as T1 hypointense and T2 fluid-attenuated inversion recovery (FLAIR) hyperintense; MRI might be more sensitive to small amounts of enhancement than CT.[4] Susceptibility weighted imaging (SWI) sequences can show calcification or, less commonly, hemorrhage; both of them are more common with oligodendrogliomas than astrocytomas.[4] Positron emission tomography (PET) scanning, diffusion and perfusion MRI and 1H magnetic resonance spectroscopy are usually of value in differentiating low-grade gliomas from non-neoplastic lesions and high-grade gliomas but are not routinely performed .[7]

Magnetic resonance spectroscopy for 2-hydroxyglutarate, which is elevated in IDH-mutant low-grade gliomas, has protruded as a research tool; technical refinements may eventually allow its use to follow low-grade glioma growth and response to therapy.[8]

Pathogenesis and etiology

Low grade glioma (LGG) and secondary glioblastoma, which originates from a preexisting low grade glioma (LGG), were shown to harbor characteristic, neomorphic, heterozygous mutations in Isocitrate Dehydrogenase 1 (IDH1).[9]This cytosolic, NADP+ dependent enzyme physiologically forms a homodimer and patriciate in the conversion of isocitrate to α-ketoglutarate (α-KG), which can be used for multiple cellular

functions.[10] Additionally, low grade glioma (LGGs) lacking a mutation in IDH1 may have an analogous mutation in IDH2, a mitochondrial enzyme that also produces α-KG, firstly for the TCA cycle.[11] .IDH mutations were found in >80% of tumors histologically classified as LGG [9][17].

Further analysis of genomic sequencing revealed the being of two distinct molecular subclasses within LGG (Fig. 1).[18] The larger of these subclasses is characterized by inactivating mutations in the tumor suppressor gene TP53 and the chromatin remodeling enzyme ATRX (Fig. 1A,B).[19][20] The Tumors which contain this set of mutations correspond to astrocytoma, as identified by histopathology [21].The smaller subclass is characterized by the codeletion of chromosome 1p/19q and promoter mutations in telomerase reverse transcriptase (TERT) (Fig. 1B)[21].This latter group of tumors responsible for oligodendroglioma [18].

IDH mutant and P53/ATRX mutated (astrocytic) low grade glioma has a more aggressive clinical course [21]. While IDH mutant1p/19q co-deleted glioma (oligodendroglioma) has a less aggressive behavior, significant neurological decay and mortality does occur [22][23].

All this classification neglects the small percentage of histopathologically graded low-grade gliomas (LGGs) which do not exhibit a mutation in IDH1/2[18]. It has been suggested that these IDH wild-type gliomas behave like glioblastoma [18]. Indeed, if one looks for markers of IDH wild-type glioblastoma (EGFR amplifiers, H3F3A K27M or TERT promoter mutation), they can be found in half of these patients [23] These patients survive about 1.23 years, comparable to glioblastoma [12]. However, the other half of IDH wild type low grade gliomas do not have these mutations and have a clinical course resembling more closely that of LGG with survival of more than 7 years [23][24].

The most recent update to the World Health Organization guidelines on the classification of CNS tumors has incorporated the molecular features discussed above into the classification of adult low-grade glioma [18]. Histopathology remains critical in first diagnosing a tumor as a diffuse glioma and then in deciding tumor grade [12]. If a tumor is determined to be a diffuse glioma and grade II or III, then molecular diagnostics command further classifications [12].

Mutation in IDH1/2 in a combination with loss of ATRX andTP53 results in the diagnosis of a diffuse astrocytoma or anaplastic astrocytoma, grade II, and grade III [25]. If IDH mutations are found in combination with chromosomal1p/19q co-deletion, then the diagnosis of oligodendroglioma or anaplastic oligodendroglioma is confirmed [25].

The diagnosis of oligoastrocytoma, previously defined as a tumor with both astrocytic and oligodendroglial histology, still in the updated guidelines but is much less common by the new definition [12]. Oligoastrocytomas now must have distinct tumor cell

populations with the molecular features of both astrocytoma and oligodendroglioma, but these are exceedingly rare [26]. Finally, tumors which are histologically grade II or III and do not have mutations in the previously discussed genes are grouped by histology into IDH wild-type astrocytoma or oligodendroglioma not otherwise specified (NOS) [25].

Symptoms

Individuals with LGG cope with the burden of long-term symptoms and the associated challenges created by those outstanding symptoms [27]. [28] almost all patients with LGG are able to care for themselves, less than half of patients were able to perform unrestricted, normal activities of daily living and 45% reported low overall [27] patients with LGG reported more fatigue, cognitive impairment, speech difficulties, pain, sleep problems, and mood disturbances [28].

Symptoms of Low-Grade Glioma depend on the size, the location of the tumor, rate of growth and consequences of increased intracranial pressure [29]. Most of the research on symptoms affecting the Quality of life (QoL) of glioma populations has been focuses on fatigue, sleep, pain, seizures, cognitive impairment, and mood disturbances [27]. For low grade glioma (LGG), a small study demonstrated that fatigue had the strongest relationship with Quality of life (QOL) [31].

Seizures are the most common presenting symptom of low-grade glioma (LGG), occurring in 65% to 85% of patients [32]. Uncontrolled seizures in patients with low grade glioma (LGG) have been reported in approximately 30% of patients, leading to cognitive fall and significant morbidity that can impact QoL. [32][33].

The management of seizures with anti-epileptic agents can also contribute to cognitive slowing and decrease QoL [27]. Mood disturbances, mostly described as anxiety, can occur in up to 60% of individuals with gliomas [34][35].

Studies have reported that the depression at rates from 40% to 90% of patients in this population [34][35][36]. As such, a diagnosis of low-grade glioma (LGG) is an important predictor of anxiety and depression [34][35]. In a cohort study of low-grade glioma (LGG), depressive symptoms were noted to be the most important independent predictor of decreased QoL and survival [36][37][38]. Psychological problems can worsen cognitive dysfunction (including memory) [39][40].

In 90% of long-term survivors of LGG, cognitive impairment has been found as the most serious challenge to cope with and adapt to post-treatment.[44][45] Even “symptom-free” survivors still have documented cognitive deficits on formal neurocognitive testing [46].

Classifications

The 2016 WHO Classification of Tumors of the Central Nervous System [47] is an update of the earlier classification from 2007 that includes, for the first time, molecular and genetic parameters, in addition to histopathologic features, to define and sub-categorize brain tumor entities [48]. This is a breakthrough in pathological diagnosis that particularly restructures the diagnosis of diffuse gliomas [48].

Historically, it was not uncommon that mixed oligoastrocytic tumors were frequently diagnosed at some centers while they were rarely encountered at others [49]. The combination of histologic and genotypic parameters adds objectivity and inter-observer concordance, which results in improving the diagnostic accuracy [48].

The limiting factor for this new classification method is the actual availability and choice of genotyping or surrogate genotyping assays [48].

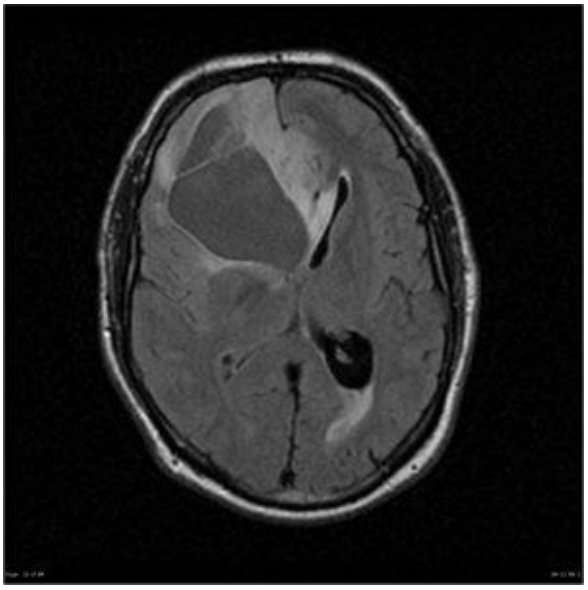
The Tumors which do not fit into the newly defined categories or those not being tested for molecular parameters are now classified under a NOS (Not Otherwise Specified) designation [49]. Diffuse gliomas are now grouped together according to the cell type of origin [48]. The reason is that they have same growth pattern, clinical behavior, genetic mutations and prognostic markers [48]. Diffuse gliomas now include WHO grade II and III astrocytomas and oligodendrogliomas, grade IV glioblastomas, midline gliomas and diffuse gliomas of the childhood [49]. Grade II diffuse astrocytomas and grade III anaplastic astrocytomas are now divided into three categories each: IDH-mutant (the great majority), IDH wild type (very rare) and NOS [48]. Nevertheless, the prognosis of IDH mutant cases appear to be more favorable than IDH-wild type for both grade II and grade III astrocytomas [53].

More changes on the 2016 WHO classification include the deletion of two diffuse astrocytoma variants: protoplasmic astrocytoma and fibrillary astrocytoma (which overlaps with the standard diffuse astrocytoma) [48]. However, the gemistocytic astrocytoma remains an IDH mutant distinct variant [53]. The diagnosis of diffuse astrocytoma is dependent on the confirmation of the mutant IDH status plus ATRX loss and TP53 mutation, both characteristic although not needed for diagnosis [48].

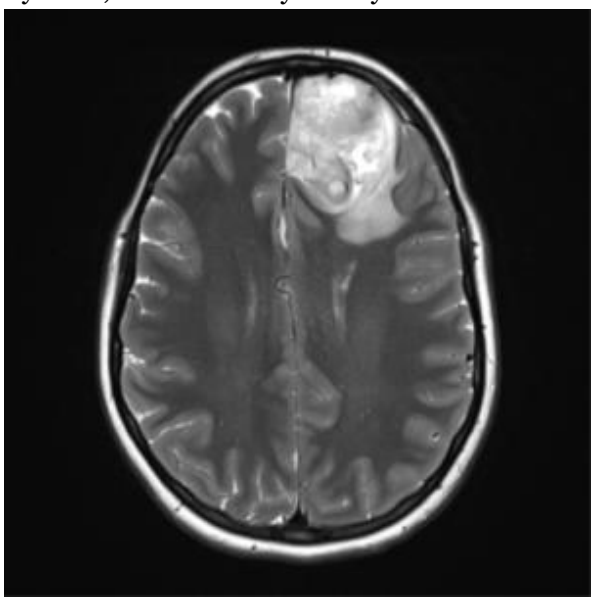
Grade II oligodendrogliomas and grade III anaplastic oligodendrogliomas both exhibit IDH gene family mutations and 1p/19p codeletion, but no ATRX and TP53 mutations [53]. This fact statements an easy differentiation from astrocytomas [48].

However, the diagnosis of oligoastrocytoma is strongly discouraged by the 2016 WHO classification, and it is assigned to a NOS designation, since every mixed phenotypic tumor can be classified either as astrocytic or oligodendrocytic using genetic testing [54]. It is important to note that according to this new classification, grade II

oligodendroglioma may progress to grade III oligodendroglioma but does not lead to grade IV glioblastoma, which always seems to derive from an astrocytic precursor [53] (figure 1, and 2).



Diffuse astrocytoma, Case courtesy of Royal Melbourne Hospital,[55].



Case courtesy of Assoc Prof Frank Gaillard [56].

Prognostic factors

A wide range of outcomes exists among patients with LGG [57]. Patient subsets can be identified with an average survival of as little as 2 years or greater than a dozen years [57]. Knowledge of prognostic factors is thus critical for therapeutic decision making and patient education [57].

Historically, neuro-oncologists depended upon readily available clinical, radiographic and neuropathologic features to determine prognosis [57]. Among clinical prognostic factors, age is powerful: younger patients do better than older patients, leading some studies to classify patients older than 40 years of age as high risk [57].

Presentation with isolated seizures is also favorable, possibly because of lead time bias; conversely, fixed neurologic deficits or mental status changes are prognostically adverse [57]. Tumor size also important, although whether preoperative or postoperative size is more critical remains uncertain [58][59]; similarly, involvement of the corpus callosum is a recognized adverse characteristic [60].

Neuropathologic assessments provide valuable prognostic information [60]. It has long been appreciated that median survival of oligodendrogliomas is nearly twice that of astrocytomas.[61] Newer molecular tests allow more refined prognoses and to what extent incorporation of such tests might reduce the importance of some aforementioned clinical factors is still unknown [60].

The first molecular test of prognostic value was 1p/19q codeletion status, which correlates to some extent with classic histology but avoids interpreter discrepancy; for example, one study found a median survival of 12 years in co-deleted LGG versus 8 years in non-codeleted tumors, [62] the danger ratio for overall survival for patients with 1p deletion was 0.59, similarly supporting the favorable prognosis of codeleted tumors [63].

The recently discovered IDH mutation present in most LGG has a similar favorable prognostic effect, 11 years [64] Classifying LGGs into three molecular groups (1p/19q-codeleted, IDH mutated but 1p/19q intact, and neither alteration) yields three distinct survival curves with median survivals of approximately 9, 6, and 2 years, respectively [65]. Additional molecular markers (e.g., TERT mutations) will certainly improve molecular prognostication in coming years [66].

- # Diagnostic neuroimaging for gliomas

Magnetic resonance imaging (MRI) of low-grade glioma demonstrates lesions that are isointense/hypointense on T1-weighted images, are homogeneously hyperintense on T2-weighted images and do not enhance with contrast administration [67].

Some of these characteristics are shared with high-grade gliomas (HGGs), with the exception of contrast enhancement, which is usually, but not always, seen in more aggressive grades of high grade glioma, [68] calcifications can be revealed in about 20% of lesions and appear as distinct hyperintense foci on T1-weighted images and hypointense foci on T2-weighted images[69].

Vasogenic edema and necrosis are not typical of Low-grade gliomas, owing to their slow growth rate [67]. More sophisticated MRI techniques, such as MR spectroscopy, have been used to differentiate glioma grades and even to detect key Low grade glioma metabolic mutations, such as those of the isocitrate dehydrogenase1 (IDH1) gene [67].

These tumors were also graded with use of proton MR spectroscopy of metabolite ratios (choline/creatine, choline/N-acetylaspartate and N-acetylaspartate/creatine), which yielded significant differences between Low grade gliomas and high grade gliomas ($P < .01$); sensitivity, specificity, PPV, and NPV rates were 93.3%, 60.0%, 87.5% and 75%, respectively[70].

An increased choline-creatinine ratio on MR spectroscopy also gets along with heightened risk of transformation, with a sensitivity of 80% and a specificity of 94%.[71] Interestingly, work has now determined that proton MR spectroscopy can detect Low grade glioma -specific oncometabolites, such as 2-hydroxyglutarate, a metabolite of mutant IDH1.[72]

A prospective study of 27 patients shows that elevated choline and decreased glutathione values correlated with IDH1 mutation in gliomas [57]. Tumors with this mutation follow a better prognosis and may be responsive to certain chemotherapy regimens.[67]

Although IDH1 mutations are not exclusive to low grade gliomas, this strategy provides surgeons with a noninvasive prognostic marker.[67] Yet, metabolic imaging of low-grade gliomas extends beyond the use of magnetic resonance and is increasingly explored with use of positron emission tomography (PET).[67]

Both fluorodeoxyglucose-PET (FDG-PET) and fluorothymidine-PET (FLT-PET) have been used to evaluate LGG metabolism and proliferation [67]. A prospective study of 60 patients with cerebral gliomas evaluated the ability of FDG-PET to differentiate low grade gliomas from HGGs [67]. The investigators mention a PPV of 97.3% and an NPV of 70.2% [73].

Additionally, a study of 25 patients with newly diagnosed or previously treated gliomas demonstrated that decreased FLT-PET uptake correlated with a lower Ki-67 index and the Low-grade glioma classification [74].

Perfusion MRI is one of several new physiologic imaging modalities with promising utility for grading low grade erw67]. A few retrospective studies have indicated that relative cerebral blood volume (rCBV) can be used as a preoperative predictor of Low-grade glioma histology [67]. The sensitivity and specificity of using rCBV for differentiating Low grade gliomas and HGGs is 80% to 95% and 94% to 96%, respectively.[67]

Additionally, a study of 69 patients demonstrated an inverse correlation between rCBV and time to progression or death, with an odds ratio of 1.87 (95% confidence interval [CI],(1.14-3.08).[75] This finding was supported by a subsequent study of 20 patients in whom increased rCBV was associated with rapid progression of Low grade gliomas[67]. Similarly, diffusion tensor imaging (DTI) is under investigation to differentiate LGGs and HGGs histologic appearances [67].

A retrospective study of 78 patients with gliomas found an inverse correlation between tumor grading and axial diffusivity (AD), radial diffusivity (RD) and the apparent diffusion coefficient (ADC) [76]. DTI analysis of 79 gliomas also explain a correlation with the tumor grade and was able to differentiate LGGs from HGGs with a sensitivity of 92% to 94% and a specificity of 53% to54% [77].

These findings are supported by a retrospective study of 25 patients that explain specificity and sensitivity of 86% and 80%, respectively, for differentiating LGGs from HGGs with use of spherical isotropy coefficients (CP and CS) and fractional anisotropy (FA) [77]. Both rCBV and DTI are promising new modalities to better characterize tumor heterogeneity and prophesy regional transformation [67].

Functional MRI (fMRI) is based on the increasing in blood flow to local vasculature that accompanies neural and metabolic activities in the brain [67]. This increase results in a corresponding local reduction in deoxyhemoglobin because the increasing in blood flow occurs in the absence of a comparable increase in oxygen extraction. Deoxyhemoglobin is used as an endogenous contrast enhancing agent and serves as the source of the signal during fMRI.

Functional MRI results can be consistent with those of electrophysiology, PET, cortical stimulation, and magnetoencephalography (MEG) and are used to provide preoperative functional and structural information for neurosurgery. Cortical stimulation, which still the gold standard for functional localization is based on local circuit disruption or activation and best identifies areas that are essential to language processing [67].

In contrast, fMRI is an activation-based method that identifies all regions of the brain that demonstrate activity related to a specific task, regardless of whether those areas are essential or supplementary [67].

Consequently, areas that show negative for language when cortical stimulation is used may still demonstrate fMRI activation, producing false-positive results. Decreasing in specificity may also be expected because fMRI is a perfusion-based method and does not directly detect neuronal activity.

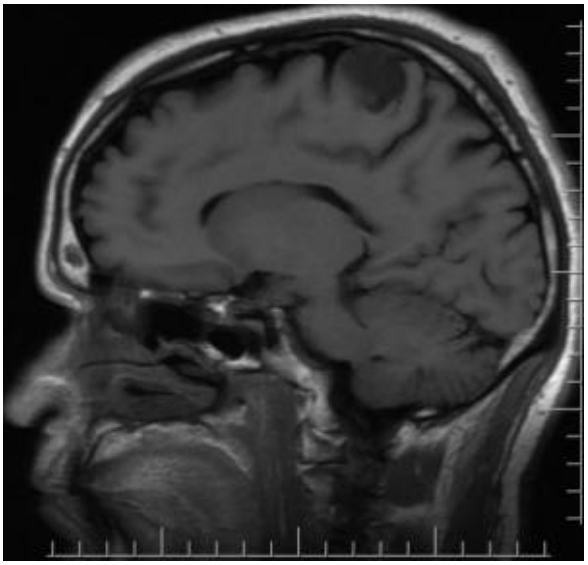
Magnetoencephalography (MEG) is also used for preoperative functional mapping [67]. Magnetoencephalography (MEG) imaging reconstructs the spatiotemporal dynamics of brain sources from magnetoencephalographic data.[67] When co-registered with an

anatomical scan, such as a high-resolution MR image, magnetoencephalography (MEG) imaging can be integrated into a neuronavigation system and offer intraoperative guidance to the surgical team. [67]

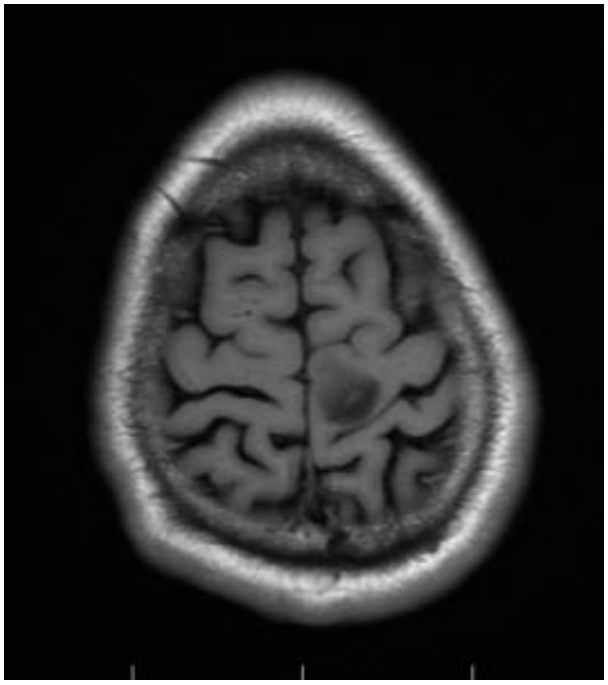
Preoperative MEG maps of the motor cortex have been validated compared to intraoperative direct cortical stimulation (DCS) maps and are a useful modality for preoperative localization of this region. Compared to fMRI and PET, MEG has the advantage of higher temporal resolution because it measures direct neuronal activation instead of indirect hemodynamic change.

Previous studies have also suggested that MEG is more accurate than fMRI in identifying functional cortices that have been distorted by a nearby tumor.[67] Overall, MEG is a robust and credible functional imaging modality that is now used to identify the cortical location of motor and sensory pathways.

Integrating MEG data with DTI information into a neuronavigational workstation directs the neurosurgeon toward potential functional sites that can be intraoperatively assured with stimulation mapping [67]. Magnetic source imaging (MSI), which is based on the magnetoencephalographic detection of the late neuromagnetic field extracted by simple speech sounds [78] is another mapping technique that can be useful for mapping the somatosensory cortex and determining hemispheric dominance, and it may serve as a replacement of the Wada test [67].



Sagittal T1, low grade glioma, Case courtesy of Dr Prashant Mudgal [79]



Axial T1, low grade glioma, Case courtesy of Dr Prashant Mudgal [80].

Treatment

Low grade gliomas (LGGs) are treated depending on where they are found, they are commonly treated with surgery, which is sometimes followed by chemotherapy and radiation, when surgery is not possible, other options can be considered, including observation, chemotherapy, or radiation.

Surgical decision making

After MRI shows an abnormality compatible with a low-grade glioma, the question becomes whether to intervene surgically and, if so, whether to biopsy or to perform maximal safe resection of the tumor [60]. When a patient has neurologic deficits or significant mass effect, the need to intervene is necessary [60].

However, the patient with an incidentally revealed lesion or well-controlled seizures presents a different problem [60]. Currently, no compulsory evidence exists that early intervention improves outcome over observation, with surgery when the lesion grows, supporting a watch and wait approach in some cases [60]. Countering this philosophy is the reality that (LGG) grow continuously, so detection of growth is simply a matter of time [61].

Moreover, approximately 50% of anaplastic gliomas, tumors that should be treated promptly after diagnosis do not enhance and thus may resemble (LGG) on MRI [60].

Patient preference and prognostic factors, including age, tumor size and location must be considered in the approach to this decision [60]. If observation is selected, patients should be carefully followed with serial imaging compared to the initial abnormal scan to ensure that large changes in tumor size that might preclude effective interventions, such as debulking, are not missed. Once the patient and neurosurgeon have decided to pursue eventual diagnosis, the next question is whether to resect or biopsy the tumor [60].

Level one, evidence is lacking and unlikely ever to be available [60]. A retrospective population-based parallel cohort study in Norway compared patients who underwent maximal safe resection to patients who underwent biopsy followed by observation until progression in both groups proved improved overall survival in the first group. [62]

A large series of 216 patients with (LGG) who underwent resection found that extent of resection correlated significantly with overall survival, with a 5-year overall survival of 97% with an extent of resection greater than 90% but only 76% with an extent of resection less than 90%.[63] Also, a study of 170 patients from Johns Hopkins reported 5-year overall survival of 95% with gross total resection compared to 70% with subtotal resection [64]. Admittedly, bias undoubtedly found in terms of which patients undergo aggressive resection versus limited resection or biopsy. [60]

Some studies have shown that although extensive surgery predicts improved overall survival on univariate analysis, this finding is lost when data are controlled for other prognostic factors [61]. Admittedly advantage of debulking is its improved diagnostic accuracy: needle biopsies have a substantial misdiagnosis rate as they may undersample a heterogeneous tumor with foci of anaplastic glioma. [65][66]

For these reasons, most authorities favor maximal safe resection, with the understanding that tumors involving the corticospinal pathway, speech areas and other eloquent regions may not be docile to aggressive surgery.[60] Functional MRI (fMRI), intraoperative mapping [67], awake craniotomy and intraoperative MRI are techniques that help the surgeon in the quest for maximal safe resection [68].

Role of radiation and chemotherapy

The optimal management of (LGG) remains one of the most contentious areas in neuro-oncology, with questions about the timing and sequence of radiation and chemotherapy largely unresolved [60]. One issue is if patients who have had excellent resections may be observed without additional treatment [60].

A prospective study of observation in patients younger than 40 years of age who had undergone gross total resection of a (LGG) found that slightly more than 50% recurred within 5 years of surgery [81].

Thus, while initial observation is a reasonable postoperative option in low-risk patients, they need long-term surveillance imaging, and the follow-up scans should be compared to the early postoperative MRIs instead of the most recent scan so that tumor progression can be accurately detected [60]. Observation is sometimes selected following aggressive debulking in higher-risk patients, but the likelihood of early recurrence is correspondingly increased [60]. Once the decision is made for treatment, options include fractionated radiation therapy, chemotherapy, or the combination of the two modalities [60]. Fractionated external beam radiation therapy has been the initial treatment. [60]

As doses from 45 Gy to 64 Gy in 1.8 Gy to 2 Gy daily fractions achieve similar tumor control, a dose of 50 Gy to 54 Gy to the tumor and margins over 5 to 6 weeks has become standard [82][83]. 30% of patients experience significant tumor shrinkage.[60]

It is difficult to quantifying the survival benefit of radiation, since a study that proscribed radiation would be unethical [60]. A phase 3 European study randomly assigned patients with (LGG) to early radiation versus observation, with radiation allowed for tumor progression [60].

Early radiation prolonged progression-free survival by 2 years, but overall survival was the same between the groups. [84] This study can be interpreted to support either early treatment or observation depending on one's viewpoint [60]. It is difficult to Determine of tumor activity is sometimes challenging after radiation therapy, as the treatment itself often produces delayed white matter changes that may resemble progressive tumor [60]. Recently devised criteria for (LGG) tumor response provide some guidelines for subsequent scan interpretation [85]

Radiation therapy always produces some short-term fatigue and studies of cognitive functions often show at least temporary decline in memory [60]. Since patients with low grade gliomas commonly experience a slow decline in performance status over years following diagnosis, much of this has been blamed on radiation therapy [60].

Recent studies suggest that in the first several years after radiation, most cognitive decline is referred to the tumor itself or concomitant medications such as anticonvulsants [86]. Nonetheless, with longer follow-up, it is clear that even modern radiation techniques and dosing are associated with measurable cognitive decline in long-term survivors with (LGGs) [87].

The recognition in the 1990s that anaplastic oligodendrogliomas were chemosensitive, coupled with the hope of deferring cognitive risks of radiation, created interest in exploring chemotherapy as the initial antineoplastic therapy in (LGGs) [60].

Studies were done about the combination of procarbazine, thenitrosourea CCNU (lomustine), andvincristine (PCV) used for anaplastic oligodendrogliomas; with the

emergence of temozolomide and it has improved side effect profile, attention shifted to this agent [60]. Small phase 2 chemotherapy studies have demonstrated that tumor response rates close to those of radiation therapy, with tumor stabilization ranging from 3 to 5 years [60].

These encouraging results led to a large phase 3 trial (European Organization for Research and Treatment of Cancer [EORTC]22033-26033) that randomly assigned patients with high-risk LGG (older than 40 years of age, symptomatic, or with tumors growing under observation) to either 1 year of temozolomide or standard radiationtherapy [60].

Initial results, with median follow-up of 4 years, were published in 2016.35 For co-deleted (LGGs), median progression-free survival was similar with temozolomide and radiation (55.0 versus 61.6 months) [60]. On the other hand, for IDH-mutant non–co-deleted tumors, progression-free survival was markedly inferior with temozolomide (36.0 versus 55.4 months =.004), suggesting that this approach is not justified in this tumor profile [60].

Given the ultimately fatal outcome of low-grade gliomas and the relative successes combining radiation with chemotherapy in higher-grade gliomas, it is unsurprising that combined chemotherapy and radiation approaches for low-grade glioma are being studied [60]. Preliminary results of a relatively large single-arm phase 2 study (Radiation Therapy Oncology Group [RTOG] 0424) combining radiation therapy with temozolomide suggest improved survival compared to a historic control group treated with radiation therapy alone,[88] and a phase 3 trial randomly assigning high-risk patients with LGG to radiation with or without temozolomide (Eastern Cooperative Oncology Group [ECOG] E3F05) was launched[60].

Recently updated results incorporating long-term follow-up from an old low-grade glioma trial suggest that radiation therapy alone is inadequate therapy for low-grade gliomas. In 1998, a phase 3 trial that randomly assigned patients with LGGs to radiation with or without subsequent PCV were launched [60]. The original publication of trial results in 2012 did not demonstrate an overall survival advantage with the addition of chemotherapy despite an improvement in progression-free survival [89].

The tails on the overall survival curve were diverging [60]. With 6 additional years of follow-up, [90] a statistically worthy benefit in overall survival favoring the PCV arm (13.3versus 7.8 years) was seen [60]. Unfortunate, inadequate tumor tissue precluded breaking down these results by IDH and 1p/19q status; similar studies in anaplastic gliomas demonstrated that the bulk of benefit from adjuvant PCV was in codeleted tumors. Nonetheless, patients with LGGs requiring treatment with radiation should strongly be considered for combined chemotherapy and radiation [60].

Whether temozolomide, a better-tolerated oral agent, can substitute for the three-drug PCV combination remains unknown and will presumably require a prospective randomized trial to address; the ongoing radiation therapy with concomitant and adjuvant Temozolomide versus radiation therapy with adjuvant PCV chemotherapy in patients with anaplastic glioma or LGG (CODEL) trial (NCT00887146) comparing temozolomide to PCV in codeleted anaplastic gliomas was recently amended to include codeleted low grade gliomas and may help address this.[60] An important unresolved issue is how an initial approach of using chemotherapy alone to defer radiation therapy followed by using combined chemotherapy and radiation at progression compares to initial combined chemotherapy and radiation, both in terms of overall survival and quality of survival from a cognitive and quality-of-life perspective[60].

It is possible that the early use of alkylating agent chemotherapy could reduce the effectiveness of further chemotherapy added to radiation therapy at tumor progression or lead to the development of added harmful mutations in the tumor [91]. How the heterogeneous group of patients with IDH-wild type grade II gliomas should be treated is uncertain; many including most older patients will have a clinical course consistent with glioblastoma and presumably should be treated. Regardless of initial treatment, LGGs eventually resume growing. The majority will then develop increasing enhancement and if operated on again, will be found to have transformed into higher-grade gliomas [60].

Although this phenomenon is often called malignant transformation, that term overlooks the fact that LGGs themselves are low-grade malignancies [60]. At progression, patients who firstly received radiation therapy are candidates for chemotherapy and vice versa [60].

The Patients who progress after receiving temozolomide may receive a nitrosourea alone or as part of PCV, while those progressing after nitrosoureas go on to temozolomide. Bevacizumab, an active agent for glioblastoma, was studied in recurrent/progressive LGGs in a 2016 randomized phase 2 trial; the addition of bevacizumab to temozolomide did not appear to afford benefit in contrast-enhancing recurrent tumors, which is unsurprising since LGGs are not vascular endothelial growth factor (VEGF) Y driven tumors [92]. LGGs are fatal, although clinical trials targeting the mutant IDH protein are under way [60].

Conclusion

Innovations within the diagnostic, therapeutic, and molecular domains are intertwining and helping us understand and treat low grade gliomas (LGGs) more effectively.

Prognostic factors derived from genetic analysis and clinical characteristics allow us to apply patients into proper treatment groups to maximize therapeutic benefit.

Stereotactic biopsies provide information to clinician regarding pathologic grade, which is used to give the patient a prognosis and suggest more effective treatment options. Additionally, large retrospective multi-institutional studies have shown that maximizing the extent of resection can delay recurrence and improve the time to transformation. However, this approach must be balanced with preservation of neurologic function, which can be better by using intraoperative mapping.

Evidence also shows that chemotherapy with radiation therapy may prolong Progression free survival and Overall survical. Many challenges have been overcome, in terms of providing an accurate prognosis and assigning treatment regimens, but our findings are limited because low grade gliomas (LGGs) are not homogeneous and small genetic changes can significantly affect outcomes.

Future clinical trials that classify patients according to novel prognostic factors maybe aid increasing patient-specific treatment plans with better outcomes.

References

[1] T. Komori, "The 2016 WHO classification of tumours of the central nervous system: The major points of revision," *Neurologia Medico-Chirurgica*, vol. 57, no. 7. Japan Neurosurgical Society, pp. 301–311, 2017, doi: 10.2176/nmc.ra.2017-0010.

[2] H. Duffau and L. Taillandier, "New concepts in the management of diffuse low-grade glioma: Proposal of a multistage and individualized therapeutic approach," *Neuro-Oncology*, vol. 17, no. 3, pp. 332–342, 2015, doi: 10.1093/neuonc/nou153.

[3] P. Wessels *et al.*, "For personal use. Only reproduce with permission from The Lancet Publishing Group. Reviews Supratentorial grade II astrocytoma: biological features and clinical course." [Online]. Available: http://neurology.thelancet.com.

[4] D. Schiff, "Low-grade Gliomas."

[5] Q. T. Ostrom *et al.*, "CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2009-2013," *Neuro-Oncology*, vol. 18, pp. v1–v75, Oct. 2016, doi: 10.1093/neuonc/now207.

[6] P. D. Delgado-López, E. M. Corrales-García, J. Martino, E. Lastra-Aras, and M. T. Dueñas-Polo, "Diffuse low-grade glioma: a review on the new molecular classification, natural history and current management strategies," *Clinical and Translational Oncology*, vol. 19, no. 8. Springer-Verlag Italia s.r.l., pp. 931–944, Aug. 01, 2017, doi: 10.1007/s12094-017-1631-4.

[7] S. J. Fouke, T. Benzinger, D. Gibson, T. C. Ryken, S. N. Kalkanis, and J. J. Olson, "The role of imaging in the management of adults with diffuse low grade glioma: A systematic review and evidence-based clinical practice guideline," *Journal of Neuro-Oncology*, vol. 125, no. 3. Springer New York LLC, pp. 457–479, Dec. 01, 2015, doi: 10.1007/s11060-015-1908-9.

[8] C. Choi *et al.*, "Prospective longitudinal analysis of 2-hydroxyglutarate magnetic resonance spectroscopy identifies broad clinical utility for the management of patients with IDH-mutant glioma," *Journal of Clinical Oncology*, vol. 34, no. 33, pp. 4030–4039, Nov. 2016, doi: 10.1200/JCO.2016.67.1222.

[9] H. Yan *et al.*, "IDH1 and IDH2 Mutations in Gliomas ," *New England Journal of Medicine*, vol. 360, no. 8, pp. 765–773, Feb. 2009, doi: 10.1056/nejmoa0808710.

[10] R. Vinekar, C. Verma, and I. Ghosh, "Functional relevance of dynamic properties of Dimeric NADP-dependent Isocitrate Dehydrogenases.," *BMC bioinformatics*, vol. 13 Suppl 17, 2012, doi: 10.1186/1471-2105-13-S17-S2.

[11] J. T. Grier, T. Batchelor, and C. Pappas, "Neuro-Oncology Low-Grade Gliomas in Adults." [Online]. Available: www.TheOncologist.com.

[12] D. Bready and D. G. Placantonakis, "Molecular Pathogenesis of Low-Grade Glioma," *Neurosurgery Clinics of North America*, vol. 30, no. 1. W.B. Saunders, pp. 17–25, Jan. 01, 2019, doi: 10.1016/j.nec.2018.08.011.

[13] F. Farshidfar*et al.*, "Erratum: Integrative Genomic Analysis of Cholangiocarcinoma Identifies Distinct IDH-Mutant Molecular Profiles (Cell Reports (2017) 18(11) (2780–2794) (S2211124717302140) (10.1016/j.celrep.2017.02.033))," *Cell Reports*, vol. 19, no. 13. Elsevier B.V., pp. 2878–2880, Jun. 27, 2017, doi: 10.1016/j.celrep.2017.06.008.

[14] K. E. Yen, M. A. Bittinger, S. M. Su, and V. R. Fantin, "Cancer-associated IDH mutations: Biomarker and therapeutic opportunities," *Oncogene*, vol. 29, no. 49. pp. 6409–6417, Dec. 09, 2010, doi: 10.1038/onc.2010.444.

[15] C. Bonnet *et al.*, "Characteristics of gliomas in patients with somatic IDH mosaicism," *Acta neuropathologica communications*, vol. 4, p. 31, Mar. 2016, doi: 10.1186/s40478-016-0302-y.

[16] M. F. Amary*et al.*, "Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of IDH1 and IDH2," *Nature Genetics*, vol. 43, no. 12, pp. 1262–1265, Dec. 2011, doi: 10.1038/ng.994.

[17] J. Balss, J. Meyer, W. Mueller, A. Korshunov, C. Hartmann, and A. von Deimling, "Analysis of the IDH1 codon 132 mutation in brain tumors," *Acta Neuropathologica*, vol. 116, no. 6, pp. 597–602, 2008, doi: 10.1007/s00401-008-0455-2.

[18] D. Bready and D. G. Placantonakis, "Molecular Pathogenesis of Low-Grade Glioma," *Neurosurgery Clinics of North America*, vol. 30, no. 1. W.B. Saunders, pp. 17–25, Jan. 01, 2019, doi: 10.1016/j.nec.2018.08.011.
[19] "Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas," *New England Journal of Medicine*, vol. 372, no. 26, pp. 2481–2498, Jun. 2015, doi: 10.1056/NEJMoa1402121.
[20] J. Balss, J. Meyer, W. Mueller, A. Korshunov, C. Hartmann, and A. von Deimling, "Analysis of the IDH1 codon 132 mutation in brain tumors," *Acta Neuropathologica*, vol. 116, no. 6, pp. 597–602, 2008, doi: 10.1007/s00401-008-0455-2.
[21] D. N. Louis *et al.*, "The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary," *Acta Neuropathologica*, vol. 131, no. 6. Springer Verlag, pp. 803–820, Jun. 01, 2016, doi: 10.1007/s00401-016-1545-1.
[22] P. Wesseling, M. van den Bent, and A. Perry, "Oligodendroglioma: pathology, molecular mechanisms and markers," *Acta Neuropathologica*, vol. 129, no. 6. Springer Verlag, pp. 809–827, Jun. 26, 2015, doi: 10.1007/s00401-015-1424-1.
[23] J. E. C. Bromberg and M. J. van den Bent, "Oligodendrogliomas: Molecular Biology and Treatment," *The Oncologist*, vol. 14, no. 2, pp. 155–163, Feb. 2009, doi: 10.1634/theoncologist.2008-0248.
[24] A. Aibaidula*et al.*, "Adult IDH wild-type lower-grade gliomas should be further stratified," *Neuro-Oncology*, vol. 19, no. 10, pp. 1327–1337, Oct. 2017, doi: 10.1093/neuonc/nox078.
[25] P. Kleihues*et al.*, "The WHO Classification of Tumors of the Nervous System," 2002. [Online]. Available: http://jnen.oxfordjournals.org/.
[26] J. T. Huse, E. L. Diamond, L. Wang, and M. K. Rosenblum, "Mixed glioma with molecular features of composite oligodendroglioma and astrocytoma: A true 'Oligoastrocytoma'?," *Acta Neuropathologica*, vol. 129, no. 1. Springer Verlag, pp. 151–153, Jan. 01, 2015, doi: 10.1007/s00401-014-1359-y.
[27] M. louAffronti*et al.*, "Pilot Study to Describe the Trajectory of Symptoms and Adaptive Strategies of Adults Living with Low-grade Glioma," *Seminars in Oncology Nursing*, vol. 34, no. 5. W.B. Saunders, pp. 472–485, Dec. 01, 2018, doi: 10.1016/j.soncn.2018.10.006.
[28] M. Gustafsson, T. Edvardsson, and G. Ahlström, "The relationship between function, quality of life and coping in patients with low-grade gliomas," *Supportive Care in Cancer*, vol. 14, no. 12, pp. 1205–1212, Dec. 2006, doi: 10.1007/s00520-006-0080-3.
[29] M. Gustafsson, T. Edvardsson, and G. Ahlström, "The relationship between function, quality of life and coping in patients with low-grade gliomas," *Supportive Care in Cancer*, vol. 14, no. 12, pp. 1205–1212, Dec. 2006, doi: 10.1007/s00520-006-0080-3.
[30] S. W. Fox, D. Lyon, and E. Farace, "Clinical Scholarship Symptom Clusters in Patients With High-Grade Glioma."
[31] M. Gustafsson, T. Edvardsson, and G. Ahlström, "The relationship between function, quality of life and coping in patients with low-grade gliomas," *Supportive Care in Cancer*, vol. 14, no. 12, pp. 1205–1212, Dec. 2006, doi: 10.1007/s00520-006-0080-3.
[32] L. B. E. Shields and A. K. Choucair, "Management of Low-Grade Gliomas: A Review of Patient-Perceived Quality of Life and Neurocognitive Outcome," *World Neurosurgery*, vol. 82, no. 1–2. Elsevier Inc., pp. e299–e309, 2014, doi: 10.1016/j.wneu.2014.02.033.
[33] D. J. Englot, M. S. Berger, N. M. Barbaro, and E. F. Chang, "Predictors of seizure freedom after resection of supratentorial low-grade gliomas: A review," *Journal of Neurosurgery*, vol. 115, no. 2. pp. 240–244, Aug. 2011, doi: 10.3171/2011.3.JNS1153.
[34] N. S. Litofsky*et al.*, "Depression in Patients with High-grade Glioma: Results of the Glioma Outcomes Project," *Neurosurgery*, vol. 54, no. 2, pp. 358–367, 2004, doi: 10.1227/01.NEU.0000103450.94724.A2.
[35] S. D. Arnold *et al.*, "Evaluation and characterization of generalized anxiety and depression in patients with primary brain tumors," *Neuro-Oncology*, vol. 10, no. 2, pp. 171–181, Apr. 2008, doi: 10.1215/15228517-2007-057.
[36] G. Pelletier, M. J. Verhoef, N. Khatri, and N. Hagen, "Quality of life in brain tumor patients: the relative contributions of depression, fatigue, emotional distress, and existential issues," 2002.
[37] A. Mainio, H. Hakko, A. Niemelä, J. Koivukangas, and P. Räsänen, "Depression and functional outcome in patients with brain tumors: a population-based 1-year follow-up study," 2005.
[38] A. G. Rooney, A. Carson, and R. Grant, "Depression in cerebral glioma patients: A systematic review of observational studies," *Journal of the National Cancer Institute*, vol. 103, no. 1, pp. 61–76, Jan. 2011, doi: 10.1093/jnci/djq458.
[39] M. J. B Taphoorn*et al.*, "Cognitive Functions and Quahty of Me in Patients with Low-Grade Gliomas: The Impact of Radiotherapy," 1994.
[40] "s0140-6736%2802%2911398-5 (1)."
[41] M. Klein *et al.*, "N e u r o b e h a v i o r a l S t a t u s a n d H e a l t h-R e l a t e d Q u a l i t y o f L i f e i n N e w l y D i a g n o s e d H i g h-G r a d e G l i o m a P a t i e n t s," 2001.
[42] B. v Taylor *et al.*, "Effects of Radiation and Chemotherapy on Cognitive Function in Patients With High-Grade Glioma," 1998.
[43] M. Gustafsson, T. Edvardsson, and G. Ahlström, "The relationship between function, quality of life and coping in patients with low-grade gliomas," *Supportive Care in Cancer*, vol. 14, no. 12, pp. 1205–1212, Dec. 2006, doi: 10.1007/s00520-006-0080-3.
[44] L. B. E. Shields and A. K. Choucair, "Management of Low-Grade Gliomas: A Review of Patient-Perceived Quality of Life and Neurocognitive Outcome," *World Neurosurgery*, vol. 82, no. 1–2. Elsevier Inc., pp. e299–e309, 2014, doi: 10.1016/j.wneu.2014.02.033.
[45] M. J. B. Taphoorn, "Neurocognitive Sequelae in the Treatment of Low-Grade Gliomas," in *Seminars in Oncology*, 2003, vol. 30, no. 6 SUPPL. 19, pp. 45–48, doi: 10.1053/j.seminoncol.2003.11.023.
[46] R. Liu, M. Page, K. Solheim, S. Fox, and S. M. Chang, "Quality of life in adults with brain tumors: Current knowledge and future directions," *Neuro-Oncology*, vol. 11, no. 3. pp. 330–339, Jun. 2009, doi: 10.1215/15228517-2008-093.
[47] D. N. Louis *et al.*, "The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary," *Acta Neuropathologica*, vol. 131, no. 6. Springer Verlag, pp. 803–820, Jun. 01, 2016, doi: 10.1007/s00401-016-1545-1.
[48] P. D. Delgado-López, E. M. Corrales-García, J. Martino, E. Lastra-Aras, and M. T. Dueñas-Polo, "Diffuse low-grade glioma: a review on the new molecular classification, natural history and current management strategies," *Clinical and Translational Oncology*, vol. 19, no. 8. Springer-Verlag Italia s.r.l., pp. 931–944, Aug. 01, 2017, doi: 10.1007/s12094-017-1631-4.

[49] D. N. Louis *et al.*, "The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary," *Acta Neuropathologica*, vol. 131, no. 6. Springer Verlag, pp. 803–820, Jun. 01, 2016, doi: 10.1007/s00401-016-1545-1.
[50] U. Herrlinger*et al.*, "Gliomatosis cerebri: no evidence for a separate brain tumor entity," *Acta Neuropathologica*, vol. 131, no. 2, pp. 309–319, Feb. 2016, doi: 10.1007/s00401-015-1495-z.
[51] A. Olar*et al.*, "IDH mutation status and role of WHO grade and mitotic index in overall survival in grade II–III diffuse gliomas," *Acta Neuropathologica*, vol. 129, no. 4, pp. 585–596, Apr. 2015, doi: 10.1007/s00401-015-1398-z.
[52] D. E. Reuss *et al.*, "IDH mutant diffuse and anaplastic astrocytomas have similar age at presentation and little difference in survival: a grading problem for WHO," *Acta Neuropathologica*, vol. 129, no. 6, pp. 867–873, Jun. 2015, doi: 10.1007/s00401-015-1438-8.
[53] D. N. Louis *et al.*, "The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary," *Acta Neuropathologica*, vol. 131, no. 6. Springer Verlag, pp. 803–820, Jun. 01, 2016, doi: 10.1007/s00401-016-1545-1.
[54] F. Sahm*et al.*, "Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma," *Acta Neuropathologica*, vol. 128, no. 4, pp. 551–559, 2014, doi: 10.1007/s00401-014-1326-7.
[55] radiopaedia, "diffuse astrocytoma." radiopaedia.org/articles/diffuse-astrocytoma-1?lang=us (accessed Jan. 22, 2021).
[56] Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org. From the case rID: 59598
[57] V. W. Stieber, "Low-grade Gliomas," *Current Treatment Options in Oncology*, vol. 2, pp. 495–506, 2001.
[58] F. Pignatti*et al.*, "Prognostic factors for survival in adult patients with cerebral low-grade glioma," *Journal of Clinical Oncology*, vol. 20, no. 8, pp. 2076–2084, Apr. 2002, doi: 10.1200/JCO.2002.08.121.
[59] D. Schiff, P. D. Brown, and C. Giannini, "Outcome in adult low-grade glioma The impact of prognostic factors and treatment VIEWS & REVIEWS," 2007.
[60] D. Schiff, "Low-grade Gliomas."
[61] F. Pignatti*et al.*, "Prognostic factors for survival in adult patients with cerebral low-grade glioma," *Journal of Clinical Oncology*, vol. 20, no. 8, pp. 2076–2084, Apr. 2002, doi: 10.1200/JCO.2002.08.121.
[62] R. B. Jenkins *et al.*, "A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma," *Cancer Research*, vol. 66, no. 20, pp. 9852–9861, Oct. 2006, doi: 10.1158/0008-5472.CAN-06-1796.
[63] B. G. Baumert *et al.*, "Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study," *The Lancet Oncology*, vol. 17, no. 11, pp. 1521–1532, Nov. 2016, doi: 10.1016/S1470-2045(16)30313-8.
[64] C. Houillier*et al.*, "IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas From the Service de Neurologie 2-Mazarin (C Supplemental data at www.neurology.org," 2010. [Online]. Available: www.neurology.org.
[65] "Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas," *New England Journal of Medicine*, vol. 372, no. 26, pp. 2481–2498, Jun. 2015, doi: 10.1056/NEJMoa1402121.
[66] J. E. Eckel-Passow*et al.*, " Glioma Groups Based on 1p/19q, IDH , and TERT Promoter Mutations in Tumors ," *New England Journal of Medicine*, vol. 372, no. 26, pp. 2499–2508, Jun. 2015, doi: 10.1056/nejmoa1407279.
[67] richardwinn, *youmans and winnneurlogicalsurgery* . 2017.
[68] M. Watanabe, R. Tanaka, and N. Takeda, "Diagnostic Neuroradiology Magnetic resonance imaging and histopathology of cerebral gliomas," 1992.
[69] E. Dugdale and G. Gerrard, "Low-grade gliomas in adults," *CME Cancer Medicine*, vol. 3, no. 3. pp. 40–45, 2006, doi: 10.3171/2011.7.jns10238.
[70] M. Law *et al.*, "Glioma Grading: Sensitivity, Specificity, and Predictive Values of Perfusion MR Imaging and Proton MR Spectroscopic Imaging Compared with Conventional MR Imaging."
[71] R. Leiguarda', I. J. Sierra, and C. P. David Zambranod, "Effect of Large Doses of Méthylprednisolone on Supratentorial Intracranial Tumors A Clinical and CAT Scan Evaluation," 1985.
[72] A. Elkhaled*et al.*, "Magnetic Resonance of 2-Hydroxyglutarate in IDH1-Mutated Low-Grade Gliomas." [Online]. Available: www.ScienceTranslationalMedicine.org.
[73] M. Watanabe, R. Tanaka, and N. Takeda, "Diagnostic Neuroradiology Magnetic resonance imaging and histopathology of cerebral gliomas," 1992.
[74] E. Dugdale and G. Gerrard, "Low-grade gliomas in adults," *CME Cancer Medicine*, vol. 3, no. 3. pp. 40–45, 2006, doi: 10.3171/2011.7.jns10238.
[75] M. L. Bondy*et al.*, "Brain tumor epidemiology: Consensus from the Brain Tumor Epidemiology Consortium," *Cancer*, vol. 113, no. 7. pp. 1953–1968, Oct. 01, 2008, doi: 10.1002/cncr.23741.
[76] E. H. Raabe *et al.*, "BRAF activation induces transformation and then senescence in human neural stem cells: A pilocytic astrocytoma model," *Clinical Cancer Research*, vol. 17, no. 11, pp. 3590–3599, Jun. 2011, doi: 10.1158/1078-0432.CCR-10-3349.
[77] H. Yan *et al.*, "IDH1 and IDH2 Mutations in Gliomas A bs tr ac t," 2009.
[78] A. Poretti, A. Meoded, K. J. Cohen, M. A. Grotzer, E. Boltshauser, and T. A. G. M. Huisman, "Apparent diffusion coefficient of pediatric cerebellar tumors: A biomarker of tumor grade?," *Pediatric Blood and Cancer*, vol. 60, no. 12, pp. 2036–2041, Dec. 2013, doi: 10.1002/pbc.24578.
[79] Case courtesy of Dr Prashant Mudgal, Radiopaedia.org. From the case rID: 26827
[80] Case courtesy of Dr Prashant Mudgal, Radiopaedia.org. From the case rID: 26827

[81] E. G. Shaw *et al.*, "Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: Results of a prospective clinical trial - Clinical article," *Journal of Neurosurgery*, vol. 109, no. 5, pp. 835–841, Nov. 2008, doi: 10.3171/JNS/2008/109/11/0835.
[82] E. Shaw *et al.*, "Prospective randomized trial of low-versus high-dose radiation therapy in adults with supratentorial low-grade glioma: Initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group Study," *Journal of Clinical Oncology*, vol. 20, no. 9, pp. 2267–2276, May 2002, doi: 10.1200/JCO.2002.09.126.
[83] A. B. M F Karim *et al.*, "549 550 I. J. Radiation Oncology 0," 1996.
[84] M. Bolla*et al.*, "Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: Long-term results of a randomised controlled trial (EORTC trial 22911)," *The Lancet*, vol. 380, no. 9858, pp. 2018–2027, 2012, doi: 10.1016/S0140-6736(12)61253-7.
[85] M. J. van den Bent *et al.*, "Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diff use low-grade gliomas," *Lancet Oncology*, vol. 12, pp. 583–593, 2011, doi: 10.1016/S1470.
[86] "s0140-6736%2802%2911398-5 (2)."
[87] L. Douw *et al.*, "Articles Cognitive and radiological eff ects of radiotherapy in patients with low-grade glioma: long-term follow-up," *The Lancet Neurology*, vol. 8, pp. 810–818, 2009, doi: 10.1016/S1474.
[88] B. J. Fisher *et al.*, "Phase 2 study of temozolomide-based chemoradiation therapy for high-risk low-grade gliomas: Preliminary results of radiation therapy oncology group 0424," in *International Journal of Radiation Oncology Biology Physics*, Mar. 2015, vol. 91, no. 3, pp. 497–504, doi: 10.1016/j.ijrobp.2014.11.012.
[89] E. G. Shaw *et al.*, "Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: Initial results of RTOG 9802," *Journal of Clinical Oncology*, vol. 30, no. 25, pp. 3065–3070, Sep. 2012, doi: 10.1200/JCO.2011.35.8598.
[90] J. C. Buckner *et al.*, "Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma," *New England Journal of Medicine*, vol. 374, no. 14, pp. 1344–1355, Apr. 2016, doi: 10.1056/nejmoa1500925.
[91] F. Chen and M. A. Krasnow, "Progenitor outgrowth from the niche in drosophila trachea is guided by FGF from decaying branches," *Science*, vol. 343, no. 6167, pp. 186–189, 2014, doi: 10.1126/science.1241442.
[92] A. Idbaih*et al.*, "OS5.7 FIRST RESULTS OF THE RANDOMIZED PHASE II TAVAREC TRIAL ON TEMOZOLOMIDE WITH OR WITHOUT BEVACIZUMAB IN 1P/19Q INTACT 1ST RECURRENCE GRADE II AND III GLIOMA."

Article topic: Epidural Hematoma.

Author: Rahaf AlFukaha.

Editor: Zain Alsaddi, Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Overview

An epidural hematoma (EDH) is an extra-axial blood accumulation within the space between the inner table of the skull and the dura mater which is the outermost layer of the meninges. [1] It takes a biconvex lenticular shape due to the dura's adherence to the calvarium, thus not allowing the blood collection to move across sutures.

Intracranial epidural hematomas make up about 1% of all head trauma injuries [2], and while that might seem uncommon, they should be taken seriously when evaluating a serious head injury, as they can be life-threatening if not dealt with immediately and appropriately. EDHs are more common in the young adults age group, 20- to 30-year-olds being the most prone [3] as the dura is not yet heavily attached to the calvarium at this age. And studies showed that its more common in men than women. [1]

Etiology and Pathophysiology

An epidural hematoma is mainly caused by a traumatic injury to the head, like accidental falls (30%), physical abuse (8%), or a motor vehicle crash (53%) [4], but on rare occasions, it could also be due to non-traumatic events such as sinusitis, coagulation disorders, dural metastasis, vascular malformations of the dura, hemorrhagic tumors [5][6], and very rarely, Langerhans cell histiocytosis [7].

The blood collection in epidural hematomas is mostly from an arterial origin, specifically the middle meningeal artery, seeing as almost all the cases of epidural hematomas are largely associated with a fractured skull (approximately 75% in children and 91% in adults), [8] this in turn usually causes a direct tear in the middle meningeal artery due to its close proximity to the dura mater and the table of the skull, with the pterion being the most common site of rupture. In addition to the arterial origin, blood could come from lacerated dural venous sinuses or the middle meningeal vein, though it is less common, accounting to up to 32% in both children and adult age groups. [9] The most common locations an epidural hematoma could manifest in are the temporal or the temporoparietal region if it were an arterial EDH, and the posterior cranial fossa if it were a venous EDH, [10] with the right side being more predominant than the left side.

An earlier study done in 1999 showed that 2 to 5% of patients presented with bilateral epidural hematomas. [11]

Epidural hematomas can also occur at the spinal level, and similarly to intracranial epidural hematomas, they could be due to traumatic, and non-traumatic conditions like arterio-venous malformations of the epidural plexus, spinal tumors, hemangiomas, or systemic disease with an elevated risk of bleeding. [12][13] This entity is called a spinal epidural hematoma, and it is a rare condition that presents with acute back pain at the site of bleeding with radiation to the extremities with probability of Neurological deficits. [14]

Another type of epidural hematomas is the heat hematoma which is usually seen in burned bodies. It is caused by thermal burns which cause contraction and peeling of the dura mater from the skull and then, excretion of the blood from the venous sinuses. Contrary to blunt trauma epidural hematomas, heat hematomas are crescent shaped, like subdural hematomas, and they occur in any intensely burned area, regardless of suture lines. [15]

Clinical Presentation and Complications

Patients with epidural hematomas have a classical presentation of initial loss of consciousness right after the impact, followed by a lucid interval period of several hours [16] in which there is a temporary recovery of consciousness with complete or partial return of neurological status. It is fair to mention that, according to a case study in 1984, 21% of patients with EDHs come with the classical presentation of the lucid interval. [4] And after that, due to the continued expansion of the hematoma, this results in a rapid deterioration of neurological status. The source of bleeding mainly arterial injury of Middle Meningeal artery and could be venous or from bone sources. The mass effect of the hematoma causes an increased cranial pressure, and according to the Monro-Kellie principle; that states that the sum of blood, CSF, and brain volumes in the cranium are constant, [17] this eventually leads to a transtentorial uncal herniation. A series of clinical features develop in response to these events, including ipsilateral pupillary dilation (anisocoria) caused by parasympathetic oculomotor nerve compression, contralateral hemiparesis because of compression of the cerebral peduncle, and the compression to the brain stem causes Cushing triad (elevation in Blood pressure , Bradycardia and Irregular Breathing), and might lead to coma and death if not relieved as soon as possible. Other signs of increased ICP could present like headache, nausea, and vomiting. Early seizures presented in 8% of pediatric patients [18], and 27% of patients were neurologically intact. [8]

The presentation of all these symptoms depends on how rapidly the epidural hematoma is growing within the cranial vault, and the smaller the EDH is, the more likely it will be asymptomatic, it is a rare occasion though.

Also, epidural hematomas may present in a delayed fashion; up to 10% of patients who have sustained a head trauma, were found to have a normal head CT in the initial hours after the event, only for their neurological function to deteriorate rapidly and in a sudden manner, hours later. [19] Delayed epidural hematomas are more associated with a venous injury, rather than an arterial one. [1]

Work up and Diagnosis

Traumatic brain injury cases should be managed thoroughly, starting with following the general trauma protocols. Immediate commencement of neuroprotective measures takes priority over diagnostics, to prevent or minimize secondary brain injuries. Therefore, maintenance of normal O2 saturation, normocapnia, normotension, and euglycemia is essential as a first step of primary survey.

When an epidural hematoma is suspected based on the clinical features, an immediate head CT without IV contrast should be considered as a first line diagnostic procedure. [20] A head CT scan is the golden standard diagnostic model in showing the location of the hematoma, its amount, effect, and the other possible head injuries. An EDH forms a biconvex hyper-dense lesion with smooth margins on a CT scan, it could be accompanied with mass effect signs such as a midline shift (Figure 1). Although some recent studies showed that there is a possibility of the hematoma crossing suture lines in exceedingly rare cases, [21] it mostly does not due to the tight attachment of the dura mater to the skull at the sutures. Focal hypodense areas or presence of "swirl sign" within the EDH indicate active hyperacute bleeding in most patients (Figure 2).

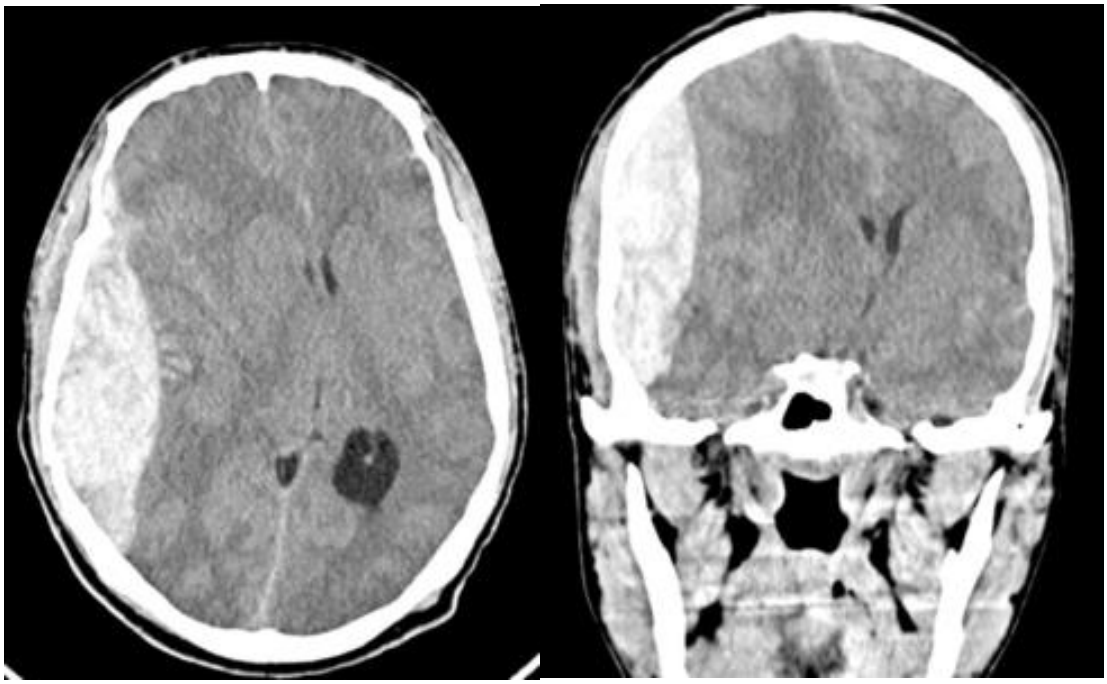


Figure (1) A. Axial non-contrast CT. **B.** Coronal non-contrast CT.

Large right convexity lentiform collection with several mass effect on the right cerebral hemisphere, leftward midline shifts with a right temporal bone fracture. Case courtesy of Dr Michael P Hartung. [30]

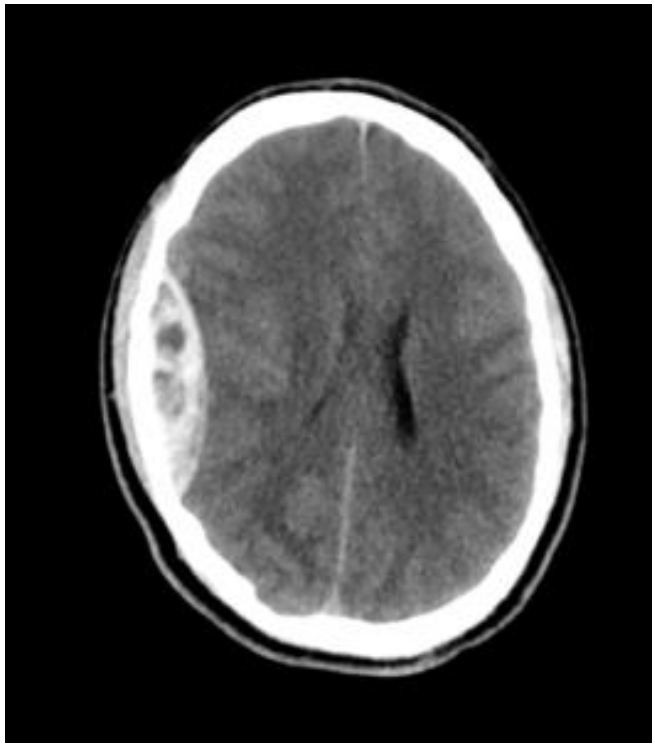


Figure (2) Axial non-contrast CT.
Heterogeneous appearance of a swirl sign, suggestive of active bleeding.

Case courtesy of Dr Henry Knipe. [31]

A repeat of head CT scan is highly recommended for trauma patients who have suffered significant head injuries, and have either failed to improve, have had a secondary neurological deterioration, or have had an inexplainable increase in intracranial pressure, as a delayed epidural hematoma should be suspected [22] [23]. Repetition of the CT scan allows for a more comprehensive observation of the growth of the hematoma on subsequent scans.

Head MRI without contrast could be considered in patients with neurological decline that is not explained by CT findings. It could also be used when having a difficulty differentiating between an epidural and a subdural hematoma or empyema on a CT scan. Epidural hematomas on MRI have similar features to those on CT scan, they show focal hypo-intensity on T2 sequence. While MRI is the preferred imaging tool in cases of suspected spinal EDH, because of its higher resolution properties, when compared to a spinal CT. [1]

Furthermore, CT angiography should be considered if vascular malformations are suspected, [24] and venography if cerebral venous sinus thrombosis is suspected. [25]

Other laboratory studies, like coagulation panel, and liver function tests, should be done to check for underlying coagulopathies or bleeding tendencies.

Treatment and Management

As aforementioned, it is extremely important to effectively diagnose an epidural hematoma and to set a management plan as soon as possible, because the outcome of the patients after treatment depends on how fast they get it, amongst other factors. Management of EDH patients starts with the general ABC principle, maintenance of ICP, and then a rapid neurologic evaluation to decide the next steps of treatment. [26]

The primary modality of treatment of an EDH is surgical evacuation, as it is considered a surgical emergency. The procedures which usually performed are craniotomy or decompressive craniectomy, they are both effective, but craniectomy performed for Epidural hematoma with moderate to severe brain edema in which we evacuate the hematoma and remove the bone. There is also a conservative, non-surgical choice, and the decision to choose between a surgical and a non-surgical approach depends on patient's neurologic evaluation and characteristics of their hematoma. An epidural hematoma could be managed conservatively if it is less than 30 cm^3, less than 15 mm in thickness, with a midline shift of no more than 5 mm, and the patient's Glasgow coma scale (GCS) is above 8 with no visible neurological deficits. The patient should undergo a

series of CT scans and should be closely monitored, as the hematoma could expand. As for surgery indications, an acute epidural hematoma with a volume more than 30 cm^3, regardless of the GCS, or an epidural hematoma in a patient whose GCS is less than 9 and has pupillary abnormalities, should be immediately evacuated. [8]

Risk factors and Prognosis

Numerous studies showcased the different prognostic factors and their effect on patient outcome following treatment, they all mostly agreed that older age, time taken before treatment initiation, presence of lucid interval and pupillary abnormalities, GCS score on admission, CT findings including signs of active bleeding, and high postoperative ICP, are all related to poorer prognosis, while the exact location of the hematoma and the cause of the trauma had no influence whatsoever on the outcome of EDH patients. [27] Epidural hematomas have a better prognosis than other brain lesions following a head trauma. [28] It has a high mortality rate that can reach up to 10% in centers with neurosurgical facilities. [29]

Prevention

Since most cases of EDHs are traumatic in nature, prevention consists of raising awareness about the importance of using seatbelts and car seats, and wearing helmets for riding bikes, skateboards, and horses.

References

1- Khairat A, Waseem M. Epidural Hematoma. 2021 Feb 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 30085524.

2- Maugeri, Rosario et al. “Conservative vs. Surgical Management of Post-Traumatic Epidural Hematoma: A Case and Review of Literature.” *The American journal of case reports* vol. 16 811-7. 14 Nov. 2015, doi:10.12659/ajcr.895231

3- Chicote Álvarez E, González Castro A, Ortiz Lasa M, Jiménez Alfonso A, Escudero Acha P, Rodríguez Borregán JC, Peñasco Martín Y, Dierssen Sotos T. Epidemiology of traumatic brain injury in the elderly over a 25 year period. Rev Esp Anestesiol Reanim. 2018 Dec;65(10):546-551.

4- Bricolo, A. P., & Pasut, L. M. (1984). *Extradural Hematoma: Toward Zero Mortality. Neurosurgery, 14(1), 8–12*. doi:10.1227/00006123-198401000-00003

5- Kihara K, Sato M, Kado K, Fukuda K, Nakamura T, Yamakami I. [A case of acute intracranial epidural hematoma caused by chronic nasal sinusitis]. No Shinkei Geka. 2015 Jan;43(1):69-74. Japanese. doi: 10.11477/mf.1436202949. PMID: 25557102.

6- Saha, Biplab, and Aditi Saha. “Spontaneous Epidural Hemorrhage in Sickle Cell Disease, Are They All the Same? A Case Report and Comprehensive Review of the Literature.” *Case reports in hematology* vol. 2019 8974580. 26 Jun. 2019, doi:10.1155/2019/8974580

7- Lee KW, McLeary MS, Zuppan CW, Won DJ. Langerhans' cell histiocytosis presenting with an intracranial epidural hematoma. Pediatr Radiol. 2000 May;30(5):326-8. doi: 10.1007/s002470050750. PMID: 10836596.

8- Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute epidural hematomas. *Neurosurgery*. 2006;58(suppl 3):S7-S15, discussion Si-Siv.

9- Mohanty A, Kolluri VR, Subbakrishna DK, Satish S, Mouli BA, Das BS. Prognosis of extradural haematomas in children. Pediatr Neurosurg. 1995;23(2):57-63. doi: 10.1159/000120936. PMID: 8555096.

10- Mutch CA, Talbott JF, Gean A. Imaging Evaluation of Acute Traumatic Brain Injury.. *Neurosurg Clin N Am*. 2016; 27 (4): p.409-39. doi: 10.1016/j.nec.2016.05.011

11- Wester K. Decompressive surgery for "pure" epidural hematomas: does neurosurgical expertise improve the outcome? Neurosurgery. 1999 Mar;44(3):495-500; discussion 500-2. doi: 10.1097/00006123-199903000-00034. PMID: 10069586.

12- Hsieh CT, Chiang YH, Tang CT, Sun JM, Ju DT. Delayed traumatic thoracic spinal epidural hematoma: a case report and literature review. Am J Emerg Med. 2007 Jan;25(1):69-71. doi:10.1016/j.ajem.2006.05.033. PMID: 17157687.
13- Heppner PA, Monteith SJ, Law AJ. Spontaneous spinal hematomas and low-molecular-weight heparin. Report of four cases and review of the literature. J Neurosurg Spine. 2004 Sep;1(2):232-6. doi: 10.3171/spi.2004.1.2.0232. PMID: 15347012.
14- Al-Mutair, Abdulaziz BHSc, MBChB, FRCSC; Bednar, Drew A. MD, FRCSC Spinal Epidural Hematoma, American Academy of Orthopaedic Surgeon: August 2010 - Volume 18 - Issue 8 - p 494-502
15- Kawasumi, Y., Usui, A., Hosokai, Y., Sato, M., & Funayama, M. (2013). *Heat haematoma: Post-mortem computed tomography findings. Clinical Radiology, 68(2), e95–e97.* doi:10.1016/j.crad.2012.10.019
16- Ganz, J. C. (2013). *The lucid interval associated with epidural bleeding: evolving understanding. Journal of Neurosurgery, 118(4), 739–745.* doi:10.3171/2012.12.jns121264
17- Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. Neurology. 2001 Jun 26;56(12):1746-8. doi: 10.1212/wnl.56.12.1746. PMID: 11425944.
18- Ben Abraham R, Lahat E, Sheinman G, Feldman Z, Barzilai A, Harel R, Barzilay Z, Paret G. Metabolic and clinical markers of prognosis in the era of CT imaging in children with acute epidural hematomas. Pediatr Neurosurg. 2000 Aug;33(2):70-5. doi: 10.1159/000028990. PMID: 11070432.
19- Di Rocco, A., Ellis, S. J., & Landes, C. (1991). Delayed epidural hematoma. Neuroradiology, 33(3), 253–254. doi:10.1007/bf00588229
20- Cooper PR, Maravilla K, Moody S, Clark WK. Serial computerized tomographic scanning and the prognosis of severe head injury. Neurosurgery. 1979 Nov;5(5):566-9. doi: 10.1227/00006123-197911000-00004. PMID: 534064.
21- Huisman TA, Tschirch FT. Epidural hematoma in children: do cranial sutures act as a barrier? J Neuroradiol. 2009 May;36(2):93-7. doi: 10.1016/j.neurad.2008.06.003. Epub 2008 Aug 12. PMID: 18701165.
22- Bucci MN, Phillips TW, McGillicuddy JE. Delayed epidural hemorrhage in hypotensive multiple trauma patients. Neurosurgery. 1986 Jul;19(1):65-8. doi: 10.1227/00006123-198607000-00009. PMID: 3748339.
23- Fankhanser H, Uske A, de Tribolet N (1983) Les hematomes epiduraux retardes. Neurochirurgie 29:255-260
24- Shankar JJ, Lum C, Chakraborty S, Dos Santos M. Cerebral vascular malformations: Time-resolved CT angiography compared to DSA. *The neuroradiology journal*. 2015; 28 (3): p.310-5. doi: 10.1177/1971400915589682
25- Mutch CA, Talbott JF, Gean A. Imaging Evaluation of Acute Traumatic Brain Injury. *Neurosurg Clin N Am*. 2016; 27 (4): p.409-39. doi: 10.1016/j.nec.2016.05.011
26- Vella MA, Crandall ML, Patel MB. Acute Management of Traumatic Brain Injury. Surg Clin North Am. 2017 Oct;97(5):1015-1030. doi: 10.1016/j.suc.2017.06.003. PMID: 28958355; PMCID: PMC5747306.
27- Servadei, F. (1997). *Prognostic factors in severely head injured adult patients with epidural haematoma's. Acta Neurochirurgica, 139(4), 273–278.* doi:10.1007/bf01808821
28- Maas AI, Steyerberg EW, Butcher I, Dammers R, Lu J, Marmarou A, Mushkudiani NA, McHugh GS, Murray GD. Prognostic value of computerized tomography scan characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007 Feb;24(2):303-14. doi: 10.1089/neu.2006.0033. PMID: 17375995.
29- HOOPER R. Observations on extradural haemorrhage. Br J Surg. 1959 Jul;47:71-87. doi: 10.1002/bjs.18004720114. PMID: 14403008.
30- Case courtesy of Dr Henry Knipe, Radiopaedia.org. From the case rID: 46346
31- Case courtesy of Dr Michael P Hartung, Radiopaedia.org. From the case rID: 74950

Article topic: Cerebral Vasospasm.

Author: Mahmoud Algharabli.

Editor: Philip Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

History of cerebral vasospasm

Cerebral vasospasm was firstly described by an English physician called Sir William's gull in 1859. He had published a case report of Mrs. Fanny S—, a 30-year-old female patient. It had all started with a subarachnoid hemorrhage (SAH) in November 4,1850 that involved transient loss of consciousness, vomiting and nausea. She was admitted to the hospital on the next day comatosed with right hemiplegia. On the third day of admission, she had regained her consciousness and was able to eat. On the fourth day of admission, she was able to recognize a family member like her "cousin." However, on the fifth day of admission, she had developed progressive neurological deterioration and died 6 days post SAH. At autopsy, a large middle cerebral artery (MCA) aneurysm rupture was recognized close to a second unruptured aneurysm in a background of large clot in the sylvian fissure and there was softening in many areas of the brain. The findings that were discovered at autopsy and the timeline of the signs and symptoms of the patient are all directing to cerebral infarction due to cerebral vasospasm, although it wasn't known at that time.(1) Since sir William first description about cerebral vasospasm, many investigators to date are studying this phenomenon to understand its pathophysiology and causes.

Introduction

Cerebral vasospasm is a phenomenon that can be defined in 2 ways, a clinical or an angiographic definition. Angiographic cerebral vasospasm is defined as the narrowing of the dye column seen in major cerebral arteries that is often focal but could be diffuse. This narrowing depends on the timeline of the SAH which is rarely pronounced before day 4 of the initial hemorrhage and reach the peak at day 7. At that window of time, 40 to 60% will have some reduction in the diameter of the one or more of the arteries of circle of willis. (2-13) On the other hand, clinical vasospasm is defined as the consequences of cerebral arterial narrowing and is marked by the insidious onset of confusion and decreased level of consciousness followed by motor and sensory focal deficits. Although, clinical vasospasm usually parallels with the presence of angiographic vasospasm, there are 70% of patients that may develop angiographic

narrowing of arteries and only 20% to 30% will manifest neurological deficits. (14-17) The contradiction between the incidence of angiographic and clinical vasospasm is best understood by the differences in the location and degree of arterial narrowing and the adequacy of collateral circulation. There are studies reporting that the timeline onset of vasospasm occurs at least 3 days after the aneurysmal rupture of arteries and usually parallels with clinical deterioration. It was found that Vessel narrowing peak at 5 to 14 days and gradually resolves within 2 to 4 weeks.(18-20), a term called delayed cerebral ischemia (DCI) which is defined as neurological deterioration presumed to be related to reduced blood supply that lasts for more than an hour and does not have an identifiable cause.(21)

Because of this, arterial narrowing became accepted as the underlying mechanism of DCI. Although Cerebral vasospasm occur due to aneurysmal SAH in clinical practice, there are reasons that may lead to it as a rare consequence of traumatic subarachnoid hemorrhage (SAH), ruptured vascular malformations, hemorrhagic brain tumors, and for sure any condition that results in extensive bleeding into the subarachnoid space beneath the brain.

Epidemiology, etiology, pathophysiology, diagnosis and different types of cerebral vasospasm prevention and treatments will be discussed in this article.

Epidemiology

The incidence and prevalence of cerebral vasospasm is strongly correlated to aSAH as it is the main reason. It was estimated that 30.000 of north American patients experience aneurysmal subarachnoid hemorrhage (aSAH) each year and of these 12-30% has been estimated to get cerebral vasospasm. (22-23) 50% of patients suffering from aSAH die before reaching medical care. Of those who reach an acceptable neurosurgical center and have their aSAH treated, an estimated 14% die or sustain a significant morbidity due to cerebral vasospasm. (23) Overall incidence of Angiographic vasospasm after rupture of an aneurysm is from 50% to 90%. (24)

Predication of vasospasm

Vasosapasm can be predicated in patients after SAH based on CT-finding of the initial hemorrhage and non-CT predicative risk factors. C. Miller Fisher was the first one to develop a grading scale to assess the risk of developing vasospasm based on CT-findings in 1980. He had concluded that a localized clot or diffuse blood greater than 1 mm was highly predicative risk factor of developing vasospasm.(25) The scale was criticized greatly and many modifications has been made on it due to lack in difference between grade 1,2 in the clinical picture with grade 3,4 and the presence of interventricular bleeding (IVB) with thick cisternal clots doesn't change the patient clinical picture.(26-

29) As a a matter of fact, a modified fisher grade had been developed by n, Frontera et al which it was found as a good predictive of symptomatic vasospasm (not DCI) (30-31) "**Figure 1**".

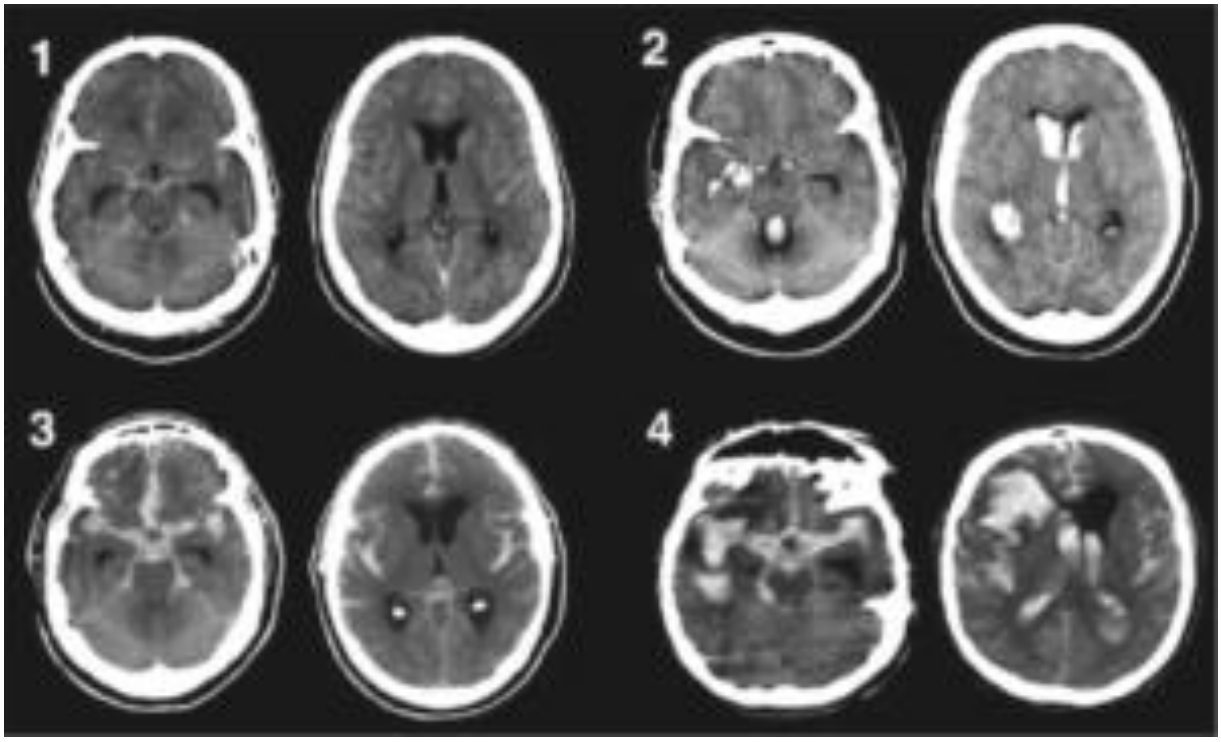


Figure 1: The Modified Fisher CT rating scale: Grade 1 (minimal or diffuse thin SAH without IVH), indicating low risk for symptomatic vasospasm; Grade 2 (minimal or thin SAH with IVH); and Grade 3 (thick cisternal clot without IVH), indicating intermediate risk for symptomatic vasospasm; and Grade 4 (cisternal clot with IVH), indicating high risk for symptomatic vasospasm. (Reproduced with permission from Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, Connolly ES Jr, Mayer SA: Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. Stroke 32:2012-2020, 2001. From: Frontera: Neurosurgery, Volume 59(1). July 2006.21-27(30-31)

FISHER GRADE

Group	Blood on CT
1	No SAH detected
2	Diffuse or vertical layer of subarachnoid blood < 1mm thick
3	Localised clot and/or vertical layer within the subarachnoid space > 1mm thick
4	ICH or IVH with diffuse or no SAH

MODIFIED FISHER GRADE

		No SAH	Thin SAH	Thick SAH	IVH
0	No SAH, no IVH	+	-	-	-
1	Thin diffuse or focal SAH, no IVH	-	+	-	-
2	Thin diffuse or local SAH with IVH	-	+	-	+
3	Thick focal or diffuse SAH, no IVH	-	-	+	-
4	Thick local or diffuse SAH with IVH	-	-	+	+

Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES, Loch Macdonald R, Mayer SA. Prediction of symptomatic vasospasm after subarachnoid haemorrhage: the modified Fisher scale. Neurosurgery 2006; 59(7): 21-27
On the commentary section of the paper Dr Christopher S Ogilvy correctly noted that "same incidence of vasospasm for Grade 2 and 3 patients with identical odds ratios". He further suggested because of this the grading system should have had one less grade

Figure 2: the difference between the classical and modified fisher scales (30-31)

Non-CT findings predicative of vasospasm

They include loss of consciousness (LOC) at the time of rupture, smoking, diabetes mellitus (DM), hyperglycemia or bad neurological grade on admission. (32-34) The location of the ruptured aneurysm as distal anterior cerebral aneurysm also has a high incidence of symptomatic vasospasm (35).

Etiology and pathogenesis

As we discussed above, the etiology of cerebral vasospasm has many reasons but are rare except aSAH. This allowed us to explore the pathogenesis of cerebral vasospasm in the background of aSAH. The pathogenesis of cerebral vasospasm is poorly understood. The uncertainty of vasospasm mechanism is due to the controversy of histopathological changes in the involved arteries as it was reported that the morphology of narrowed arteries are normal following experimental SAH (36), in comparison to the microscopic alterations that occur in vasospasm which we have few information about them. Many changes have been described such as: platelet adhesion within the lumen and aggregation with white blood cells adhesion and thrombus formation, (37-38) increased endothelial pinocytotic activity or channel formation, intimal swelling, proliferation, degeneration, and desquamation also opening of interendothelial junctions (39-44) and many more. There was no conclusive evidence forthcoming to indicate whether or not any of these changes are direct causes to the arterial narrowing and development of neurological deficits. Furthermore, to date there is a better perception that blood in the subarachnoid space is related to the development of vasospasm and that there is a very

tight association between vasospasm and the amount of blood in the subarachnoid space (45-51). The bleeding into the subarachnoid space appears to be the core initiating event and knowledge of specific spasmogenic substances released from the clot has not been done definitively (52). Spasmogens supposed to be released include epinephrine, norepinephrine, and angiotensin (53-60). Furthermore, it must be noted that subarachnoid hemorrhage is associated with a sudden increase in intracranial pressure (ICP) and blood pressure with some degree of hypoxia and cerebral ischemia as these factors are implicated in development of vasospasm (61-64). However, the most major modern hypothesis concerning about arterial narrowing is as follows:

1) cerebral arterial smooth muscle cells contraction due to vasoactive substances found in the CSF (52, 65-68), denervation exaggerated sensitivity (69-71,72,73,) or a prostacyclin/thromboxane A2 imbalance. (74-76)

2) Abnormalities of vasodilatory activity due to firstly, prostacyclin/thromboxane A2 imbalance. Arterial wall prostaglandins amount declines progressively following SAH, and this is in association with the progressive endothelial degeneration. (74-76) second of all, hemorrhagic CSF has Oxyhemoglobin which has been shown to inhibit acetylcholine-mediated vasodilatation (77). This acetylcholine-mediated vasodilatation is inhibited by hypoxia from hemorrhage (78) and the arterial adventitial pores may get clogged by fibrin and red blood cells which also contributes to arterial muscle cell hypoxia (79). Furthermore, the hemoglobin (Hgb) found in the CSF may suppress neurogenic vasodilatation (80), and it can also inhibit endothelial derived relaxing factor-induced vasodilatation (Fujiwara S, Kassell NF, unpublished data).

3) Proliferative vasculopathy due to Mitogenic substances found in the thrombocytes which is either found in the subarachnoid clot or those that stuck to the arterial lumen, also the injured endothelium releases a substance that is like those mitogenic factors which may cause proliferation of smooth muscle cells and fibroblasts in the media. (81-82)

4) Vasospasm may be in a part due to an underlying immunoreactive process as it has been shown that IgG and C3 deposits in the medial layer of the arterial wall of patients with chronic spasm. (83) It has been shown that there is an increase in circulating immune complexes. (84)

5) Vasospasm may be an inflammatory process. There was a considerable amount of indirect evidence proposing that vasospasm is a result of inflammatory process taking place in the arterial wall which is also initiated by the surrounding clot (84-88). There are multiple morphological changes congruent with an inflammatory process (87, 88 ,89) as there are leukocytes within the blood vessel wall (91) or stuck to the endothelial surface (Nazar G, Kassell NF, unpublished data), in addition to the experimental responses to nonsteroidal anti-inflammatory agents (NSAIDs) that back up the concept (92-93).

6) Mechanical phenomena are a cause of arterial narrowing as it could be compressed either by periarterial clot or due to deformation of the arachnoid bands which tether the major cerebral arteries in the subarachnoid cisterns (94).

It is obvious that the above hypotheses are pointing toward the substances liberated from the subarachnoid clot as the cause of the development of arterial narrowing.

Recently, it has been proposed that damaged endothelium resulting from the SAH may be linked to the arterial narrowing (95). The underlying mechanism of endothelial damage has not been established but arterial hypertension, increased intracranial pressure and specifically subarachnoid blood all increase transendothelial permeability acutely, either by achieving a higher degree of vesicular transport or channel formation (Sasaki T, Kassell NF, unpublished data). Clinically, contrast enhancement was observed in the basal cisterns where the major cerebral arteries are found indicating increased arterial permeability occurring in certain patients following aneurysmal rupture and these patients are most prone to develop vasospasm (96-99).

In further stages of SAH as subacute or chronic, the endothelial cells of arteries degenerate and there will be a gap of the interendothelial tight junctions which will result in disturbance of blood arterial wall barrier (95). This disturbance of barrier may permit the access of several constrictor substance as catecholamines or prostaglandins to inside smooth muscle cells. Furthermore, platelets may release more constrictor substances as serotonin when they adhere to either disrupted endothelium or naked subendothelium (100-101), also it has been clear that there is depolarization of arterial smooth cells caused by subarachnoid hemorrhage making them in a risk of contraction (102). In addition, damaged endothelium may lead to loss of extraordinarily strong vasodilators as prostacyclin, (66-68) while the secretion of thromboxane A2 from platelets is continuously unopposed.

Moreover, adhering platelets and white blood cells may additively release some vasoactive substances (100-101,103-104). Platelet derived growth factor (PDGF) secreted either from platelets found in the clot of SAH or platelets found stuck on the luminal surface of the arterial wall or related substances released from damaged endothelium, (105-106) or the effects of thrombin, plasmin and fibrinogens spasminogens (107) which all results in proliferation of smooth muscles cells and fibroblasts which may lead to medial thickening and luminal narrowing of arteries.

As a summary, of the above discussion it can be stated that the pathogenesis of cerebral vasospasm is overly complicated, not clearly understood and a multifactorial process.

Clinical presentation

As we discussed previously, vasospasm has multiple terminologies as DCI, clinical and angiographic vasospasm and our concern now is symptomatic vasospasm and delayed cerebral ischemia not angiographic vasospasm.

As we discussed, vasospasm rarely starts before day 3 from the initial insult and its peak is at 7 days so if it occurs and had symptoms it is called clinical cerebral vasospasm. It typically refers to the clinical worsening of symptoms after the initial SAH. A Japanese study discovered through a survey that symptoms were mainly focal deficits coming at first followed by motor paresis then decline in the level of consciousness and no other cause for the neurological worsening can be noticed except cerebral vasospasm in addition to presence for worsening headache, low-grade fever, elevation of blood pressure (108), in the context of exclusion other possible causes of deterioration as hydrocephalus, seizures, metabolic derangement, infection or oversedation. Symptomatic vasospasm is a subjective diagnosis which can be limited to poor prognosis cases in which neurological examination can be difficult as it could be subtle (109). Delayed cerebral ischemia is known as symptomatic vasospasm, infarction attributable to vasospasm, or both (110).

Diagnosis

Detection and monitoring of cerebral vasospasm after aSAH is necessary as both cerebral vasospasm (CV) and delayed cerebral ischemia must be prevented as possible and if they occur then it should be treated as soon as possible (111). Asymptomatic arterial narrowing is extremely frequent after SAH and CV becomes symptomatic only in about 30 % of patients. (112-113) Detection of CV is not based on standardized criteria also neither are the exams to assess related hypoperfusion and ischemia. (114) The following methods are most used in diagnosing cerebral vasospasm:

Transcranial Doppler (TCD) ultrasound

TCD ultrasound is considered the main non-invasive diagnostic tool of cerebral vasospasm (115). Despite variable sensitivity and specificity of TCD, it has class A, level 2 evidence supporting its use in a reliable way in diagnosing cerebral vasospasm. (116) The underlying mechanism of TCD is when the artery narrows, blood flow velocity within it gets high, causing a doppler shift frequency between emitted and reflected waves (117). It is used often to monitor patients with SAH for increases in intracranial blood flow velocity which could be sign of imminent vasospasm. The TCD consists of a 2 MHz ultrasound probe while a probe can be fixed in headset or manually applied on the acoustic windows which is all dependent on the duration of the procedure. Ultrasound waves need to be transmitted to the cerebral circulation, and this can be done through acoustic windows which are regions of the skull either thin bone or foramina and they include the transtemporal, transorbital, suboccipital and submandibular windows (118).

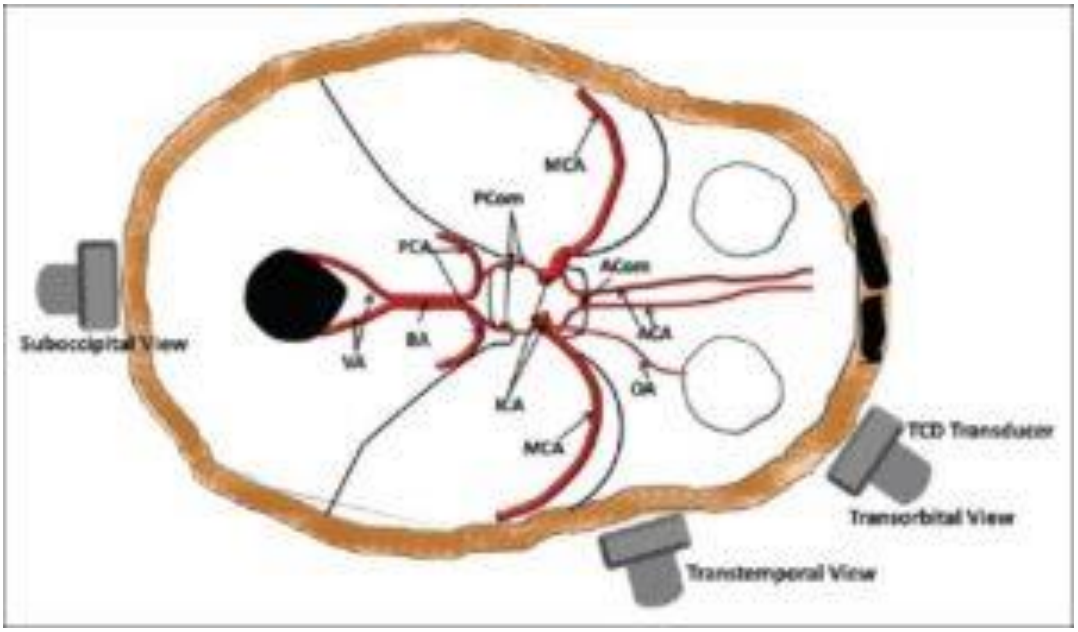


Figure 3: Acoustic windows for insonation of cerebral arteries (118).

Detection of proximal cerebral vasospasm by TCD is excellent as there are segmental and diffuse increases in blood flow velocity in these vessels compared to more distal vessels. (117) Factors such as blood pressure and cerebral blood flow can affect the velocity so distinguishing between vasospastic and hyperemic increases in blood velocity have been established to be facilitated by measuring cervical internal carotid artery (ICA) velocity and intracranial blood velocity. Furthermore, a good association between TCD velocities and vasospasm was established, as velocities in middle cerebral artery (MCA) greater than 120cm/sec are indicative of some degree of vasospasm and those more than 200cm/sec is strongly correlated with severe vasospasm (119).

There are parameters such as Lindegaard ratio (LR), SVIRI ratio and mean flow velocity which all are derived from TCD. The LR can be taken by dividing the mean flow velocity of MCA by those of ipsilateral cranial ICA. The SVIRI ratio can be taken by dividing mean flow velocities of basilar artery (BA) by those of extracranial vertebral artery (VA) (120-121). LR greater than 3 is consistent with vasospasm but in hyperemia the ratio is the same as there is an increase in velocities in both MCA and ICA (117,119).

Utilization of TCD is best when MCA values are clearly low (less than 120cm/sec or very high as more than 200cm/sec), and the respective negative and positive predicative values for significant angiographic vasospasm will reach 90% (122-123). In distal branches (peripheral) TCD is not preferably used as it is unreliable (124), which could be the reason for its failure in correlating with perfusion deficits detected on cerebral blood flow (CBF) studies (125). Based on the above parameters (ratios) vasospasm can be classified into mild moderate and severe and the table will demonstrate it.

Degree of MCA vasospasm (121)	Mean flow velocity(cm/sec)	LR
mild	120-149	3-6
Moderate	150-199	3-6
severe	More than 200	More than 9
Degree of BA vasospasm (126)	**Mean flow velocity(cm/sec)**	**SVIRI ratio**
Presence of vasospasm	More than 70	More than 2
Moderate or severe	More than 85	More than 2.5
severe	More than 85	More than 3

TCD ultrasonography done by skilled technicians is considered useful in many neurosurgical units in surveillance of SAH, but the results must be individualized along with all other information available.

Vascular imaging

The main imagining modalities of medium and large cerebral arteries are computed tomography angiograph (CTA) and digital subtraction angiography (DSA) (127). Magnetic resonance imaging is also considered a useful tool in terms of the information it provides but it is difficult to be done on critically ill-patient (128).

CTA

It is considered a reliable and accurate tool in terms of illustrating the anatomy of intracranial vessels and provides the possibility of rapid diagnosis and monitoring of CV. (129) It is considered the initial screening test which had shown in 10 recent studies that CTA had a cumulative sensitivity and specificity of 80% and 93% respectively but it had failed to be more accurate than DSA (130). However, computed tomography perfusion (CTP) scans recently have been proved to have more diagnostic utility than CTA (131). Utilization of an intuitive visual grading scale as: non, mild (less than 30% narrowing), moderate (between 30% and 60%) and severe (more than 60%) can be used to quantify CV based on each proximal vessel of circle of Willis till its secondary branches (132). CTA interpretation of CV can be limited by the clips and coils used in aneurysmal treatment as they produce artifact. This limitation can be reduced by increasing clip-gantry angle and the use of titanium clips rather than cobalt alloy clips which will reduce the artifact (133).

On admission angiography, early vasospasm within 48 hours of aneurysmal rupture has been noticed in a small percentage of patients with SAH, however without a baseline angiography it is not clear how this diagnosis can be made accurately in all cases (134). To correctly evaluate the degree of CV and to prevent the bias of vessel hypoplasia, each narrowed arterial segment should be compared with the same segment shown in the

previous baseline CTA or even DSA (if it was done at admission for aneurysmal diagnosis and/or early after aneurysm treatment) (132).

DSA

It is considered the gold standard for diagnosing CV the 2-dimensional DSA (2d-DSA) (133-134). It allows accurate quantitively assessment of every intracranial artery, and it allows for the possibility of endovascular intervention if needed (135-136). However, because its invasive nature as a procedure and the is risk of developing complications related to the angiography in 1.3–2.4 % of patients in which about 0.5 % these deficits can be permanent (137-138). Due to its difficulty as it is invasive and it could be complicated, it is necessary to limit angiography only to selected cases to confirm diagnosis and treat resistance to medical therapy.

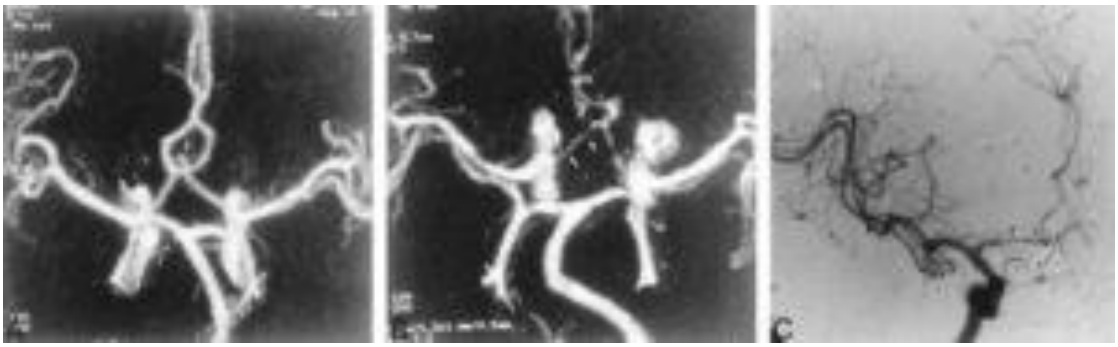


Figure 4: 56-year-old woman with SAH. A Preoperative MIP image from a CTA study shows an anterior communicating artery aneurysm (arrow). B, Postoperative CTA shows clipping of the aneurysm and narrowing of the anterior cerebral artery (arrows), consistent with vasospasm.C, DSA, anteroposterior view, confirms vasospasm involving the A1 segment of the anterior cerebral artery (arrows) (139).

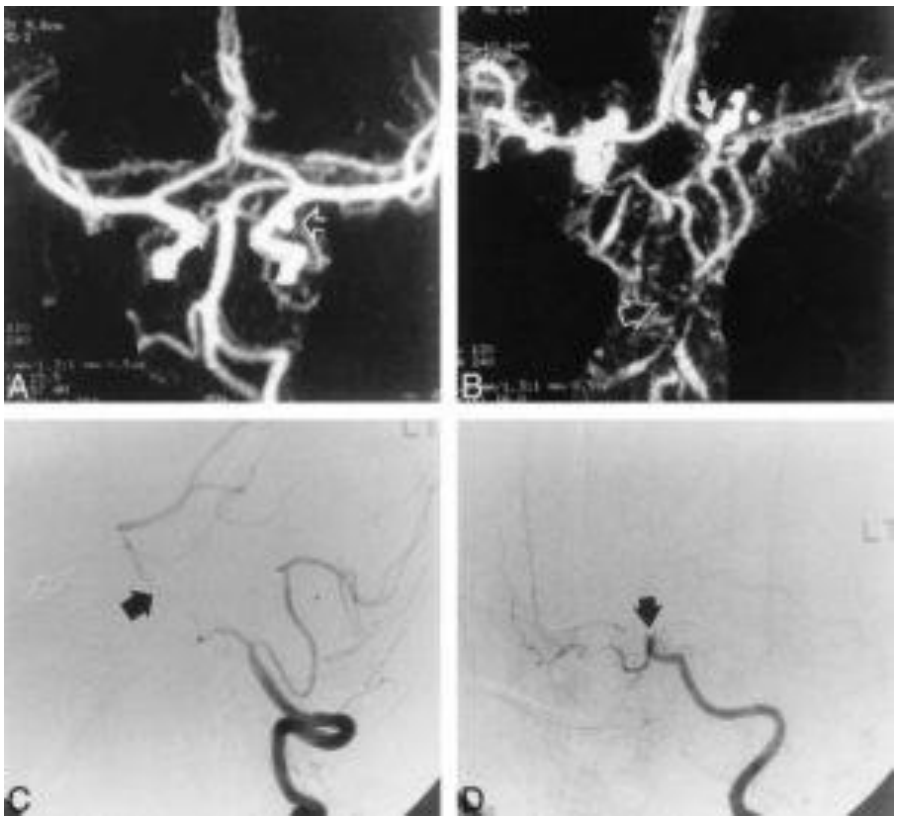


Figure 5: 28-year-old man with an aneurysmal SAH. A, Preoperative CTA, MIP image, reveals a posterior communicating artery aneurysm (arrow). B, Postoperative CTA shows severe basilar artery spasm (open arrow) and carotid artery occlusion (solid arrow). C, DSA, lateral view, confirms basilar arteryvasospasm (arrow). D, DSA, lateral oblique view, verifies supraclinoid ICA occlusion (arrow) (139).

MRI for CV

Perfusion-weighted MRI has been shown to reveal small regions of early ischemic injury, which indicate areas suffering from vasospasm (140). Diffusion weighed MRI shows Decreases in relative cerebral blood volume (CBV) and mean transit time that help in the selection of patients who benefit from triple-H therapy (141).

On the other hand, Magnetic Resonance Angiography (MRA) was initially used for the diagnosis of intracranial aneurysms and vascular stenosis associated with atherosclerosis, it was not routinely applied to the diagnosis of vasospasm until 1995 (142). MRA may now be performed using various flow-independent strategies and is has the ability of addressing both radiographic vessels narrowing, and physiological measurements related to vasospasm (143-144).

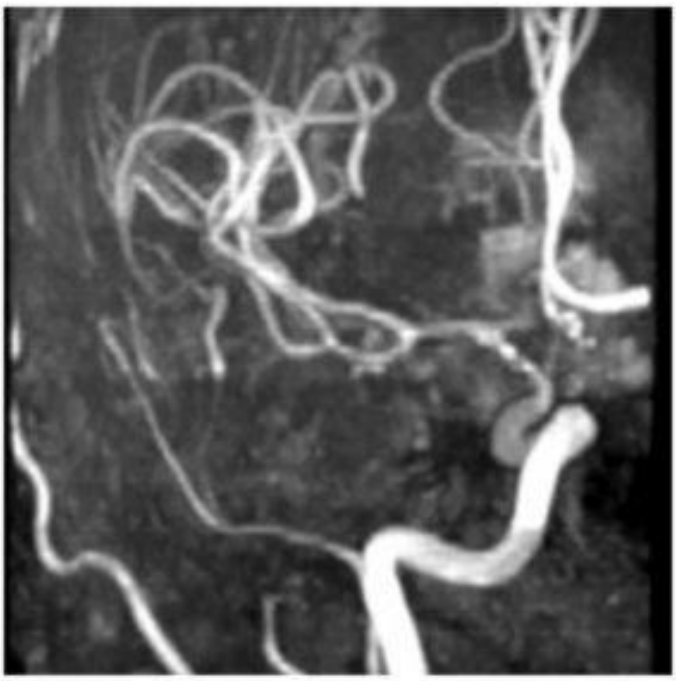


Figure 6: MRA, Vasospasm of the supraclinoid left internal carotid artery, middle cerebral artery, and anterior cerebral artery demonstrated on time-of-flight MRA (145).

Cerebral blood flow and perfusion measurements

There are several modalities for examining cerebral blood flow (CBP) and perfusion. Many of them are old as, positron emission tomography (PET), xenon-enhanced CT (Xe-CT), and single-photon emission computed tomography (SPECT) which are used in evaluation of brain tissue distal to vessels undergoing vasospasm (146).

Xe-CT

This method works based on the administration of intravenous or inhalation of radioactive xenon which is a radiopaque diffusible gas that dissolves quickly in the blood after inhalation and diffuses rapidly into the parenchyma according to blood flow. Xe-CT provides only snapshots over time and measures only the CBF (147).

SPECT

A nuclear imaging tool that measures CBF by detecting flow-dependent uptake of a radioactive tracer which is commonly a technetium-99m coupled to hexamethyl propyleneamine oxime (148). This accumulates in the brain parenchyma proportionally to blood flow, particularly during first pass through the microcirculation (149). Thus, parenchymal flow reduction is noticed independently from its etiology (proximal and or distal CV, brain oedema, hypotension, etc.). Through this diagnostic tool, the entire

brain can be visualized, although resolution is relatively low. In comparison to DSA the Sensitivity and specificity for CV are 89 and 75 %, respectively (150).

PET

A nuclear medicine technique which provides quantitative hemodynamic measures including CBF, CBV, OXYGEN extraction fraction (OEF) and cerebral metabolic rate of oxygen (CMRO2). Tracers include several oxygens (O2) bound isotopes as an example for the isotopes are, 15O-labeled water (151-152) to measure CBF, 15O-labeled carbon monoxide (153) to measure CBV and 15O-labeled oxygen to measure regional OEF (154).

CTP scan

A tool that measures the CBF by studying the cerebral flow dynamic (155) and it works based on a helical CT scanner with an appropriate postprocessing software. It has been used in patients with SAH (156,157), and it is increasingly becoming more popular due to its ease of use, speed of image acquisition and good correlation with DSA for angiographic vasospasm (158). Angiographic vasospasm discovered in patients with 50% and more narrowing are prone to have perfusion deficits with reduced CBF (159), and the degree of angiographic vasospasm correlates with the degree of perfusion impairment as the vascular areas of the spastic vessels is proportional to the more hypoperfused regions (160). CTP can early detect the presence of reduced CBF, delay in mean transit time which are indicative of ischemia, and the status of cerebral blood volume, which is normally kept in penumbral brain but is markedly decreased in established infarcts (161). The sensitivity of CTP In patients with confirmed angiographic vasospasm is 74% and specificity is 93% found in recent meta-analysis (162).

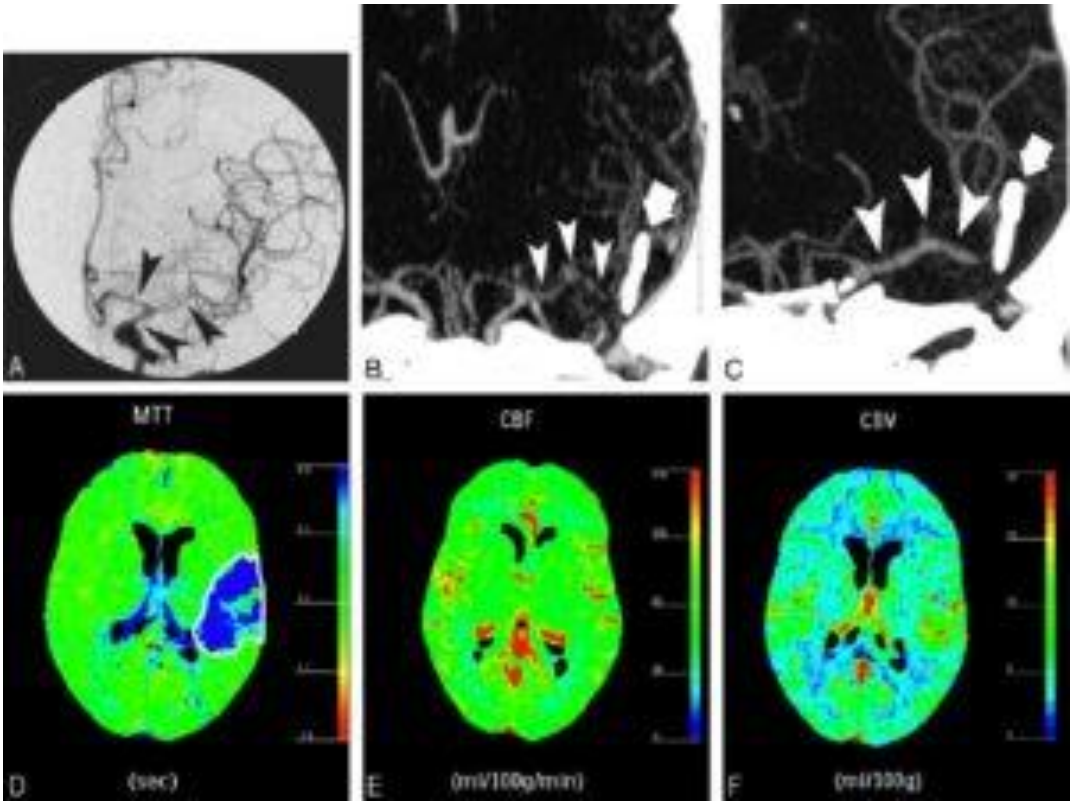


Figure 7: A 44-year-old man with right-sided hemiparesis attributed to cerebrovascular vasospasm occurring 9 days after SAH consecutive to a ruptured aneurysm of the anterior communicating artery, treated by surgical clipping. DSA (*A*) showed moderate vasospasm on M1 segment of left MCA and focal severe vasospasm on the M2 segment (*arrowheads*). These findings were confirmed by MIP MSCTA reconstruction (*B*) and volume-rendered MSCTA reconstruction (*C*). Perfusion CT performed during the same CT session revealed an increase in MTT (*D*) and a decrease in rCBF (*E*), with slight increase of rCBV (*F*). This pattern of perfusion alterations corresponds to a reversible ischemic lesion consecutive to vasospasm. The patient was then treated by a local intra-arterial nimodipine infusion and a balloon angioplasty of the left M1 segment (163).

Invasive Tissue Monitoring

It includes Brain Tissue Oxygen Monitoring and Microdialysis. Brain tissue oxygen monitoring (ptiO2) of SAH showed low cerebral tissue Ph and higher pco2 compared to controls in 2000 the first time it was used (164), and it was evident by subsequent investigation that there is a strong correlation between PtiO2 and vasospasm (165). There is a separate study which suggested that PtiO2 pressure reactivity is a reliable indicator of impaired autoregulation and, by warrant, vasospasm effect (166). There was a questioning about the utility and reliably of Ptio2 as it was explored by some that the relationship between pressure- and oxygen-related indices of vasospasm and clinical outcome had showed a disproportionate relationship (167).

On the other hand, Cerebral microdialysis is a tool that can measure local levels of different metabolic markers including glutamate (168–170), lactate (168, 171), and glucose (171); and correlating these values to areas of ischemia and clinical outcome. Microdialysis has been shown to be by 89% specific for ischemia, through the capability of detecting huge changes in concentrations of lactate, glucose, and glutamate levels before a patient becomes symptomatic in a specific study (172). Higher levels of lactate, nitrite, and taurine was associated with poor neurologic outcome after SAH and all of them was measured by microdialysis (173). Microdialysis by its nature is an invasive tool so it carries risks of cerebral hematoma and infection, along with the possibility of probe malfunctioning or misplacement (174).

Near infrared specterscopy (NIRS)

A tool that may prove to be useful for bedside monitoring of cerebral ischemia following SAH as it is simple, non-invasive tool (175-177). It works by measuring changes in deoxyhemoglobin concentration in cortical vessels (178-179). Quantitative assessment of hemoglobin concentration can be done by specifically time resolved NIRS and in one pilot study it was found to be more sensitive than TCD in diagnosis of CV (180). NIRS detect decline of cortical oxygen saturation, total hemoglobin and oxyhemoglobin during CV (181). Despite some limits as NIRS measures blood oxygenation predominantly in cortical venous blood in specific cortical region in addition to the CSF, the skull, and the other layers of the human head can interfere with the photon signals (182). Eventullay, NIRS provides a continuous and noninvasive metabolic monitoring which can be useful in multimodal approach to management.

Prevention

Over the past few decades, many methods of preventing vasospasm and subsequent DCI were examined but no major breakthroughs in complete prevention have been identified. In the following, we will discuss the most common preventive methods used.

General preventive methods and fluid management

In the acute setting of SAH, patients tend to have volume contraction, (183) and hypovolemia should be avoided. Intentional induction of Hypervolemia and volume expansion therapy is not obviously clear that it is useful in terms of prevention of vasospasm or ischemia, or even possible in patients with normal renal function (184-187). Hydration with 3L of isotonic fluids should be done for all patients daily and there is some evidence that additional colloid infusions such as albumin are beneficial (188). Some patients with SAH may experience excessive natriuresis, known as cerebral salt wasting which is usually related to elevations in brain natriuretic peptide, and they are susceptible to the development of hyponatremia during this time. There may be an

increase in the risk for vasospasm (189) in addition there is an association of cerebral infarction in poor grade patients with hyponatremia. (190) As a result of those facts, hyponatremia in the setting of SAH should be treated with salt replacement in the form of normal or 3% hypertonic saline, combined with fludrocortisone (Florinef) administration (0.3 mg/ day) if the patient is experiencing vasospasm not with fluid restriction. (190,191) Cerebral perfusion pressure (CPP) is very important parameter to monitor and maintain at 70 mm Hg or greater in poor-grade patients in patients with external ventricular drains.(192) Furthermore, perfect ventilation and oxygenation, prevention of fever, maintenance of euglycemia and good nutrition, and attention to electrolytes especially sodium is important in reduction the effects of vasospasm and delayed ischemia.

Calcium channel blockers (CCB)

In terms of prevention of secondary ischemia, CCB was rationally introduced due to its mechanism of blocking the dihydropyridine-type calcium channel, thereby preventing the influx of calcium into the vascular smooth-muscle cells and decreasing the rate of cerebral vasospasm. (193) Nimodipine is considered the only drug that showed decreased cerebral ischemia and improved outcomes in patients with SAH when it is given within 72 hours of presentation. Furthermore, the British aneurysm nimodipine trial that was published in 1989 remains the only drug treatment regimen that has class 1A evidence of efficacy. The study was a double-blind, placebo-controlled trial that randomized 554 patients presenting with SAH to receive either placebo or nimodipine 60 mg every 4 hours, starting within 96 h of presentation. The therapy was for a whole 21 days. At 3 months duration the 2 groups were compared for rates of infarction and poor outcome, as defined by the Glasgow Outcome Scale (GOS) of 1–3 (dead, vegetative state, or severe disability); and rebleeding. In patients given nimodipine, the incidence of cerebral infarction was 22% compared with 34% in patients who received placebo, a statistically significant decrease. In addition, the rate of poor outcome was significantly reduced from 33% in the placebo group to 20% in the treatment group.(194) However, angiographic vasospasm was not reduced (195).

Other calcium channel blockers as nicardipine and diltiazem beneficial effect is inconclusive, in improving outcomes after SAH. Therefore, the exact underlying mechanism by which nimodipine is beneficial remains unknown. (196)

Prophylactic transluminal balloon angioplasty

A prophylactic transluminal balloon angioplasty was tested in a multi-center randomized trial. (197) No benefit was observed in the procedure, and it was responsible for 3 deaths (4%) from vessel rupture, an incidence greater than the 1.1% reported in the literature. (198)

Clot clearance

The process of Clearance of subarachnoid clots is speeded by the use of intracisternal thrombolysis with either recombinant tissue plasminogen activator or urokinase and there is evidence that this is associated with prevention of vasospasm and less cerebral ischemia. (199)

Intrathecal vasodilators

It was observed in a single-center study, nonrandomized cohort study that a Prolonged-release nicardipine implants placed in the subarachnoid space of patients with thick clots and undergoing surgical clipping results to be significantly preventable of vasospasm and ischemia. (200) Similar results were observed in a previous study with papaverine pellets being used. (201) However hopeful, this nicardipine therapy is not clear how it can be used in patients undergone endovascular clipping of aSAH.

Statins

Statins, or 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, shown to be promising in preventing vasospasm. It increases the NO biosynthesis and metabolism which is the proposed mechanism of neuroprotection in vasospasm, as it leads to dilation of cerebral vessels and improved CBF. (202-204)

It was observed that although the delayed ischemic deficits (DID) were less common in the statin-treated patients, there was no significant reduction in poor neurological outcome in meta-analysis of six randomized controlled statin trials. (205) Failure in detection of any benefit in the use of simvastatin on the short or long term, when is given 40mg per day, started within 96 hours of the accident for up to 3 weeks was observed in the international, randomized, and double-blind trial STASH (simvastatin aneurysmal Subarachnoid Hemorrhage) which gathered 803 patients up till 2013. (206) Till now, patients with SAH appeared to not benefit from the addition of statins during the acute stage.

Treatment

As discussed above, preventative methods had a limited impact established so more aggressive interventions are often implemented. The point for instituting these interventions differs widely across centers. Some intervene when there is a rising TCD velocities; others intervene in the setting of angiographic vasospasm in asymptomatic patients, while some require a neurological deterioration before starting aggressive measures. The perfect therapeutic combination is when CBP is improved, reverse or

attenuate DID and low adverse events. Medical and endovascular approaches are being used in combination to reach the ideal management.

Medical therapy

In 1951, it was noted by denny-brown that patients with vasospasm who had concomitant hypotension often developed a worsening neurologic examination. (207-208) In 1982, Wood proposed a hematocrit goal of 30 would be ideal for oxygen transport and improved perfusion. (209) After this, the “Triple-H Therapy”: hypervolemia, hypertension, and hemodilution was proposed. Triple-H therapy theory is based on that the expanded intravascular volume and reduction in blood viscosity would be beneficial in enhancing cerebral perfusion in the setting of vasospasm. (195) Deterioration reversal was observed in in 47 of 58 patients with cerebral vasospasm when given the triple-H therapy. (210) However, no evidence has been appeared indicating that lower than normal packed red blood cell volume is beneficial in stroke as no randomized trials have been performed about it. (211) Hypertension induction is more beneficial than aggressive hypervolemia in improving cerebral oxygenation in patients with vasospasm and has fewer complications. (212) As a matter of fact, when a symptomatic vasospasm is diagnosed or strongly suspected, triple-H therapy can commence by additional volume expansion with an isotonic crystalloid infusion, which elevated CBP in vasospastic territories without a significant change in cardiac indices in euvolemic patients. (213) The risk of hemorrhage from unsecured, unruptured aneurysms in the acute and short-term natural history is not increased by hypertension and hypervolemia. (214) Triple-H therapy important risks are cardiac failure and infarction, pulmonary edema, the complications associated with either central venous catheter or PAC placement, and possibly cerebral edema and raised ICP. (215-217)

Endovascular therapy

If goals of triple-H therapy are not easily met in a patient with persistent signs of cerebral ischemia and the neurological signs do not fade within several hours of hypertension induced therapy toward the target range, or if a patient has poor cardiopulmonary status, it is accepted to proceed directly to endovascular treatment of vasospasm. The most effective way to prevent cerebral infarction and improve neurologic function in medically refractory patients is to start aggressive treatment in less than 2 hours. (218) Delayed treatment (>2 h), however, may still be useful for a considerable number of patients and should be considered even at 12–24 h period after symptom onset (219-220). Standard endovascular therapy includes transluminal balloon angioplasty and intra-arterial vasodilators infusion

Transluminal balloon angioplasty

SAH induced cerebral vasospasm therapy by balloon angioplasty was firstly introduced by Zubkov and colleagues in 1984 (221). It was noted that mechanical angioplasty efficacy was 100% with a complication rate of 1% (222). In contrast to earlier series, in which the efficacy ranged from 11% to 93% and a complication rate of 5% including vessel rupture in 1.1% (223). Results of dilation in Canine models of vasospasm have shown a lasting effect for up to 3 weeks (224-225). This is reflected on the clinical experience as balloon angioplasty is typically effective for the rest of the vasospasm episode and patients rarely require another balloon dilation (226-228). However, it is only effective on the artery where the balloon is inflated, and it is possible to develop symptomatic vasospasm later in an adjacent arterial segment usually distally located.

Moreover, reintervention can occasionally be necessary by balloon dilation of the same vasospastic segment, but it is very uncommon (229). However, a repeated treatment is usually required for an adjacent arterial segment which is morE common (230-231). Although there is a wide consensus that bigger vessels 2–3 mm in diameter, including intradural internal carotid artery, M1 segment of the middle cerebral artery, A1 segment of the anterior cerebral artery, V4 segment of the vertebral artery, basilar artery, and P1 segment of the posterior cerebral artery, may be considered for angioplasty treatment (232), there is a recent report which performed 175 safe angioplasties in distal vessels without procedure-related symptomatic complications (230).

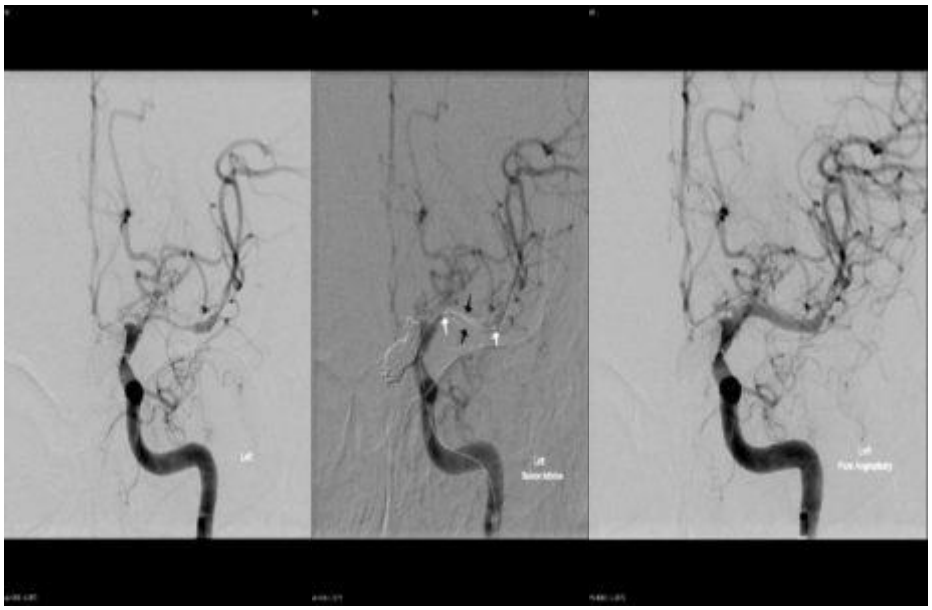


Figure 8: Balloon angioplasty for cerebral vasospasm, Case courtesy of Prof Alan Coulthard, the pre-treatment image shows vasospasm involving the left M1 and A1 segments. An endovascular balloon catheter has been passed through a guiding catheter in the left ICA and directed into the left M1 segment over a micro guide wire. The two markers indicate the proximal and distal extent of the balloon (white arrows). The balloon has been inflated in the middle cerebral artery (black arrows) After angioplasty

the left MCA is of normal caliber. Left hemisphere perfusion is significantly improved (233).

Intra-arterial vasodilators infusion agents

Nicardipine

It is a CCB, which is reported to have improvements in TCD velocities, stable to marginal improvements in ICPS and clinical improvements in majority of patients given nicardipine (234-235). It mainly reverses angiographic vasospasm in treated vessels, with no sustained effect on intracranial pressure or cardiovascular function (236).

verapamil

A CCB, it is observed in severely spastic vessels, intraarterial administration of verapamil can results in up to 53% increase in vessel diameter (44%+- 9%) (237). It is reported to reduce angiographic vasospasm and improve the clinical picture in one third of cases without significant adverse events (237). However, precautions should be taken into account with verapamil use as it is a negative inotrope and may cause heart block and it is known to cause seizures (238-239).

Nimodipine

It was discussed above as a preventive method but as an intraarterial agent, it has similar favorable superior results as verapamil and nicardipine in two small retrospective series (240-241).

Fasudil

It is CCB which primarily works through the inhibition of the Rho-kinase signaling pathway, thus dilating blood vessels through the activation of myosin phosphatase (195, 242-243). Angiographic improvement in all cases and clinical improvement in 44% of cases was reported on 23 consecutive patients. There was a statistically significant decline in MAP and increase in ICP (244).

Milrinone

It is a selective phosphodiesterase III inhibitor affecting cyclic adenosine monophosphate pathways and has inotropic and vasodilatory capabilities (245). Many scattered reports of the potential beneficial effects on the clinical and experimental vasospasm were found when milrinone is administered intravenously, intraarterially or into subarachnoid cisterns (246-249). Milrinone has been used to reverse CV

successfully in patients with confirmed DCI (250-254). Although a recent European survey especially in France showed milrinone potential to become the second most common drug used to treat DCI (255), no randomized controlled trial was done searching for the neurological outcomes. Fifteen full text journal articles were identified using milrinone arterially or venously to treat patients with confirmed DCI in a recent systematic analysis (256).

Prognosis

The prognosis of patients who had cerebral vasospasm and DCI after aSAH is strongly proportional to the severity of SAH and the clinical condition of patient once the accident had occurred. The risk of severe vasospasm is strongly related to those factors. It is necessary to consider angiographic vasospasm is not always correlated to clinical deterioration of the patient. In conclusion, patients suffering from vasospasm are at high risk of cerebral ischemia thus poor neurological outcome (257).

On the horizon “future directions to cerebral vasospasm”

Unfortunately to date, the present literature provides few definitive answers on the strategies of decreasing the impact of the vasospasm following SAH. There are many factors contributing to the difficulty in defining the treatment and preventive methods of vasospasm as the incompletely understood underlying mechanism of vasospasm, complexity of SAH make it hard. Multiple neuroprotective approaches as well as the use of multimodal treatment regimens are being constructed and hold promising results in treatment or preventing vasospasm (258). Some of the future direction will be discussed here as:

Enoxaparin

A randomized clinical trial was done in SAH to study this drug which is a low molecular weight heparin (259). The results showed decline in the incidence of DID and infarcts but the admission characteristics of the two groups were not well balanced.

Nitric oxide donors

It is a free radical gas formed from the substrate L-arginine. In 1987, it was discovered and appeared to play a key role in controlling cerebral vasomotor tone (260). The release of NO is considered an important regulator of resting CBF as inhibiting NO release constrict cerebral arteries and decrease CBF (261-263). Sodium nitroprusside a NO donor given intraventricularly to patients with medically refractory vasospasm had

diverse impacts on CBF and a high rate of adverse events (264). In a study where intrathecal nitroprusside was administered it resulted in clinical and angiographic improvement of vasospasm and excellent outcome without systemic or neurological complications in three patients (265). CTP scan was done, and it had resulted in increased CBF in the nitroglycerin group (266). At present, large randomized and controlled trials of NO donors in SAH are in the planning stage.

Endothelin-1 antagonists

Clazosentan, an ET_A antagonist showed decline in the incidence and severity of angiographic vasospasm in a study of phase IIa trial (267). In addition, Side effects were close to placebo. Furthermore, $ET_{A/B}$ antagonist, TAK-044, was also studied in a phase II trial (268). This drug was tolerated, and it had resulted in Delayed ischemic deficits which occurred in 29.5% of patients taking active treatment and 36.6% of patients on placebo (risk reduction by 0.8). clazosentan was tested very recently in a controlled clinical trial registering 413 patients with SAH (269). It had resulted in considerable reduction in Moderate to severe angiographic spasm, although there was no effect on outcome.

References

1- Gull SW. Cases of aneurism of the cerebral vessels. Guys Hospital Reports 1859;5:281–304.
2- Kassell NF, Drake CG: Review of the management of saccular aneurysms. Neurological Clinics of North America 1: 73-86, 1983 3.
3- Walker MD, Chap XXI-1 Brain and peripheral nervous system tumors in Holland and Frei (eds) Cancer Medicine. Phila: Lee & Ferberger, 1982, p 1603 4. 4-Matsumoto N, Whisnant JP, Kurland LT, Okazaki H: Natural history of stroke in Rochester, Minnesota, 1955 through 1969: An extension of a previous study, 1945 through 1954. Stroke 4: 20-29, 1972
5- Sacco RL, Wolf PA, Kannel WB, McNamara PM: Survival and recurrence following stroke The Framingham study. Stroke 13: 290-295, 1982
6- Graf CJ, Nibbelink DW: Cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Stroke 5: 559-610, 1974
7-Saito I, Sano K: Vasospasm after aneurysm rupture: Incidence, onset, and course. In Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore, Williams & Wilkins, 1980, pp 294-301
8- Bergvall U, Galera R: Time relationship between subarachnoid hemorrhage, arterial spasm, changes in cerebral circulation and posthemorrhagic hydrocephalus. Acta Radiol (Diagn) 9: 229- 237, 1969
9- Kwak R, Niizuma H, Ohi T, Suzuki J: Angiographic study of cerebral vasospasm following rupture of intracranial aneurysms: Part 1. Time of appearance. Surg Neurol 11: 257-262, 1979
10-Weir B, Grace M, Hansen J, Rothberg C: Time course of vasospasm in man. J Neurosurg 48: 173-178, 1978
11-Kagstrom E, Greitz T, Hanson J, Galera R: Changes in cerebral blood flow after subarachnoid hemorrhage. In deVet AC (ed): Proceedings of the Third International Congress of Neurological Surgery, Amsterdam, Excerpta Medica Foundation, 1965, pp 629-633
12- Allcock JM, Drake CG: Ruptured I-C Aneurysms: the role of arterial spasm. J Neurosurg 22: 21-29, 1965 13. Odom GL: Cerebral vasospasm. Clin Neurosurg 22: 29-58, 1975
13- Fletcher TM, Taveras JM, Pool JL: Cerebral vasospasm in angiography for intracranial aneurysms: Incidence and significance in one hundred consecutive angiograms. Arch Neurol 1: 38—47, 195
14-Sundt TM Jr, Whisnant JP: Subarachnoid hemorrhage from intracranial aneurysms. Surgical management and natural history of disease. N Engl J Med 299: 116-122, 1978
15-Post KD, Flamm ES, Goodgold A, Ransohoff J: Ruptured intracranial aneurysms. Case morbidity and mortality. J Neurosurg 46: 290-295, 1977
16-Nibbelink DW, Torner JC, Henderson WG: Intracranial aneurysms and subarachnoid hemorrhage. A cooperative study. Antifibrinolytic therapy in recent onset subarachnoid hemorrhage. Stroke 6: 622-629, 1975
17-Kodama N, Mizoi K, Sakurai Y, Suzuki J: Incidence and onset of vasospasm. In Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore, Williams & Wilkins, 1980, pp 361-365

18- Kagstrom E, Greitz T, Hanson J, Galera R. Changes in cerebral blood flow after subarachnoid hemorrhage, in Proceedings of the Third International Congress of Neurological Surgery, 1965. International Congress Series No. 110. Amsterdam: Excerpta Medica 1966:629-633.
19-. Fisher CM, Roberson GH, Ojemann RG. Cerebral vasospasm with ruptured saccular aneurysm–the clinical manifestations. *Neurosurgery*. 1977;1:245–248.
20-Graham DI, Macpherson P, Pitts LH. Correlation between angiographic vasospasm, hematoma, and ischemic brain dam- age following SAH. *J Neurosurg*. 1983;59:223–230
21-Fisher CM, Roberson GH, Ojemann RG. Cerebral vasospasm with ruptured saccular aneurysm–the clinical manifestations. *Neurosurgery*. 1977;1:245–248
22-Kreiter KT, Mayer SA, Howard G, Knappertz V, Ilodigwe D, Sloan MA, et al. Sample size estimates for clinical trials of vasospasm in subarachnoid hemorrhage. *Stroke*. 2009 Jul. 40 (7):2362-7.
23-Kassell NF, Sasaki T, Colohan AR, Nazar G. Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Stroke*. 1985 Jul-Aug. 16 (4):562-72.
24-1. Dorsch NWC, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage: I. Incidence and effects. J Clin Neurosci. 1994;1:19-
25-Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery. 1980;6(1):1–9.
26-Lagares A, Gómez PA, Alen JF, Lobato RD, Rivas JJ, Alday R. A comparison of different grading scales for predicting outcome after subarachnoid haemorrhage. *Acta Neurochir (Wien)*. 2005 Jan. 147(1):5-16; discussion 16.
27-Ogilvy CS, Carter BS. A proposed comprehensive grading system to predict outcome for surgical management of intracranial aneurysms. *Neurosurgery*. 1998 May. 42(5):959-68; discussion 968-70.
28-Klimo P Jr, Schmidt RH. Computed tomography grading schemes used to predict cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a historical review. *Neurosurg Focus*. 2006. 21(3):E5.
29-Hijdra A, Brouwers PJ, Vermeulen M, van Gijn J. Grading the amount of blood on computed tomograms after subarachnoid hemorrhage. *Stroke*. 1990 Aug. 21(8):1156-61.
30-Frontera JA, Claassen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59(1):21–7
31- Rosen DS, Macdonald RL. Subarachnoid hemorrhage grading scales. UpToDate Inc. UpToDate Web site. https://www.uptodate.com. Published 2020. Updated November 19, 2019. Accessed 5 Feb 2020
32-Harrod, CG, Bendok, BR, Batjer, HH. Prediction of cerebral vasospasm in patients presenting with aneurysmal subarachnoid hemorrhage: a review. *Neurosurgery*. 2005;56:633-654.
33-de Rooij, N, Rinkel, G, Danbaar, J, Frijins, CJ. Delayed cerebral ischemia after subarachnoid hemorrhage: a systematic review of clinical, laboratory, and radiological predictors. *Stroke*. 2013;44:43-54.
34-de Rooij, N, Greving, J, Rinkel, G, Frijins, CJ. Early prediction of delayed cerebral ischemia after subarachnoid hemorrhage: development and validation of a practica
35-Abla, A, Wilson, D, Williamson, R, et al. The relationship between ruptured aneurysm location, subarachnoid hemorrhage clot thickness, and incidence of radiographic or symptomatic vasospasm in patients enrolled in a prospective randomized controlled trial. *J Neurosurg*. 2014;120:391-397
36- Weir B, Erasmo R, Miller J, Mclntyre J, Secord S, Milke B: Vasospasm in response to repeated subarachnoid hemorrhage in the monkey. J Neurosurg 33: 395-406, 1970
37- Grady PA, Blaumanis OR, Nelson ER: Morphology and flow dynamics of focal arterial constriction. In Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore, Williams & Wilkins, 1980, pp 107-112
38- Nelson E, Geitz SD, Rennels ML, Forbes MS, Kawamura J: Scanning transmission electron microscopic studies of arterial endothelium following experimental vascular occlusion. In Cervos-Navarro J, Betz E, Mistokos F, Willenweber R (eds) The Cerebral Vessel Wall. New York: Raven Press, 1976, pp 33-39
39- Sasaki T, Kassell NF, Yamashita M, Fujiwara S: Disturbances of blood-brain barrier and cerebral arterial permeability following experimental subarachnoid hemorrhage. Xllth Annual Meeting of the Society of Neurosurgical Anesthesia and Neurologic Supportive Care, pp 20-22, 1984
40- Fein JM, Flor WJ, Cohan SL, Parkhurst J: Sequential changes of vascular ultrastructure in experimental cerebral vasospasm. Myonecrosis of subarachnoid arteries. J Neurosurg 41: 49-58, 1974
41- Alksne JF, Smith RW: Experimental models of spasm. Clin Neurosurg 24: 216-227, 1977
42- Simeone FA, Ryan KG, Cotter JR: Prolonged experimental cerebral vasospasm. J Neurosurg 29: 357-366, 1968
43- Tanabe Y, Sakata K, Yamada H, Ito T, Takada M: Cerebral vasospasm and ultrastructural changes in cerebral arterial wall. J Neurosurg 49: 229-238, 1978
44- Joris I, Majno G: Endothelial changes induced by arterial spasm.Am J Pathol 102: 346-358, 1981
45-Fisher CM, Kistler JP, David JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery 6: 1-9, 1980
46-. Mizukami M.TakemaeT, Kin H, KawaseT, Araki G: Computed tomography of ruptured intracranial aneurysm in acute stage relationship between vasospasm and high density on CT scan. Brain and Nerve (Tokyo) 30: 861-866, 1978
47- Mizukami M, Takemae T, Tazawa T, Kawase T, Matsuzaki T: Value of computed tomography in the prediction of cerebral vasospasm after aneurysmal rupture. Neurosurgery 7: 583-586. 1980
48- Symon L, Bell BA, Kendall B: Relationship between effused blood and clinical course and prognosis in aneurysmal subarachnoid hemorrhage: A preliminary computerized tomography scan study. In Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore, Williams & Wilkins, 1980, pp 409-411
49- Saito I, Sano K: Vasospasm following rupture of cerebral aneurysms. Neurol Med Chir (Tokyo) 19: 103-107. 1979

50- Suzuki J, Komatsu S, Sato T, Sakurai Y: Correlation between CT findings and subsequent development of cerebral infarction due to vasospasm in subarachnoid hemorrhage. Acta Neurochir (Wien)55: 63-70, 1980
51- Kistler JP, Crowell RM, Davis KR, Heros R. Ojemann RG, Zervas T, Fisher CM: The relation of cerebral vasospasm to the extent and reaction of subarachnoid blood visualized by CT scan: A prospective study. Neurology (NY) 33(4): 424-436, 1983
52 Sasaki T, Asano T, Takakura K, Sano K, Kassell NF: Nature of the vasoactive substance in CSF from patients with subarachnoid hemorrhage. J Neurosurg 60: 1186-1191, 1984
53- Nielsen KC. Owman C: Contractile response and amine receptor mechanisms in isolated middle cerebral artery of the cat. Brain Res 27: 33-42, 1971
54- Allen GS, Henderson LM, Chou SN, French LA: Cerebral arterial spasm. Part 1: In vitro contraction of vasoactive agents on canine basilar and middle cerebral arteries. J Neurosurg 40: 433-441,1974
55- Allen GS, Gross CJ: Cerebral arterial spasm. Part 7: In vitro effects of alpha adrenergic agents on canine arteries from six anatomical sites and six blocking agents on serotonin-induced contractions of the canine basilar artery. Surg Neurol 6: 63-70,1976
56- Zervas NT, Lavyne MH. Negoro M: Neurotransmitters and the normal and ischemic cerebral circulation. N Engl J Med 293:812-816, 1975
57- Toda N: Influence of dopamine and norepinephrine on isolated Downloaded from http://ahajournals.org by on March 5, 2021CEREBRAL VASOSPASM//Cfl.v.se// et al 569 cerebral arteries of the dog. Br J Pharmacol 58: 121-126, 1976
58- Toda N: Alpha adrenergic receptor subtype in human, monkey and dog cerebral arteries. J Pharmacol Exp Ther 226: 861-868,1983
59-. Raynor RB. McMurtry JG, Pool JL: Cerebrovascular effects of topically applied serotonin in the cat. Neurology (Minneap) 11:190-195, 1961
60- Kapp J, Mahaley MS, Odom GL: Cerebral arterial spasm. Part 2: Experimental evaluation of mechanical and humoral factors in pathogenesis. J Neurosurg 29: 339-349, 1968
61- Farrar JK Jr: Chronic cerebral arterial spasm: The role of intracranial pressure. J Neurosurg 43: 408-417, 1975
62- Johnston IH, Rowan JO. Haper AM, Jennett WB: Raised intracranial pressure and cerebral blood flow. J Neurol Neurosurg Psychiatry 35: 285-296, 1972
63- Farrar JK Jr, Roach MR: The effects of increased intracranial pressure on flow through major cerebral arteries in vitro. Stroke 4:795-806, 1973
64- Beks JWF: Cerebral vasospasm and increased intracranial pressure. In Wilkins RH (ed). Cerebral Arterial Spasm, Baltimore,William & Wilkins, 1980, pp 412-413
65-Allen GS, Gross CJ, French LA, Chou SN: Cerebral arterial spasm. Part 5: In vitro contractile activity of vasoactive agents including human cerebrospinal fluid on human basilar and anterior cerebral arteries. J Neurosurg 44: 594-600, 1976
66- Boullin DJ, Mohan J, Grahame-Smith DG: Evidence for the presence of a vasoactive substance (possibly involved in the aetiology of cerebral arterial spasm) in cerebrospinal fluid from patients with subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry39: 756-766, 1976
67- Brandt L, Ljunggren B, Anderson KE, Hindfelt B, Teasdale G:Vasoconstrictive effects of human post-hemorrhagic cerebrospinal fluid on catpial arterioles in situ. J Neurosurg 54: 351-356,1981
68- Okwuasaba FK, Weir BKA, Cook DA, Krueger CA: Effects ofvarious intracranial fluids on smooth muscle. Neurosurgery 9: 402-406, 1981
69- Peerless SJ, Kendall MJ: Cerebral vasospasm. Experimental cerebral vasospasm. In Whisnant JP, Sandok BA (eds): Proceedings of the Ninth Princeton Conference on Cerebral Vascular Disease. New York, Grune & Stratton, 1975, pp 49-58
70- Fraser RAR, Stein MM, Barrett RE. Pool JL: Noradrenergic mediation of experimental cerebrovascular spasm. Stroke 1: 356-362, 1970
71- Owman C, Edvinsson L, Sahlin C, Svendgaard NA: Transmitter changes in perivascular sympathetic nerves after experimental subarachnoid hemorrhage. In Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore, Williams & Wilkins, 1980. pp 279-283
72- Lobato RD, Marin J, Salaices M, Burgos J, Rivilla F, Garcia AG: Effect of experimental subarachnoid hemorrhage on the adrenergic innervation of cerebral arteries. J Neurosurg 53: 477-479, 1980
73- Lobato RD, Marin J, Salaices M, Rivilla F, Burgos J: Cerebrovascular reactivity to noradrenaline and serotonin following experimental subarachnoid hemorrhage. J Neurosurg 53: 480-485, 1980
74- Sasaki T, Murota S, Wakai S, Asano T, Sano K: Evaluation of prostaglandin biosynthetic activity in canine basilar artery following subarachnoid injection of blood. J Neurosurg 55: 771-778, 1981
75- Maeda Y, Tani E, Miyamoto T: Prostaglandin metabolism in experimental cerebral vasospasm. J Neurosurg 55: 779-785,1981
76- Walker V, Pickard JD, Smythe P, Eastwood S, Perry S: Effects of subarachnoid haemorrhage on intracranial prostaglandins. J Neurol Neurosurg Psychiatry 46: 119-125, 1983
77- Martin V, Villani GM, Jothianandan D, Furchgott RF: Selective blockade of endofhelium dependent and glyceral-trinitrate induced relaxation by hemoglobin and methylene blue in the rabbit aorta. J Pharmacol Exp Ther 232: 708-716, 1985
78- Furchgott RF, Cherry PO, Zawadzki JV, Jothianandan D: Endothelial cells as mediators of vasodilation of arteries. J Cardiovasc Pharmacol 6: S336-S343, 1984
79 Liszczak TM, Varsos VG, Black P, Kistler JP, Zervas NT: Cerebral arterial constriction after experimental subarachnoid hemorrhage is associated with blood components within the arterial wall. J Neurosurg 58: 18-26, 1983
80- LeeTJF, Mcllhany MP, Sarwinski S: Erythocyte extracts enhance neurogenic vasoconstriction of dog cerebral arteries in vitro. J Cereb Blood Flow Metab 4: 474-476, 1984
81-Fox PL, Dicoleto PF. Regulation of production of a PDGF-like protein by cultured bovine aortic endothelial cells. J Cell Phys 121: 298-308. 1984
82- Schwartz SM, Ross R: Cellular proliferation in atherosclerosisand hypertension. Progress in Cardiovascular Diseases 26: 355-372, 1984

83- Pelletieri L, Carlson CA, Lindholm L: Is the vasospasm following subarachnoid hemorrhage an immunoreactive disease? Experientia 15: 1170-1171,
84- Hoshi T, Shimizu T, Kito K, Yamasaki N, Takahaski K, Takahashi M, OkadaT, Kasuya H, Kitamura K: Immunological study of late cerebral vasospasm in subarachnoid hemorrhage. Detection of immunoglobulins, C3, and fibrinogen in cerebral arterial walls by immunofluorescence method. Neurol Med Chir (Tokyo) 24: 647-654, 1984
85- Weir BKA, Okwuasaba FK, Cook DA, Krueger CA: Pharmacology of Vasospasm-Effects of various agents including blood on isolated cerebral arteries. In Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore, William & Wilkins, 1980, pp 237-243
86-. Chyatte D, SundtT: Cerebral vasospasm after subarachnoid hemorrhage. Mayo Clin Proc 59: 498-505, 1984
87- Mizukami M, Kawase T, Tazawa T, Nagata K, Yunoki K, Yoshida Y: Hypothesis and clinical evidence for the mechanism of chronic cerebral vasospasm after subarachnoid hemorrhage. In Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore, Williams & Wilkins, 1980, pp 97-106
88- Yasargil MG. In Microneurosurgery Vol. 1. New York, Georg Thieme Verlag, 1984, p 344
89- Hughes JT, Schianchi PM: A histological study at necropsy of blood vessels in cases of subarachnoid hemorrhage. J Neurosurg 48: 515-525, 1978
90- Yamashita T, Yamamota S: Cerebral artery pathology in experimental subarachnoid hemorrhage. J Neurosurg 58: 843-850, 1983
91- Crompton MR: The pathogenesis of cerebral infarction following the rupture of cerebral berry aneurysms. Brain 87: 491-510, 1964
92- White RP, Robertson JT: Comparison of piroxicam, medofenamate, ibuprofen, aspirin, and prostacyclin efficacy in a chronicmodel of cerebral vasospasm. Neurosurgery 12: 40-46, 1983
93- Chyatte D, Rusch N, Sundt TM Jr: Prevention of chronic experimental cerebral vasospasm with ibuprofen and high-dose methylprednisolone. J Neurosurg 59: 925-932, 1983
94- Dujovny M, Kaufman HH, KassoskyN, HurtelonMS, Miller M, Camel PC: Morphology of the subarachnoid space after subarachnoid hemorrhage in Wilkins RH (ed). Cerebral Arterial Spasm. Baltimore, Williams & Wilkins, 1980, pp 139-143
95- Sasaki T, Kassell NF, Yamashita M, Fujiwara S, Zuccarello M: Barrier disruption in the major cerebral arteries following experimental subarachnoid hemorrhage. J Neurosurg 1985 (in press)
96- Fox JL, Ko JP: Cerebral vasospasm: A clinical observation. Surg Neurol 10: 269-275, 1978
97- Hirata Y, Matsukado Y, Fukumura A: Subarachnoid enhancement secondary to subarachnoid hemorrhage with special reference to the clinical significance and pathogenesis. Neurosurgery 11: 367-371, 1982
98 Tazawa T, Mizukami M, Kawase T, Usami T, Togashi O, Hyodo A, Eguchi T: Relationship between contrast enhancement on computed tomography and cerebral vasospasm in patients with subarachnoid hemorrhage. Neurosurgery 12: 643-648, 198
99-Doczi T, Ambrose J, O'Laoire S: Significance of contrast enhancement in cranial computerized tomography after subarachnoid hemorrhage. J
100- Holmsen H: Platelet secretion. In Hemostasis and Thrombosis. Colman R, Hirsh J (ed), Philadelphia, LP Lippincott, 1982, pp390-403
101- Mustard JF, Kinlough-Rathbone R, Packham M: In Hemostasis and Thrombosis. Colman R, Hirsh J (ed), Philadelphia, LP Lippincott, 1982, pp 703-715
102- Peterson JW, Bun T, Cardia GJ, Ronner SF, Charnvis K, Zervas NT: Basilar arterial membrane is depolarized during cerebral vasospasm due to subarachnoid hemorrhage. Stroke 16(1): 138, 1985 (abstr)
103-. Janoffa A, Carp H: Proteases, anti-proteases and oxidants: Pathways of tissue injury during inflammation. In Monographs in Pathology, vol 23. Majno G, Cotran R. Kaufman N (ed). Baltimore, Williams & Wilkins, 1982, pp 62-82
104- Cotran R: Endothelium and inflammation. In Monographs in Pathology, vol 23. Majno G, Cotran R, Kaufman N (ed), Baltimore,Williams and Wilkins, 1982, pp 18-37
105- Garland CJ, Keatinge WR. Constrictive actions of ACH-5-HT and histamine on bovine coronary artery inner and outer muscle. J Physiol 327: 363-376, 1982
106- Grottendorst GR, Sippa HES, Kleinman HK, Martin GR: Attachment of smooth muscle cells to collagen and their migration toward platelet derived growth factor. Proc Nat Acad Sci 78:S669-S672, 1981
107- White RP, Robertson JT: Role of plasmin, thrombin and antithrombin as etiological factors in delayed cerebral vasospasm. Neurosurg 16(1): 27-35, 1985
108-S. Shirao, H. Yoneda, H. Ishihara, K. Kajiwara, M. Suzuki, and S. S. M. of J. N. Society, “A proposed definition of symptomatic vasospasm based on treatment of cerebral vasospasm after subarachnoid hemorrhage in Japan: Consensus 2009, a project of the 25 Spasm Symposium,” *Surg. Neurol. Int.*, vol. 2, p. 74, 2011, doi: 10.4103/2152-7806.81968.
109- Schmidt JM, Fernandez A, Rincon F, Claassen J, Ostapkovich ND, Badjatia N, Parra A, Connolly ES, Mayer SA. Frequency and clinical impact of asymptomatic cerebral infarction due to vasospasm after subarachnoid hemorrhage. J Neurosurg. 2008;109:1052–1059.
110- Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, Connolly ES, Mayer SA. Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: The fisher scale revisited. Stroke. 2001;32:2012–2020.
111- Kumar A, Brown R, Dhar R, Sampson T, Derdeyn CP, Moran CJ, Diringer MN (2013) Early vs delayed cerebral infarction after aneurysm repair after subarachnoid hemorrhage. Neurosurgery 73: 617–623
112- Hansen-Schwartz J (2004) Cerebral vasospasm: a consideration of the various cellular mechanisms involved in the pathophysiology. Neurocrit Care 1:235–246
113- Rabinstein AA, Friedman JA, Weigand SD, McClelland RL, Fulgham JR, Manno EM, Atkinson JL, Wijdicks EF (2004) Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. Stroke; J Cereb Circ 35:1862–1866

114- Shirao S, Yoneda H, Ishihara H, Kajiwara K, Suzuki M, Survey Study Members of Japan Neurosurgical S (2011) A proposed definition of symptomatic vasospasm based on treatment of cerebral vasospasm after subarachnoid hemorrhage in Japan: consensus 2009, a project of the 25 Spasm Symposium. Surg Neuroly Int 2:74
115- Dalessandri K, St. John JN, Carson SN. Correction and monitoring of postoperative cerebral vasospasm. *Angiology*. 1981;32:212–6. or a new world of thought. Neurological Research, 31(2),
116-Sloan, M. A., Alexandrov, A. V., Tegeler, C. H., Spencer, M. P., Caplan, L. R., Feldmann, E., et al. (2004). Assessment:Transcranial Doppler ultrasonography: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology, 62(9), 1468–1481.
117- Purkayastha S, Sorond F. Transcranial Doppler ultrasound: technique and application. Semin Neurol. 2012;32:411-420
118- Nicoletto HA, Burkman MH. Transcranial Doppler series part II: Performing a transcranial Doppler. Am J Electroneurodiagnostic Technol. 2009;49:14–27. [PubMed] [Google Scholar]
119-Lindegaard KF, Bakke SJ, Sorteberg W, et al. A non-invasive Doppler ultrasound method for the e valuation of patients with subarachnoid hemorrhage. Acta Radiol. 1986;369:96-98.
120- Aaslid R, Huber P, Nornes H. Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. *J Neurosurg*. 1984;60:37–41.
121 Sviri GE, Ghodke B, Britz GW, Douville CM, Haynor DR, Mesiwala AH, et al. Transcranial Doppler grading criteria for basilar artery vasospasm. *Neurosurgery*. 2006;59:360–6.
122- Vora YY, Suarez-Almazor M, Steinke DE, et al. Role of transcranial Doppler monitoring in the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. Neurosurgery. 1999;44:1237-1248.
123- Lysakowski C, Walder B, Costanza MC, et al. Transcranial Doppler versus angiography in patients with vasospasm due to a ruptured cerebral aneurysm. A systematic review. Stroke. 2001;32:2292-2298.
124- Okada Y, Shima T, Nishida M, et al. Comparison of transcranial Doppler investigation of aneurysmal vasospasm with digital subtraction angiographic and clinical findings. Neurosurgery. 1999;45:443-450.
125- Minhas PW, Menon DK, Smielewski P, et al. Positron emission tomographic cerebral perfusion disturbances and transcranial Doppler findings among patients with neurological deterioration and subarachnoid hemorrhage. Neurosurgery. 2003;52:1017-1024.
126-Vora YY, Suarez-Almazor M, Steinke DE, Martin ML, Findlay JM. Role of transcranial Doppler monitoring in the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. *Neurosurgery*. 1999;44:1237–47.
127- Otawara Y, Ogasawara K, Ogawa A, et al. Evaluation of vasospasm after subarachnoid hemorrhage by use of multislice computed tomographic angiography. Neurosurgery. 2002;51:939-943.
128- Hattingen E, Blasel S, DuMesnil R, et al. MR angiography in patients with subarachnoid hemorrhage: adequate to evaluate vasospasm-induced vascular narrowing. Neurosurg Rev. 2010;33: 431-439.
129-Dillon EH, Camputaro C (1993) Partial anomalous pulmonary venous drainage of the left upper lobe vs duplication of the superior vena cava: distinction based on CT findings. AJR Am J Roentgenol 160:375–379
130- Washington C, Zipfel G. Detection and monitoring of vasospasm and delayed cerebral ischemia: a review and assessment of the literature. Neurocrit Care. 2011;15:312-317.
131- J. W. Dankbaar, N. K. de Rooij, B. K. Velthuis, C. J. M. Frijns, G. J. E. Rinkel, and I. C. van der Schaaf, “Diagnosing delayed cerebral ischemia with different CT modalities in patients with subarachnoid hemorrhage with clinical deterioration,” Stroke, vol. 40, no. 11, pp. 3493–3498, 2009.
132- Shankar JJ, Tan IY, Krings T, Terbrugge K, Agid R (2012) CTangiography for evaluation of cerebral vasospasm following acutesubarachnoid haemorrhage. Neuroradiology 54:197–203
133- Zachenhofer I, Cejna M, Schuster A, Donat M, Roessler K (2010) Image quality and artefact generation post-cerebral aneurysm clipping using a 64-row multislice computer tomography angiography (MSCTA) technology: a retrospective study and review of the literature. Clin Neurol Neurosurg 112:386–391
134- Baldwin ME, Macdonald RL, Huo D, et al. Early vasospasm on admission angiography in patients with aneurysmal subarachnoid hemorrhage is a predictor for in-hospital complications and poor outcome. Stroke. 2004;35:2506-2511.
133- Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, Patel AB, Thompson BG, Vespa P, American Heart Association Stroke C, Council on Cardiovascular R, Intervention, Council on Cardiovascular N, Council on Cardiovascular S, Anesthesia, Council on Clinical C (2012) Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke; J Cereb Circ 43:1711–1737
134- Loch Macdonald R (2006) Management of cerebral vasospasm. Neurosurg Rev 29:179–193
135- Bulsara KR, Gunel M, Amin-Hanjani S, Chen PR, Connolly ES, Friedlander RM. Results of a national cerebrovascular neurosurgery survey on the management of cerebral vasospasm/delayed cerebral ischemia. *Journal of neurointerventional surgery*. 2015;7:408–411.
136-Shankar JJ, Tan IY, Krings T, Terbrugge K, Agid R. Ct angiography for evaluation of cerebral vasospasm following acute subarachnoid haemorrhage. *Neuroradiology*. 2012;54:197–203.
137- Leffers AM, Wagner A (2000) Neurologic complications of cerebral angiography. A retrospective study of complication rate and patient risk factors. Acta Radiol 41:204–210
138- Willinsky RA, Taylor SM, TerBrugge K, Farb RI, Tomlinson G, Montanera W (2003) Neurologic complications of cerebral angiography: prospective analysis of 2,899 procedures and review of the literature. Radiology 227:522–528
139-G. B. Anderson, R. Ashforth, D. E. Steinke, and J. M. Findlay, “CT Angiography for the Detection of Cerebral Vasospasm in Patients with Acute Subarachnoid Hemorrhage,” *Am. J. Neuroradiol.*, vol. 21, no. 6, pp. 1011 LP – 1015, Jun. 2000, [Online]. Available:http://www.ajnr.org/content/21/6/1011.abstract.
140- G. Rordorf, W. J. Koroshetz, W. A. Copen et al., “Diffusion- and perfusion-weighted imaging in vasospasm after subarachnoid hemorrhage,” Stroke, vol. 30, no. 3, pp. 599–605, 1999.

141-A. G. Sorensen, W. A. Copen, L. Østergaard et al., “Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time,” Radiology, vol. 210, no. 2, pp. 519–527, 1999
142- Horikoshi T, Fukamachi A, Nishi H, Yagi SI, Fukasawa I. Observation of vasospasm after subarachnoid hemorrhage by magnetic resonance angiography—a preliminary study. *Neurologia Medico-Chirurgica*. 1995;35(5):298–304. [
143-Grandin CB, Cosnard G, Hammer F, Duprez TP, Stroobandt G, Mathurin P. Vasospasm after subarachnoid hemorrhage: diagnosis with MR angiography. *American Journal of Neuroradiology*. 2000;21(9):1611–1617.
144- Carlson AP, Yonas H. Radiographic assessment of vasospasm after aneurysmal subarachnoid hemorrhage: the physiological perspective. *Neurological Research*. 2009;31(6):593–604.
145-J. N. Mills, V. Mehta, J. Russin, A. P. Amar, A. Rajamohan, and W. J. Mack, “Advanced Imaging Modalities in the Detection of Cerebral Vasospasm,” *Neurol. Res. Int.*, vol. 2013, pp. 1–15, 2013, doi: 10.1155/2013/415960.
146- S. P. Lad, R. Guzman, M. E. Kelly et al., “Cerebral perfusion imaging in vasospasm,” Neurosurgical Focus, vol. 21, no. 3, p. E7, 2006.
147- Latchaw RE, Yonas H, Hunter GJ, Yuh WT, Ueda T, Sorensen AG, Sunshine JL, Biller J, Wechsler L, Higashida R, Hademenos G, Council on Cardiovascular Radiology of the American Heart A (2003) Guidelines and recommendations for perfusion imaging in cerebral ischemia: a scientific statement for healthcare professionals by the writing group on perfusion imaging, from the Council on Cardiovascular Radiology of the American Heart Association. Stroke; J Cereb Circ 34:1084–1104
148- Reinprecht A, Czech T, Asenbaum S, Podreka I, Schmidbauer M (2005) Low cerebrovascular reserve capacity in long-term followup after subarachnoid hemorrhage. Surg Neurol 64:116–120, discussion 121
149- Bacigaluppi S, Dehdashti AR, Agid R, Krings T, Tymianski M, Mikulis DJ (2009) The contribution of imaging in diagnosis, preoperative assessment, and follow-up of moyamoya disease: a review. Neurosurg Focus 2
150- Powsner RA, O'Tuama LA, Jabre A, Melhem ER (1998) SPECT imaging in cerebral vasospasm following subarachnoid hemorrhage. J Nucl Med : Offl Pub, Soc Nu
151- Herscovitch P, Markham J, Raichle ME (1983) Brain blood flow measured with intravenous H2(15)O. I. Theory and error analysis. J Nucl Med : Offl Pub Soc Nucl Med 24:782–789
152- Raichle ME, Martin WR, Herscovitch P, Mintun MA, Markham J (1983) Brain blood flow measured with intravenous H2(15)O. II. Implementation and validation. J Nucl Med : Off Pub, Soc Nucl Med 24:790–798
153 Martin WR, Powers WJ, Raichle ME (1987) Cerebral blood volume measured with inhaled C15O and positron emission tomography. J Cereb Blood Flow Metab 7:421–426
154-Kawamura S, Sayama I, Yasui N, Uemura K (1992) Sequential changes in cerebral blood flow and metabolism in patients with subarachnoid haemorrhage. Acta Neurochir 114:12–15
155- Wintermark M, Ko NU, Smith WS, Liu S, Higashida RT, Dillon WP (2006) Vasospasm after subarachnoid hemorrhage: utility of perfusion CT and CT angiography on diagnosis and management. AJNR AmJ Neuroradiol 27:26–34
156- van der Schaaf I, Wermer MJ, van der Graaf Y, et al. Prognostic value of cerebral perfusion–computed tomography in the acute stage after subarachnoid hemorrhage for the development of delayed cerebral ischemia. Stroke. 2006;37:409-413.
157-Sviri GE, Britz GW, Lewis DH, et al. Dynamic perfusion computed tomography in the diagnosis of cerebral vasospasm. Neurosurgery. 2006;59:319-325.
158- Washington C, Zipfel G. Detection and monitoring of vasospasm and delayed cerebral ischemia: a review and assessment of the literature. Neurocrit Care. 2011;15:312-317.
159- Sanelli PC, Ougorets I, Johnson CE, Riina HA, Biondi A (2006) Using CT in the diagnosis and management of patients with cerebral vasospasm. Semin Ultrasound CT MR 27:194–206
160- Dankbaar JW, Rijsdijk M, van der Schaaf IC, Velthuis BK, Wermer MJ, Rinkel GJ (2009) Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neuroradiology
161- Dankbaar J, de Rooij N, Rijsdijk M, et al. Diagnostic threshold values of cerebral perfusion measured with computed tomography for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Stroke. 2010;41:1927-1932.
162 Greenberg E, Gold R, Reichman M, et al. Diagnostic accuracy of CT angiography and CT perfusion for cerebral vasospasm: a metaanalysis. AJNR Am J Neuroradiol. 2010;31:1853-1860.
163- S. Binaghi *et al.*, “CT Angiography and Perfusion CT in Cerebral Vasospasm after Subarachnoid Hemorrhage,” *Am. J. Neuroradiol.*, vol. 28, no. 4, pp. 750 LP – 758, Apr. 2007, [Online]. Available: http://www.ajnr.org/content/28/4/750.abstract.
164- F. T. Charbel, X. Du, W. E. Hoffman, and J. I. Ausman, “Brain tissue PO2, PCO2, and pH during cerebral vasospasm,” SurgicalNeurology, vol. 54, no. 6, pp. 432–437, 2000.
165-A. Khaldi, A. Zauner, M. Reinert, J. J. Woodward, and M. R.Bullock, “Measurement of nitric oxide and brain tissue oxygentension in patients after severe subarachnoid hemorrhage,”Neurosurgery, vol. 49, no. 1, pp. 33–40, 2001.
166-M. Jaeger, M. U. Schuhmann, M. Soehle, C. Nagel, and J.Meixensberger, “Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction,” Stroke, vol. 38, no. 3, pp. 981–986, 2007.
167-M. Barth, J. Woitzik, C. Weiss et al., “Correlation of clinical outcome with pressure-, oxygen-, and flow-related indices of cerebrovascular reactivity in patients following aneurysmal SAH,” Neurocritical Care, vol. 12, no. 2, pp. 234–243, 2010.
168- P. Enblad, J. Valtysson, J. Andersson et al., “Simultaneous intracerebral microdialysis and positron emission tomography in the detection of ischemia in patients with subarachnoid hemorrhage,” Journal of Cerebral Blood Flow and Metabolism, vol. 16, no. 4, pp. 637–644, 1996.
169- L. Persson, J. Valtysson, P. Enblad et al., “Neurochemical monitoring using intracerebral microdialysis in patients with subarachnoid hemorrhage,” Journal of Neurosurgery, vol. 84, no. 4, pp. 606–616, 1996.
170- M. K. Schulz, L. P. Wang, M. Tange, and P. Bjerre, “Cerebral microdialysis monitoring: determination of normal and ischemic cerebral metabolisms in patients with aneurysmal subarachnoid hemorrhage,” Journal of Neurosurgery, vol. 93, no.5, pp. 808–814, 2000.

171- O. G. Nilsson, L. Brandt, U. Ungerstedt, and H. Saveland, ¨"Bedside detection of brain ischemia using intracerebral microdialysis: subarachnoid hemorrhage and delayed ischemic deterioration," Neurosurgery, vol. 45, no
172- A. W. Unterberg, O. W. Sakowitz, A. S. Sarrafzadeh, G. Benndorf, and W. R. Lanksch, "Role of bedside microdialysis in the diagnosis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage," Journal of Neurosurgery, vol. 94, no. 5, pp. 740–749, 2001.
173 F. Staub, R. Graf, P. Gabel, M. Kochling, N. Klug, and W. Heiss, ¨ "Multiple interstitial substances measured by microdialysis in patients with subarachnoid hemorrhage," Neurosurgery, vol. 47, no. 5, pp. 1106–1116, 2000.
174 Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. A practical scale. Lancet 2:81–84
175- Mutoh L, Ishikawa T, Suzuki A, et al. Continuous cardiac output and near-infrared spectroscopy monitoring to assist in management of symptomatic cerebral vasospasm after subarachnoid hemorrhage. Neurocrit Care. 2010;13:331-338.
176-Zweifel C, Castellini G, Czosnyka M, et al. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. Stroke. 2010;41:1963-1968.
177 Brawanski A, Faltermeier R, Rothoerl R, et al. Comparison of near-infrared spectroscopy and tissue PO2 time series in patients after severe head injury and aneurysmal subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2002;22:605-611.
178- Jobsis FF (1977) Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 198:1264–1267
179 Reynolds EO, Wyatt JS, Azzopardi D, Delpy DT, Cady EB, Cope M, Wray S (1988) New non-invasive methods for assessing brain oxygenation and haemodynamics. Br Med Bull 44:1052–1075
180-. Yokose N, Sakatani K, Murata Y, et al. Bedside monitoring of cerebral blood oxygenation and hemodynamics after aneurysmal subarachnoid hemorrhage by quantitative time-resolved nearinfrared spectroscopy. World Neurosurg. 2010;73:508-513.
181- Shankar JJ, Tan IY, Krings T, Terbrugge K, Agid R (2012) CT angiography for evaluation of cerebral vasospasm following acute subarachnoid haemorrhage. Neuroradiology 54:197–203
182- Yoshitani K, Kawaguchi M, Miura N, et al. Effects of hemoglobin concentration, skull thickness, and the area of the cerebrospinal fluid layer on near-infrared spectroscopy measurements. Anesthesiology. 2007;106:458-462.
183- Nakagawa A, Su CC, Sato K, et al. Evaluation of changes in circulating blood volume during acute and very acute stages of subarachnoid hemorrhage: implications for the management of hypovolemia. J Neurosurg. 2002;97:268-271.
184- Lennihan L, Mayer SA, Fink ME, et al. Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: a randomized controlled trial. Stroke. 2000;31:383-391.
185-Egge A, Waterloo K, Sjoholm H, et al. Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study. Neurosurgery. 2001;49:593-606.
186-Treggiari MM, Walder B, Suter PM, et al. Systematic review of the prevention of delayed ischemic neurological deficits with hypertension, hypervolemia, and hemodilution therapy following subarachnoid hemorrhage. J Neurosurg. 2003;98:978-984.
187- Rinkel GJE, Feigin VL, Algra A, et al. Hypervolemia in aneurysmal subarachnoid hemorrhage. Stroke. 2005;36:1104-1105.
188- Suarez JI, Shannon L, Zaidat OO, et al. Effect of human albumin administration on clinical outcome and hospital cost in patients with subarachnoid hemorrhage. J Neurosurg. 2004;100:585-590.
189- McGirt MJ, Blessing R, Nimjee SM, et al. Correlation of serum brain natriuretic peptide with hyponatremia and delayed ischemic neurological deficits after subarachnoid hemorrhage. Neurosurgery. 2004;54:1369-1374.
189- Zheng B, Qiui Y, Jin H, et al. A predictive value of hyponatremia for poor outcome and cerebral infarction in high-grade aneurysmal subarachnoid hemorrhage. J Neurol Neurosurg Psychiatry. 2011;82: 213-217.
190- Rahman M, Friedman W. Hyponatremia in neurosurgical patients: clinical guidelines development. Neurosurgery. 2009;65:925-936.
191- Mori T, Katayama Y, Kawamata T, et al. Improved efficiency of hypervolemic therapy with inhibition of natriuresis by fludrocortisones in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg. 1999;91:947-952. 106. Smith MJ, Le Roux PD, Elliott JP, et al. Blood transfusion and increased risk for vasospasm and poor outcome after subarachnoid hemorrhage. J Neurosurg. 2004;101:1-7.
192- Bailes JE, Spetzler RF, Hadley MN, et al. Management and morbidity of poor-grade aneurysm patients. J Neurosurg. 1990;72: 559-566.
193- Bederson JB, Connolly ES, Jr., Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 2009;40(3):994–1025.
194-Pickard, J. D., Murray, G. D., Illingworth, R., Shaw, M. D., Teasdale, G. M., Foy, P. M., et al. (1989). Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ, 298(6674), 636–642
195-Adamczyk, P., He, S., Amar, A. P., & Mack, W. J. (2013). Medical management of cerebral vasospasm following aneurysmal subarachnoid hemorrhage: A review of current and emerging therapeutic interventions. Neurology Research International, 2013.
196-Feigin, V. L., Rinkel, G. J., Algra, A., Vermeulen, M., & van Gijn, J. (1998). Calcium antagonists in patients with aneurysmal subarachnoid hemorrhage: A systematic review. Neurology, 50(4), 876–
197-Zwienenberg-Lee M, Hartmann J, Rudisill N, Muizelaar JP. International Stroke Conference: Feb 7–9, 2007; San Francisco. San Francisco, CA; 2007. The effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage. Results of a multi-center randomized clinical trial.
198-Hoh BL, Ogilvy CS. Endovascular treatment of cerebral vasospasm: transluminal balloon angioplasty, intra-arterial papaverine, and intra-arterial nicardipine. Neurosurg Clin N Am. 2005;16:501–516. doi: 10.1016/j.nec.2005.04.004. vi
199- Amin-Hanjani S, Ogilvy CS, Barker FG 2nd. Does intracisternal thrombolysis prevent vasospasm after aneurysmal subarachnoid hemorrhage? A meta-analysis. Neurosurgery. 2004;54:326-335.
200- Kasuya H, Onda H, Sasahara A, et al. Application of nicardipine prolonged-release implants: analysis of 97 consecutive patients with acute subarachnoid hemorrhage. Neurosurgery. 2005;56:895-902.

201-Dalbasti T, Karabiyikoglu M, Ozdamar N, et al. Efficacy of controlled-release papaverine pellets in preventing symptomatic cerebral vasospasm. J Neurosurg. 2001;95:44-50.
202-Amin-Hanjani S, Stagliano NE, Yamada M, Huang PL, Liao JK, Moskowitz MA. Mevastatin, an HMG-CoA reductase inhibitor, reduces stroke damage and upregulates endothelial nitric oxide synthase in mice. Stroke. 2001;32:980–986
203-Laufs U, Fata VL, Liao JK. Inhibition of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase blocks hypoxia-mediated down-regulation of endothelial nitric oxide synthase. J Biol Chem. 1997;272:31725–31729. doi: 10.1074/jbc.272.50.31725.
204-Yamada M, Huang Z, Dalkara T, Endres M, Laufs U, Waeber C, Huang PL, Liao JK, Moskowitz MA. Endothelial nitric oxide synthase-dependent cerebral blood flow augmentation by L-arginine after chronic statin treatment. J Cereb Blood Flow Metab. 2000;20:709–717.
205-Su S, Xu W, Hai J, et al. Effects of statins-use for patient with aneurysmal subarachnoid hemorrhage: a meta-analysis of randomized controlled trials. Sci Rep. 2014;4:4573.
206- Kirkpatrick P, Turner C, Smith C, et al., STASH Collaborators. Simvastatin in aneurysmal subarachnoid hemorrhage (STASH): a multicentre randomized phase 3 trial. Lancet Neurol. 2014;13:1073-1074.
207-Denny-Brown, D. (1951). The treatment of recurrent cerebrovascular symptoms and the question of "vasospasm". The Medical Clinics of North America, 35(5), 1457–1474.
208-Sen, J., Belli, A., Albon, H., Morgan, L., Petzold, A., & Kitchen, N. (2003). Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. Lancet Neurology, 2(10), 614–621.
209- Wood, H. (1982). Hypervolemic haemodilution: Rheologic therapy for acute cerebral ischaemia. Contemporary Neurosurgery, 4, 1–6f.
210- Kassell, N. F., Peerless, S. J., Durward, Q. J., Beck, D. W., Drake, C. G., & Adams, H. P. (1982). Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. Neurosurgery, 11(3), 337–343
211-Dankbaar, J. W., Slooter, A. J., Rinkel, G. J., & Schaaf, I. C. (2010). Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: A systematic review. Critical Care, 14(1), R23.
212- Raabe A, Beck J, Keller M, et al. Relative importance of hypertension compared with hypervolemia for increasing cerebral oxygenation in patients with cerebral vasospasm after subarachnoid hemorrhage. J Neurosurg. 2005;103:974-981.
213- Jost SC, Diringer MN, Zazulia AR, et al. Effect of normal saline bolus on cerebral blood flow in regions with low baseline flow in patients with vasospasm following subarachnoid hemorrhage. J Neurosurg. 2005;103:25-30.
214- Hoh BL, Carter BS, Ogilvy CS. Risk of hemorrhage from unsecured, unruptured aneurysms during and after hypertensive hypervolemic therapy. Neurosurgery. 2002;50:1207-1212.
215- Rosenwasser RH, Jallo JI, Getch CC, et al. Complications of SwanGanz catheterization for hemodynamic monitoring in patients with subarachnoid hemorrhage. Neurosurgery. 1995;37:872-876.
216- Miller JA, Dacey RG Jr, Diringer MN. Safety of hypertensive hypervolemic therapy with phenylephrine in the treatment of delayed ischemic deficits after subarachnoid hemorrhage. Stroke. 1995;26:2260-2266.
217- Amin-Hanjani S, Schwartz RB, Sathi S, et al. Hypertensive encephalopathy as a complication of hyperdynamic therapy for vasospasm: report of two cases. Neurosurgery. 1999;44:1113-1116.
218-Rosenwasser, R. H., Armonda, R. A., Thomas, J. E., Benitez, R. P., Gannon, P. M., & Harrop, J. (1999). Therapeuticmodalities for the management of cerebral vasospasm: Timing of endovascular options. Neurosurgery, 44(5),975–979. discussion 979-980.
219-Bejjani, G. K., Bank, W. O., Olan, W. J., & Sekhar, L. N. (1998). The efficacy and safety of angioplasty for cerebral vasospasm after subarachnoid hemorrhage. Neurosurgery, 42(5), 979–986. discussion 986–977.
220-Eskridge, J. M., McAuliffe, W., Song, J. K., Deliganis, A. V., Newell, D. W., Lewis, D. H., et al. (1998). Balloon angioplasty for the treatment of vasospasm:. Results of first 50 cases. Neurosurgery, 42(3), 510–516. discussion 516–517.
221-Zubkov, Y. N., Nikiforov, B. M., & Shustin, V. A. (1984). Balloon catheter technique for dilatation of constricted cerebral arteries after aneurysmal SAH. Acta Neurochirurgica, 70(1-2), 65–79
222- Chalouhi N, Tjoumakaris S, Thakkar V, et al. Endovascular management of cerebral vasospasm following aneurysm rupture: outcomes and predictors in 116 patients. Clin Neurol Neurosurg. 2014;118:26-31.
223- Hoh BL, Ogilvy CS. Endovascular treatment of cerebral vasospasm: transluminal balloon angioplasty, intra-arterial papaverine, and intra-arterial nicardipine. Neurosurg Clin N Am. 2005;16:501-516.
224- Megyesi JF, Vollrath B, Cook DA, et al. Long-term effects of in vivo angioplasty in normal and vasospastic canine carotid arteries: pharmacological and morphological analyses. J Neurosurg. 1999;91:100-108.
225- Megyesi JF, Findlay JM, Vollrath B, et al. In vivo angioplasty prevents the development of vasospasm in canine carotid arteries. Pharmacological and morphological analyses. Stroke. 1997;28:1216-1224.
226- Grande A, Nichols C, Khan U, et al. Treatment of post-hemorrhagic cerebral vasospasm: role of endovascular therapy. Acta Neurochir Suppl. 2011;110(Pt 2):127-132.
227- Higashida RT, Halbach VV, Cahan LD, et al. Transluminal angioplasty for treatment of intracranial arterial vasospasm. J Neurosurg. 1989;71(5 Pt 1):648-653.
228-Elliott JP, Newell DW, Lam DJ, et al. Comparison of balloon angioplasty and papaverine infusion for the treatment of vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg. 1998;88:277-284.
229- Frontera JA, Gowda A, Grilo C, et al. Recurrent vasospasm after endovascular treatment in subarachnoid hemorrhage. Acta Neurochir Suppl. 2011;110(Pt 2):117-122.
230- Santillan A, Knopman J, Zink W, et al. Transluminal balloon angioplasty for symptomatic distal vasospasm refractory to medical therapy in patients with aneurysmal subarachnoid hemorrhage. Neurosurgery. 2011;69:95-101, discussion 102.
231- Tekle WG, Chaudry SA, Hassan AE, et al. High risk of new episode of symptomatic vasospasm in unaffected arteries in subarachnoid hemorrhage patients receiving targeted endovascular treatment for symptomatic focal vasospasm. Neurocrit Care. 2014;20:399-405.

232-Abruzzo, T., Moran, C., Blackham, K. A., Eskey, C. J., Lev, R., Meyers, P., et al. (2012). Invasive interventional management of post-hemorrhagic cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. Journal of NeuroInterventional Surgery, 4(3), 169–177. https://doi.org/10.1136/neurintsurg-2011-010248.
233-Radiopedia, "Balloon angioplasty for cerebral vasospasm." https://radiopaedia.org/cases/balloon-angioplasty-for-cerebral-vasospasm?case_id=balloon-angioplasty-for-cerebral-vasospasm
234-Pandey, P., Steinberg, G. K., Dodd, R., Do, H. M., & Marks, M. P. (2012). A simplified method for administration of intra-arterial nicardipine for vasospasm with cervical catheter infusion. Neurosurgery, 71(1 Suppl Operative), 77–85.
235-Tejada, J. G., Taylor, R. A., Ugurel, M. S., Hayakawa, M., Lee, S. K., & Chaloupka, J. C. (2007). Safety and feasibility of intra-arterial nicardipine for the treatment of subarachnoid hemorrhage-associated vasospasm: Initial clinical experience with high-dose infusions. AJNR. American Journal of Neuroradiology, 28(5), 844–848
236-Badjatia N, Topcuoglu MA, Pryor JC, Rabinov JD, Ogilvy CS, Carter BS, Rordorf GA. Preliminary experience with intra-arterial nicardipine as a treatment for cerebral vasospasm. Am J Neuroradiol. 2004;25:819–826.
237-Feng, L., Fitzsimmons, B. F., Young, W. L., Berman, M. F., Lin, E., Aagaard, B. D., et al. (2002). Intraarterially administered verapamil as adjunct therapy for cerebral vasospasm: Safety and 2-year experience. AJNR. American Journal of Neuroradiology, 23(8), 1284–1290.
238-Rahme, R., Abruzzo, T. A., Zuccarello, M., & Ringer, A. J. (2012). Intra-arterial veramil-induced seizures: Drug toxicity or rapid reperfusion? The Canadian Journal of Neurological Sciences, 39(4), 550–552.
239-Westhout, F. D., & Nwagwu, C. I. (2007). Intra-arterial verapamil-induced seizures: Case report and review of the literature. Surgical Neurology, 67(5), 483–486. discussion 486. h
240-Biondi A, Ricciardi GK, Puybasset L, Abdennour L, Longo M, Chiras J, Van Effenterre R. Intra-arterial nimodipine for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage: preliminary results. Am J Neuroradiol. 2004;25:1067–1076.
241-Hui C, Lau KP. Efficacy of intra-arterial nimodipine in the treatment of cerebral vasospasm complicating subarachnoid haemorrhage. Clin Radiol. 2005;60:1030–1036.
242-Baggott, C. D., & Aagaard-Kienitz, B. (2014). Cerebral vasospasm. Neurosurgery Clinics of North America, 25(3), 497–528.
243-Nakamura, K., Nishimura, J., Hirano, K., Ibayashi, S., Fujishima, M., & Kanaide, H. (2001). Hydroxyfasudil, an active metabolite of fasudil hydrochloride, relaxes the rabbit basilar artery by disinhibition of myosin light chain phosphatase. Journal of Cerebral Blood Flow and Metabolism, 21(7), 876–885
244-Tanaka, K., Minami, H., Kota, M., Kuwamura, K., & Kohmura, E. (2005). Treatment of cerebral vasospasm with intraarterial
245- Vroom MB, Pfaffendorf M, van Wezel HB, et al. Effect of phosphodiesterase inhibitors on human arteries in vitro. Br J Anaesth. 1996;76:122-129.
246 Fraticelli AT, Cholley BP, Losser MR, et al. Milrinone for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke. 2008;39:893-898.
247-Nishiguchi M, Ono S, Iseda K, et al. Effect of vasodilation by milrinone, a phosphodiesterase III inhibitor, on vasospastic arteries after a subarachnoid hemorrhage in vitro and in vivo: effectiveness of cisternal injection of milrinone. Neurosurgery. 2010;66:158-164, discussion 164.
248- Khajavi K, Ayzman I, Shearer D, et al. Prevention of chronic cerebral vasospasm in dogs with milrinone. Neurosurgery. 1997;40: 354-362, discussion 362-363.
249- Arakawa Y, Kikuta K, Hojo M, et al. Milrinone for the treatment of cerebral vasospasm after subarachnoid hemorrhage: report of seven cases. Neurosurgery. 2001;48:723-728, discussion 728-730.
250-Arakawa Y, Kikuta K, Hojo M, et al. Milrinone for the treatment of cerebral vasospasm after subarachnoid hemorrhage: report of seven cases. Neurosurgery. 2001;48:723–728.
251- Fraticelli AT, Cholley BP, Losser MR, et al. Milrinone for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke. 2008;39:893–898.
252- Romero CM, Morales D, Reccius A, et al. Milrinone as a rescue therapy for symptomatic refractory cerebral vasospasm in aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2009;11:165–171.
253- Shankar JJ, dos Santos MP, Deus-Silva L, et al. Angiographic evaluation of the effect of intra-arterial milrinone therapy in patients with vasospasm from aneurysmal subarachnoid hemorrhage. Neuroradiology. 2011;53:123–128.
254-Lannes M, Teitelbaum J, del Pilar Cortes M, et al. Milrinone and homeostasis to treat cerebral vasospasm associated with subarachnoid hemorrhage: the Montreal Neurological Hospital protocol. Neurocrit Care. 2012;16:354–362.
255- Velly LJ, Bilotta F, Fabregas N, et al. Anaesthetic and ICU management of aneurysmal subarachnoid haemorrhage: a survey of European practice. Eur J Anaesthesiol. 2015;32:168176.
256- Lannes M, Zeiler F, Guichon C, et al. The use of milrinone in patients with delayed cerebral ischemia following subarachnoid hemorrhage: a systematic review. Can J Neurol Sci. 2017;44:152–160.
257-William W Ashley, "prognosis," 2020. https://emedicine.medscape.com/article/2500045-overview#a5
258-Keller E, Krayenbuhl N, Bjeljac M, Yonekawa Y. Cerebral vasospasm: results of a structured multimodal treatment. *Acta Neurochir Suppl*. 2005;**94**:65–73
259-Wurm G, Tomancok B, Nussbaumer K, Adelwohrer C, Holl K. Reduction of ischemic sequelae following spontaneous subarachnoid hemorrhage: a double-blind, randomized comparison of enoxaparin versus placebo. *Clin Neurol Neurosurg*. 2004;**106**:97–103. doi: 10.1016/j.clineuro.2004.01.006.
260-Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature. 1987;327:524–526.
261-Faraci FM. Role of endothelium-derived relaxing factor in cerebral circulation: large arteries vs. microcirculation. Am J Physiol. 1991;261:H1038–1042.

262-Prado R, Watson BD, Kuluz J, Dietrich WD. Endothelium-derived nitric oxide synthase inhibition. Effects on cerebral blood flow, pial artery diameter, and vascular morphology in rats. Stroke. 1992;23:1118–1123. discussion 1124.
263-You J, Johnson TD, Marrelli SP, Mombouli JV, Bryan RM., Jr P2u receptor-mediated release of endothelium-derived relaxing factor/nitric oxide and endothelium-derived hyperpolarizing factor from cerebrovascular endothelium in rats. Stroke. 1999;30:1125–1133.
264-Raabe A, Zimmermann M, Setzer M, Vatter H, Berkefeld J, Seifert V. Effect of intraventricular sodium nitroprusside on cerebral hemodynamics and oxygenation in poor-grade aneurysm patients with severe, medically refractory vasospasm. Neurosurgery. 2002;50:1006–1013.
265-Thomas JE, Rosenwasser RH. Reversal of severe cerebral vasospasm in three patients after aneurysmal subarachnoid hemorrhage: initial observations regarding the use of intra-ventricular sodium nitroprusside in humans. Neurosurgery. 1999;44:48–57.
266-Reinert M, Wiest R, Barth L, Andres R, Ozdoba C, Seiler R. Transdermal nitroglycerin in patients with subarachnoid hemorrhage. Neurol Res. 2004;26:435–439.
267-Vajkoczy P, Meyer B, Weidauer S, Raabe A, Thome C, Ringel F, Breu V, Schmiedek P. Clazosentan (AXV-034343), a selective endothelin A receptor antagonist, in the prevention of cerebral vasospasm following severe aneurysmal subarachnoid hemorrhage: results of a randomized, double-blind, placebo-controlled, multicenter phase IIa study. J Neurosurg. 2005;103:9–17.
268-Shaw MD, Vermeulen M, Murray GD, Pickard JD, Bell BA, Teasdale GM. Efficacy and safety of the endothelin, receptor antagonist TAK-044 in treating subarachnoid hemorrhage: a report by the Steering Committee on behalf of the UK/Netherlands/Eire TAK-044 Subarachnoid Haemorrhage Study Group. J Neurosurg. 2000;93:992–997.
269-Macdonald RL, Kassell N, Mayer S, Schmiedek P, Weidauer S, Pasqualin A. International Stroke Conference: Feb 7–9, 2007; San Francisco. San Francisco, CA; 2007. Randomized trial of Clazosentan for prevention of vasospasm after aneurysmal subarachnoid hemorrhage.

Article topic: Central Nervous System Primitive Neuroectodermal Tumor (PNET).

Author: Ghadi Ahmad Hasan Al-Wazani.

Editor: Philip Swiedan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Keywords: Oncology, Neurosurgery, Tumor classification, PNETs.

Introduction

The terminology Central Nervous System Primary Neuroectodermal Tumors (PNET) have been removed from the diagnostic dictionary [1] and was replaced by new tumor names that reflect the new classification of these tumors. This new classification is based on newly discovered genetic and molecular classification.[2] Before the C19MC gene amplification discovery, all tumors that were not Medulloblastoma were classified as CNS Primary Neuroectodermal Tumors (PNET), or supratentorial PNETs. Nonetheless, they are now classified into various categories depending on molecular differentiation.[3]

In this new classification (WHO 2016 classification), supratentorial High grade Neuroepithelial Tumor with BCOR alteration, for example, were discovered to be high grade Gliomas or Ependymomas that were misdiagnosed as Primary Neuroectodermal Tumors (PNET) before the 2016 WHO CNS PNETs' new classification. The misdiagnosis was present in 71% of the cases.[4]
Other subtypes include Cerebral Neuroblastoma and Ganglioglioneuroblastoma. The identification of each of the previous two subtypes depend on the ganglionic differentiation.[5]
In general, these tumors are aggressive, poorly differentiated, or undifferentiated, and arise from embryonal cells. They appear in children in most cases but may present in few cases in adolescents and adults.[2]

The WHO most recent classification divides them into CNS Medulloblastoma, Embryonal Tumors with Multilayered Rosettes/ C19MC altered, CNS Neuroblastoma, and Atypical Teratoid/ Rhabdoid Tumors. Pineoblastoma have been removed from the group due to its unique molecular characteristics.[3]

When these tumors were compared through radiological imaging, they were found to be similar in their edematous changes, definition of margins, and size. Therefore, they are radiologically identical.[4]
Immunohistochemical staining demonstrated the unique characteristics for each tumor group.[4] Important molecular markers include Sonic Hedgehog (SHH) and Wingless-related Integration Site (WNT). SHH is a protein that functions in cell specialization and

growth and is encoded on the 7th chromosome, while WNT is encoded on chromosome 12 and is responsible for cell proliferation, cell fate and embryogenesis. Both markers are important in Medulloblastoma diagnosis and classification. [2]

Medulloblastoma (MDB)

It is considered the most common among embryonal tumor and is deemed WHO grade 4. They reside in the cerebellum, either in the vermis or in the cerebellar hemispheres depending on the age of occurrence. In children, they arise in the vermis and in adults in the hemispheres. In addition, the have two peak ages. Those are 7 years and 21-40 years.[5]

MDBs are frequently diagnosed after the appearance of clinical symptoms.[6]
Their histology shows sheets of densely packed cells with scarce cytoplasm and a large round nucleus. The mitotic figures are plentiful, and neuroblastic Rosettes (Homer Wright) that represent 40% or less of the tumor. It is uncommon for this tumor to have vascular proliferation with Pseudopalisading Necrosis. Their gross appearance is relatively well-circumscribed but has Leptomeningeal involvement in one third of the patients.[5]

Medulloblastoma has different variants that are based on their morphology. In Nodular or Desmoplastic Variant, the surface of the tumor appears nodular like a lymph node. Within them is poorly differentiated cells that produce reticulin-positive collagen fibers in excess amount intercellularly, and islands that are reticulin free. This variant appears in the cerebellar hemispheres [5, 1], and midline.[1] They present bimodally in young children (Gorlin positive) + adolescents, and in adults.1 In addition, it has better prognosis than other variants.[5]

Another variant is the rare infantile variant, which is the Densely Nodular Variant.[5] In <50% the appear in children <3 years old.[1] Its features include having many neurocystic nodules.1 Microscopically, they have large lobules, with neuropil-like tissue, neoplastic neurocytes, and few or non-extracellular tissue.[5] They are in the vermis in 80% of the cases.[1] They have high mitotic activity, pleomorphism, prominent nuclei, and high rate of necrosis.[5]
The Classic Variant have densely packed small round undifferentiated cells with high count of mitosis, and few pleomorphism. They present in 72% of the cases and can arise in all ages but in childhood.[1]

The Anaplastic Variant, which has pleomorphic nuclei with cell-cell wrapping, and nuclear molding. The last variant is the Large Cell Variant. This variant has cells that shows more monomorphism and are with a large-vesicular-rounded nucleus. The last two variant have morphologies that overlap, high mitotic rate, high apoptotic rate, and are both aggressive.[5]

Medulloblastoma is divided into different groups as well depending on its positivity to neuronal markers. All MDBs have glial differentiation that makes them Glial Fibrillary Acidic Protein positive in bona fide neoplastic cells. In Medulomyoblastoma, there is myogenic differentiation (Desmin, Myosin, and Myoglobin positive), while in Melanocytic MDB it has melanotic differentiation.[5]

MDBs are divided into clusters:

WNT- activated 10% of MDBs

They represent 10% of MDBs. This cluster occurs in older children and rarely in infancy. In addition, it has female to male predominance of 2:1. Their cell of origin is the lower rhombic lip progenitor cells. Their histology shows mostly the classic variant (low risk), while rarely the Anaplastic or the Large Cell variants. They favor the midline.[2]

SHH activated/ TP53 wild type

They have no gender predominance and occur in children and adults. Their cell of origin is the cerebellar granule neuron cell precursor in external granule layer and in cochlear nucleus. The predominant histology is the Desmoplastic/ Nodular variant (low risk). In infants, they have the Extensive Nodularity subtype predominantly (low risk). Other morphologies include the classic morphology (low risk), and the Large Cell morphology (uncertain clinical significance).[1]

SHH activated, TP53 mutant

It is present in childhood typically with no gender predominance. It has the same cell of origin as the TP53 wild type. The morphologies: Large Cell (high risk) is prevalent in patients aged 7-17 years, Desmoplastic/Nodular very rarely, and Classic morphology is uncommon (high risk). TP53 mutant and TP53 wild type represent 30% of the cases.[1]

None SHH, none WNT Group 3

It arises from the same cells as the previous two groups but has a male to female predominance of 2:1. The histology includes Classic variant (standard risk), and the large variant (high risk).[1]

None SHH, none WNT Group 4

It is present in all ages group with male to female predominance of 3:1. Their cell type is unknown, and have their morphological variants are the Classic Variant (standard risk) and rarely Large/ Anaplastic variant.1

MDB/ NOS

It has no genetic or histologic classification. This cluster must be differentiated from none MDB tumors before making the diagnosis. Including high grade small cell glioma, embryonal tumors that are with multilayered rosettes, atypical/rhabdoid tumors, and tumors in either the 4th ventricle or the cerebellum.[1]
Latest publications have, in fact, identified up to 12 subgroups for MDBs.

MDBs are the most common pediatric age tumors, which occur in the first decade of life.[1] They represent, as well, 2% of CNS tumors in adults.[7] They are located usually in the apex of the vermis (fastigium), in the roof of the fourth ventricle, in the posterior aspect of the brain stem, or, rarely, they can be supratentorial.[1]
MDB prognosis is dependent on multiple factors, with the following being responsible for poor prognosis: the age of the patient (1.5 cm2 postsurgical residual tumor), the presence of leptomeningeal spread, and poor Karnofsky performance score.[1] In 30% of patients, MDBs will present with leptomeningeal dissemination. However, it is rare that these tumors present with metastasis outside CNS. The five-year overall survival is 70%.[8]
Recurrence, when it happens, is in the posterior fossa.

MDB can be divided into three risk groups: standard risk, low risk, and high risk.
1) Standard risk: when the patient has total or near total resection (1.5 cm2 on early postsurgical axial plane MRI. They include patients as well with extra-CNS metastasis, or in tumors with Large Cell/ Anaplastic histology in group 3 or SHH activated with TP53 mutation.1
This risk stratification is determined to guide the management of the patient. However, this is not the only system that is present in classifying MDBs. The near total resection criterion is a controversial one, since it was placed during CT-era.[1]
Another staging system is Chang Staging System (the most MDB robust staging system) and is described below:
M0= no signs of gross subarachnoid metastasis.
M1= microscopic cells are found in the CSF.
M2= it has gross nodular seeding in either the cerebellum, cerebellar subarachnoid space, in the 3rd ventricle, or in the lateral ventricles.
M3= the seeding is in the subarachnoid space of the spine, or if there is a gross nodule.
M4= the tumor has extraneural metastasis.[1]

Embryonal Tumors with Multilayered Rosettes

These tumors have true Rosettes that are over a background of neuropil. It is both rare and aggressive tumor.[5] They affect children below the age of four years [9,10], with the majority being below two years old. They are in the cerebrum, brain stem, the cerebellum,[5, 3] Pineal Gland, and rarely in the orbits.[3] Their genetic variation is having

an amplification mutation of C19MC gene on chromosome 19. Nonetheless, when they lack this mutation, they are called ETMR, NOS. both variants are WHO grade 4.[1]

Three subtypes have been identified. These are Embryonal Tumors with Abundant Neuropil and True Rosettes, Ependymoblastoma, and Medulloepithelioma.[9,10] The C19MC amplification was demonstrated in 93% of all subtypes. The other very well-expressed protein, and which is specific and sensitive for ETMR subtypes, is LIN28A. The detection of this protein is a dependable and a fast diagnostic method. Nonetheless, in AT/RT LIN28A is expressed but in a lower percentage. In centers where molecular testing is not possible, the histological appearance of multilayered rosettes is obligatory for diagnosis.[9]

Histologically they have small round blue cells with a pseudostratified neuroepithelium that surrounds a lumen that is either empty or has eosinophilic waste material. They are positive for Cytokeatin, CD99, and Vimetin. While being focaly positive for Epithelial Membrane Antigen. In addition, their Ki-67 labeling index is remarkably high.[2]

ETMR reflects the histological appearance present in most, but not all C19MC altered tumors.[3]

Ependymoblastoma, which lack neuropil on histology, Medulloepithelioma, and Embryonal Tumor with Abundant Neuropil and True Rosettes are all put under the classification of EMTR in the WHO 2016 classification. Medulloepithelioma exhibits papillary and tubular structures that are like neuronal tube with variable neuropil. In 20-25%, ETMR will have no Rosettes, no Neuropil, but has inconstant differentiation with probable intratumor heterogenicity of the cells. Due totheir heterogenicity and rarity, advances in the methods of diagnosis for ETMR is vital. C19MC altered tumors are in about 65% of the cases localized at diagnosis. Nonetheless, they constantly have rapid prognosis and are resistant to treatment.[3]

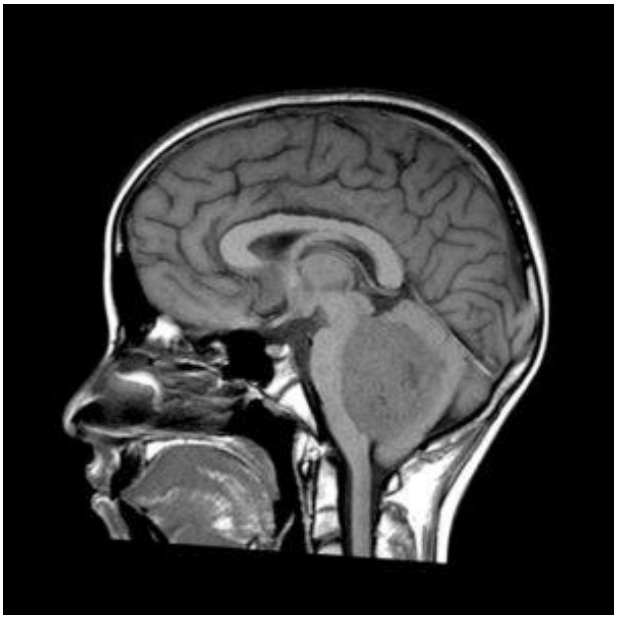


Figure 1. Case courtesy of Dr Antonio Rodrigues de Aguiar Neto Radiopedia.org [11]

Atypical Teratoid/ Rhabdoid tumors (AT/RT)

AT/RT are tumors that are rare.[5] By definition, they are poorly differentiated cells primitive neuroectodermal cells with rhabdoid cells.[1] In 75% of the cases they will be present in the posterior fossa with the rest being supratentorial.[5] Infratentorial location occurs in the Cerebellar hemispheres, Cerebropontine angle, and brain stem. 1 This tumor is a tumor of childhood and can have neuronal, glial, epithelial, mesenchymal, or a mixture of these differentiations.[5]
The genetic mutation they express is SMARCB1 (INI1), or, extremely rarely, SMARCA4 (BRG1).[1]

Histologically, the tumor has pleomorphic cells with few rhabdoid cells (an eccentric nucleus in an eosinophilic cytoplasm). Though, the diagnosis is made when loss of INI1 nuclear staining is lost due to gene mutation.[5]
When the tumor has the histological distinction, but lacks the genetic differentiation, they are called CNS embryonal tumors with rhabdoid features.[1] Few of these patients have primary renal RH tumor.[1]
Pure Rhabdoid tumors outside the CNS differs from AT/RT in the absence of INI1 germline mutation, which is present in the AT/RT. When compared with MDB, MDB kept the INI1 gene expression as well.[5] This distinction is important since it is frequently misdiagnosed as MDBs.1 AT/RT tumors can be positive for Vimetin and EMA.[2]
These tumors have poor diagnosis, but they have, nonetheless, different behaviors. In 33% of the patients at presentation they present with tumor spread. They are WHO grade 4.[1]

AT/RT tumors is divided into three groups:
1-The AT/RT-TYR: they occur in very young children, and they are infratentorial.
2-The AT/RT- MYC: the subtype that presents in older children and they are usually supratentorial.
3-The AT/RT- SHH: in this subtype, the tumor occurs in both age groups.[2]

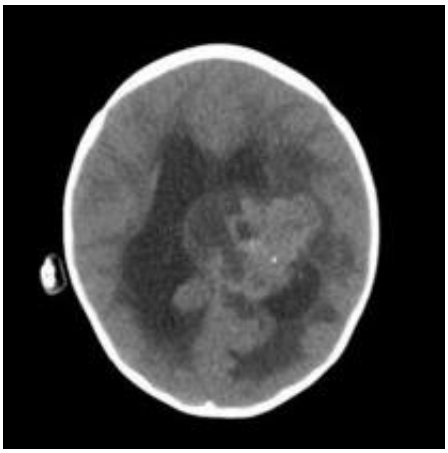


Figure 2. Case courtesy of Dr Bahman Rasuli. Radiopedia.org 12

Neuroblastoma

A very rare tumor that is poorly differentiated with neuroepithelial cells that resemble embryonic neuronal tube. [1] Their cells are small with hyperchromatic nuclei, surrounded by a halo that is clear, areas of neuropil with neurocyte or ganglion cells. Furthermore, they have nuclear palisades, vascular pseudorosettes, and Homer Wright Rosettes. They could have microvascular proliferation.[2]

Genetically, the majority are positive for FOXR1 gene mutation,[2] but some show FOXR2 gene fusion.[3] They present in <4-year-olds with slight female predominance, and they are in the Cerebral Hemispheres.[3]
CNS high grade neuroblastoma with MN1 mutation can have a combination of solid patterns with pseudopapillary ones that are associated with unique hyalinization, and they are GFAP positive. [2]
They are classified as WHO grade 4.[1]

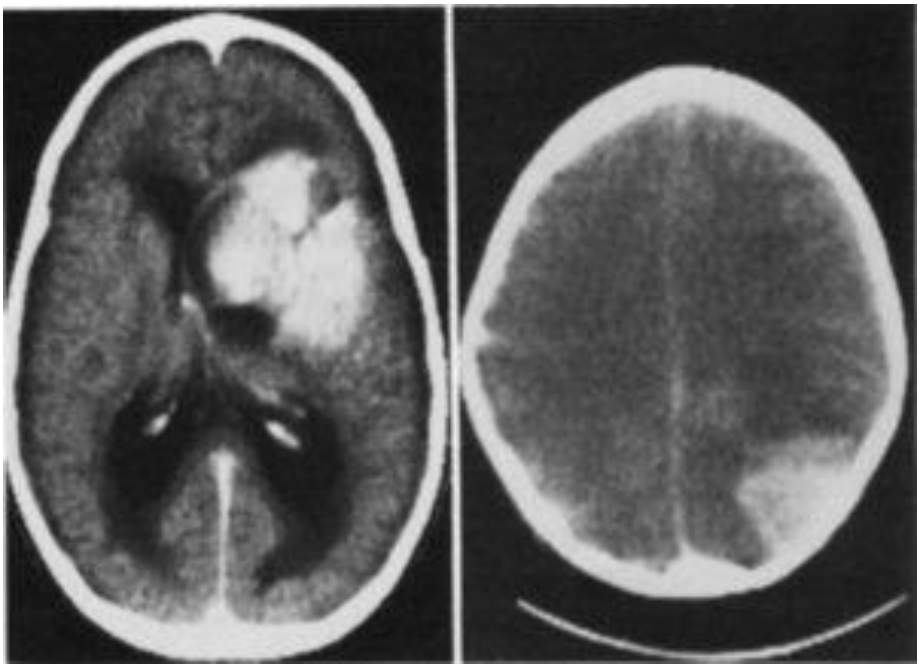


Figure 3. Case courtesy of Journal of Neurosurgery. [13]

CNS Ewing Sarcoma Family with CIC alteration

A highly cellular tumor with small round cells that are arranged in both alveolar and fascicular pattern. 2 The genetic alteration in CNS Ewing Family of Tumors is CIC gene fusion. This mutation, along with CNS high-grade Neuroepithelial Tumor with BCOR alteration, are present in extracranial soft tissue sarcomas that are poorly differentiated.[3]

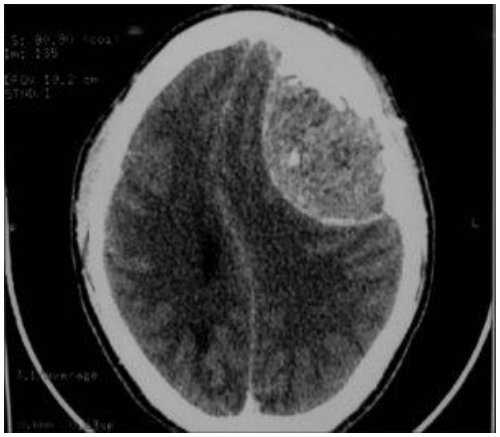


Figure 4: Case courtesy of Asian Journal of Neurosurgery. [14]

High grade Neuroepethelial tumors with BCOR alteration

It is an extremely rare tumor that has a four-year survival of 50%.2 Their location can either be in the Cerebrum or the Cerebellum. Furthermore, it presents in <4-year-olds with equal male to female ratio.[3]

The histological diagnosis of Astroblastoma is compromised by the M1N1 Neuroepithelial subtype.[3]

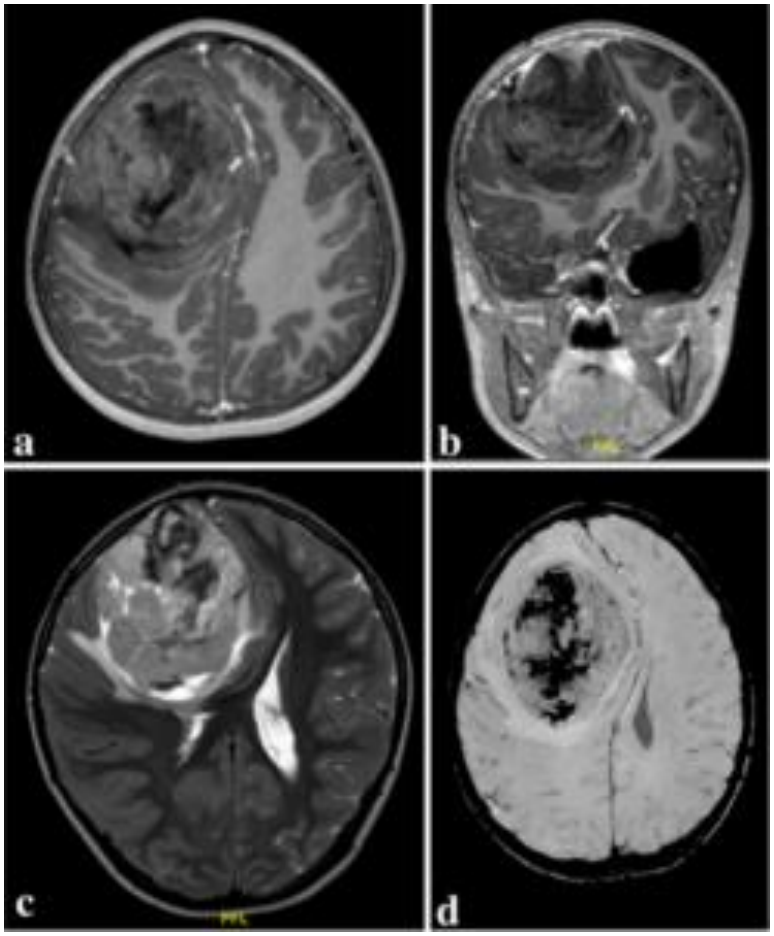


Figure 5. Case courtesy of Springer.[15]

Emberyonal tumors, NOS:

These tumors must be differentiated from supratentorial Ependymoma. Their diagnosis is done through exclusion. Depending on genetic variation, they must be differentiated from high grade Glioma, ETMRs, and AT/RT. This group is the waste basket for tumors that were in the past categorized as CNS PNET and do not fit in any of the new molecularly based categories.[2]

Clinical presentation

Patients with CNS tumors have presentations that depend on the location of the tumor (supratentorial vs. infratentorial)[1], age of the patient, and the type of tumor.[4]
Common presenting symptoms:
1) In 68% of the patients they will present with a progressive neurological deficit with 45% of them being a motor deficit.
2) In 54% the presenting symptom is headache.
3) In 25% they will have seizures that start as focal and progress to generalized.[1]

Headaches are usually morning headaches that are thought to be due to hypoventilation during sleep. These headaches are worsened by coughing or straining, and in 30% while bending forward. Nausea and vomiting will be associated with headaches in 40% of the patients. In addition, the relieving factor for these headaches is vomiting. The presence of these characters with/without a focal neurological deficit and seizures is the description of classic tumor headache. Nonetheless, tumors present with a headache that is in 77% of the cases with a history that is Tension Headache like, in 9% Migraine like, and in only 8% the classic tumor headache presentation. 2/3 of the headaches come with an increase in intercranial pressure.

Supratentorial tumors present with increased intercranial pressure (ICP) due to direct mass effect of the tumor, edema or, less commonly, due to edema. They also present with progressive focal neurological defect, headache, seizure (frequent first visit symptom), mental status changes, and TIA symptoms. Transient Ischemic Stroke occurs due to occlusion of a blood vessel by tumor cells, or hemorrhage into tumor.

However, tumors that are in infant age group usually evade the diagnosis until the tumor reaches an enormous size. This is due to the expansile nature of the young child's skull, the ability of their brain to recompensate for the lost function, and the difficulty in examining a patient with limited neurological range and is uncooperative.

The common symptoms of pediatric age group include a decline in psychomotor development, poor feeding, vomiting, macrocrania, ataxia, obstructive hydrocephalus (early if posterior fossa tumor), and seizures. The development of these symptoms usually occurs over a short period of time that is between 6 to 12 weeks. In the condition where there is spinal metastasis, there could be urinary retention, weakness, and back pain.
Other possible symptoms include extraocular muscle palsies, truncal or appendicular ataxia, papilledema, and nystagmus.1

The **most common symptoms in pediatric CNS tumors** are headache in 37.2%, vomiting 33.3%, ataxia (most common symptom in older children), and oculo-visual symptoms.[1]

Variation in symptoms occur due to age as well. Nonetheless, symptoms that are associated with increased ICP arise in all age groups and all intercranial tumors.[4] In younger children the presentation is of irritability, vomiting, visual disturbance,[2] and nonspecific symptoms.[4] Children older than 3 years, they will come with vomiting, ataxia, and headache.[2] Cerebellar and brain stem signs are the most common presentation in Medulloblastoma.[7]
The interval between initial clinical presentation and the diagnosis is short, estimated to be 20 days. The pre-diagnosis interval is even shorter in infratentorial tumors, high grade tumors, and younger age groups.[2] Medulloblastoma has a shorter pre-diagnosis interval of 15 days.[4]
The diagnosis must be tissue diagnosis.[7]

Investigations

In a CT scan without contrast, the tumor is hyperdense as a result to their high cellularity, while a CT scan with contrast will show an enhanced tumor, mostly, with calcification in 20% of the cases.[1]

In MRI, there will be a large, demarcated mass with edema surrounding it, and a significant mass effect.[2] T1W1 the tumor will be hypodense to isotense,[1] and with contrast there will be patchy pattern of enhancement.[2] On the other hand, in T2W1 it is heterogenous. This is due to the presence of tumor cysts, vessels, and calcification. Most tumors enhance in MRI with contrast.[1]
In Magnetic Resonance Spectroscopy there will be elevated Choline levels, decreased N-Acetyl Aspartate levels [1,2,] and increased ration Choline Aspartate.[2]
Spinal imaging is done either preoperatively or within 2-3 weeks after the surgery for staging of the tumor. An IV Gadolinium is given with MRI, and a water-soluble contrast with CT or Myelography. These are done to role out drop metastasis.[1]
CSF analysis, if safe, must be done as well for staging, preferably two weeks postoperatively to prevent any false-positive results.[7]

Diagnosis obstacles

Symptoms of CNS tumors are like those of other common illnesses. Therefore, it is important to demark the clinical picture of tumors to prevent unnecessary investigations and avoid delay in diagnosis.[4]

Treatment

The management of the discussed tumor lines is “triple therapy.” This includes surgery, radiation, and chemotherapy. Radiotherapy includes a craniospinal axis dose as a result to the high incidence of spinal and leptomeningeal tumor seeding. [2] The treatment protocol begins with surgery, followed by radiotherapy and chemotherapy.[8] The goal of the treatment is to maximize survival and minimize the treatment consequences.[7]

Surgery

A standard treatment protocol with the goal to remove as much as possible of the tumor without resulting in neuronal damage.[1] Tumor resection is divided into total resection, subtotal (more than 90% of the tumor is removed), and partial resection (when <90% of the tumor is removed).[4] Depending on the degree of resection, the disease outcome can be determined.[7]
When the tumor had attachment in the floor of the 4th ventricle, if there is tumor invasion, or if it is within the area of the Facial Colliculus, it is acceptable to keep residual tumor. In the condition where the posterior arches of C1, and sometimes C2, to reach the Foramen Magnum in midline tumors, the spread of the tumor with the thickening of the arachnoid matter may happen. This is known as "Sugar Coating."[1]

Permanent shunts

They are needed in 30-40% of the patients.[1]

Tumor filters

They are no longer used as frequently as before due to their high incidence of obstruction. 1

Chemotherapy

When patients are younger than 3 years, chemotherapy can be used to delay radiotherapy in about 20-40% of patients with none disseminated Medulloblastoma.[2] Patients that have a tumor relapse will benefit from chemotherapy. However, chemotherapy must be given with radiotherapy even if no indication of disease presence is apparent after the radiotherapy.[7]
The drugs used include Cisplatin, Vincristine, Lomustine, Cyclophosphamide, and Etoposide. These drugs are given instantaneously with high dose intrathecal (Methotrexate of Mafosamide), intravenous, or intraventricular Methotrexate. Adults with SHH activated MDB may possibly have an increment in the response to SMO receptor inhibitors, and those drugs that inhibit SHH (Visomodegib).[1] Vincristine, Cyclophosphamide, and Cisplatin, and Ectoposide are frequently used in combination. In addition, Intrathecal Methotrexate can be given with Topotecan as part of the treatment plan. Furthermore, Myeloablative Chemotherapy with a hematogenic Stem Cell rescue following it has been used.2 Patients younger than three years, and some who are below 4 years, are given high dose chemotherapy (Vincristine, Cisplatin, Cyclophosphamide) with Thio-peta based higher dose chemo, and peripheral stem cell rescue.[3] If sole chemotherapy treatment fails, radiotherapy is started with both CSI and local boost.[7]

Radiotherapy

Radiotherapy is given to the craniospinal axis, and to the primary tumor site in patients older than 3 years. Patients who are younger than this age will demonstrate delirious sequalae to their developing nervous system. The tumors described above are radiosensitive, and radiotherapy is the best post-surgical therapy. The purpose of the craniospinal axis irradiation (CSI) is to eliminate tumor cells that may remain hidden clinically. A greater dose of radiation is given to the tumor site. Whether primary or a residual tumor in an older child. An added radiation is given to the hypothalamus and the temporal lobes.[7]

In low-standard risk MDB, particularly those within the pediatric age group, can be treated with a decreased radiotherapy dose of 23.[4] Gy to the craniospinal axis. This is in addition to the radiotherapeutic boost of 54-55.[8] Gy to the primary site. Adjuvant chemotherapy is used as well. In high risk MDB, conventional fractionated radiotherapy once per day of 54 Gy to the primary tumor, and 18 Gy to the craniospinal axis.1When high-dose radiotherapy is used for a long duration harmful consequence will result with MDBs.[2]

To decrease the hearing damage, which scatter from the radiotherapy boost to the posterior fossa can cause, intensity modulated radiotherapy is used. Furthermore, a method that needs more studies to explore its efficacy and safety, is the use of proton beam therapy to reduce the toxic effect to none target tissues.[7]

The treatment with radiotherapy, with or without chemotherapy, post-surgically is used in patients older than 3 years.[4] This combination of therapy will result in a 5-year survival of 85-95% in a none-disseminated disease,[7] and a progression free survival (PFS) of 81-86%. In younger patients (<3 years), who have MDB, the PFS is 30-40%. Possibly due to the aggressive nature of the disease, and the omission of radiotherapy from the treatment protocol for this age group. However, Desmoplastic MDBs have PFS of 85% at 5 years even when treated with chemotherapy alone. In general, MDBs have better prognosis than the other tumors.

The use of biological agents in infants and children is being studied to improve the treatment outcome. [3]

Diet and lifestyle

A. Evasion of supplemental antioxidants is essential due to the promotion of the reduction in tumor cells death.[7]

B. In one third of the cases there will be malnutrition as proved by their calculated BMI. This problem is important to address since malnutrition has multiple disadvantages, among them is the increased rate of side effects of the drugs given for cancer patients. Cyproheptadine Hydrochloride and Megestrol Acetate are helpful in weight gain for patients suffering from cancer and cancer-treatment-related cachexia. However, if weight loss is severe and unrelenting, parenteral, and enteral feeding is necessary. Particularly if there is a neurological deficit that impairs the oral feeding. It is worth

mentioning that diet counseling was not proven to be a proper management for the malnutrition these patients suffer from.[7]

Physical and speech therapy + exercise

They enhance the outcome in adult patients postoperatively, and they are recommended in children though no studies are present.[3]

In emergency presentation, the patient should be stabilized with placement of extra-ventricular drain and administering high-dose IV steroids. Once the patient is stable, MRI should be done with or without contrast.[7]

The best overall survival is in patients who have done total resection, are given radiotherapy, high dose chemotherapy, and autologous stem cell rescue.[3]
The combination of Azacytidine with Vorinostat, and Rapamycin have a synergistic impact on ETMR cell line growth.[3]
Other promising advances in treatment include the addition of Histone Deacetylase Inhibitor, which is a differentiation agent, with the conventional chemotherapy. In addition, the therapeutics that target the SHH and WNT pathways have been suggested.[3]

Treatment complications

1) Hair loss

Patients receiving chemotherapy and radiotherapy will suffer from temporary hair loss. Depending on the radiotherapeutic dose, the degree of alopecia will occur. Radiotherapy induced alopecia remains until 2-3 months after stopping the therapy. However, full recovery may extend to a couple of months after that. When chemotherapy is taken, hair recovery is after stopping the treatment as well.[7]

2) Dermatitis

Dermatitis is generated by radiation is treatable with skin moisturizers. Nonetheless, caution should be placed when the patient is taking anti-epileptic drugs (Phenytoin and Carbamazepine) due to their increased risk for developing Steven Johnson Syndrome. The presentation is of a rash that goes beyond the radiation area.[7]

3) Myelosuppression

It is severer when both radiotherapy and chemotherapy are given in conjugation. Its management is by giving blood, platelets, and/ or GM-CSF for neutropenia.[7]

4) Mucositis and/or esophagitis could occur due to radiotherapy.

They are treated with oral anesthetics rinses (Lidocaine), proton pump inhibitors, and/or H2 blockers.

5) Radiotherapy

It can result in an increased risk for the development of strokes. In general, the exact incidence of cerebrovascular accident (CVA) is not known, but a patient with brain tumor presenting with clinical symptoms of CVA, or if they have an elevated risk, should undergo MRA. [7]

6) Neurocognitive and endocrine consequences

In one third of school-aged children they will need special education centers. The most common hormone to be affected is growth hormone. Other frequently injured sites within the endocrine system are the hypothalamus, pituitary gland, and the thyroid (hypothyroidism). Hypothyroidism results from scatter from CSI. [7]

7) Somnolence Syndrome

A syndrome where patients may suffer from fatigue, increased sleepiness that reaches up to 18 hours, nausea, and anorexia, 2 to 8 weeks after radiotherapy. On investigations, there will be electroencephalography slowing and rarely CSF pleocytosis. Only reassurance is required.[7]

8) Moya-Moya disease

This could occur years after radiotherapy.[7]

9) hearing loss

Cisplatin that is given with radiotherapy.[7]

10) Surgery complications

Septic or aseptic meningitis, CSF leak, pseudomeningiocele, diplopia, Abducens nerve injury in Bone Marrow resection (temporary for a period of a couple of months), ataxia in resection of the Vermis, incoordination of the limbs in Cerebellar Peduncle injury.[7]

Prognosis

Poor prognostic factors include those that are related to age (1.5 cm postsurgical residual tumor).[1] Other poor prognostic factor include postponement in diagnosis, insufficient initial response to treatment, a general condition that is poor, great tumor size, and poor defined margins. The median survival is less than 2 years in ATRT.[2] On the other hand, the five-year survival for MDBs is up to 70%.[8]

Appropriate diagnoses with accurate molecular identification results in a better outcome.[2] When diagnosis is delayed, there will be tumor evolution, development of hydrocephalus, and tentorial herniation. If the delay reached to the point of requiring prompt surgical resection, delirious sequelae to the neurocognitive and endocrine function, surgical morbidity, and visual outcome.[4]

If the patient has disseminated disease and an incomplete surgical resection is done, the outcome will be poor.[3] MDB usually has wide invasion, which requires limitation to the resection of the tumor (incomplete resection). In MDBs, drop metastasis should always be assessed for. In addition, MDBs have seeded the craniospinal axis in 10-35% of the cases, and in 5% extra-neural metastasis. This is sometimes promoted by shunting, even though shunts are uncommon. Children and infants are the most difficult to manage due to the aggressive nature of the disease, and their young age.[1]

CSI has shown better prognosis, while giving chemotherapy prior to radiotherapy in patients older than 3 years has worse outcome.[3]

When secondary tumors happen (Meningioma and Glioma) they have worse mortality and morbidity.[7]

Tumor type specific treatment and prognosis

1) Medulloblastoma

Due to the varying liquid biopsy biomarkers, treatment is impaired in MDBs. After standard treatment, several patients with MDBs result in recurrence of the tumor, or distant metastasis. 40% will have metastasis at the time of diagnosis, and in more aggressive tumors they can have local recurrence or metastasis after treatment.

MDBs are very heterogenous on both cellular and molecular basis. However, the presence of stem cells that are capable of self-renewal is an indicator for possible post treatment recurrence. These cells will either be normal stem cells that have undergone malignant changes, or they can be neoplastic cells that have acquired stem-cell properties by their collaboration with the extracellular factors, and microvesicles with the microenvironment surrounding the tumor.

Important prognostic factor for MDBs is the expression of c-erbB-2 (HER2/neu) oncogene. (radiopedia/ medulloblastoma)

The most common MDB subtypes that are associated with poor prognosis due to the

recurrence after treatment (surgical, radiotherapeutic, and chemotherapeutic) are SHH subtype, group 3, and group 4. Both SHH and group 3 are associated with 70% recurrence in a year. The recurrence in groups 3 and 4 is the hardest to treat.[6]

2) ETMR

It has a uniform dismal prognosis even with ultimate multidisciplinary management.[9,10] Optimal treatment protocol is not yet identified.[9,10] However, several doctors recommend the combination of surgical resection, CSI, and chemotherapy. To enhance the outcome, it has been suggested that extensive resection of up to 1 cm should be done. This is performed on the tumor's nearby brain tissue, or infiltrated tissue. Extended surgical resection method includes the use of high dose chemotherapy and decreased prophylactic CSI dose. Using this management protocol was reported to encompass enhanced outcome as compared to giving chemotherapy and high dose chemotherapy alone post operatively. Nonetheless, since most ETMR patients are younger than 4 years, the impact of CSI on the neurocognitive function must be kept in mind.[9]

At diagnosis, some cases had leptomeningeal invasion, invasive involvement of the extracranial soft tissue, and metastasis. If not present at the time of diagnosis, these features were developed in several cases with time. A recent study showed that tumors that recur after treatment show increment in somatic single nucleotide variant, which were discovered to be associated with a mutation that occurs as a result to the exposure to Platinum based agents. This implies possible association with treatment; a finding that can explain the reason behind rising chemotherapeutic resistance and suggests the importance of early radiation.

Studies show that the percentage of metastasis at diagnosis is 13%, encouraging the possibility of using radiotherapy that is focused on tumor site only, if given early. In addition, the poor sequalae after radiation can be decreased to a limited degree based on the use of focal, low radiation exposure, and proton therapy.

Intrathecal administration of either Etoposide alone, or Etoposide used interchangeably with liposomal or aqueous Cytarabine with/without Topotecan was shown to decrease the leptomeningeal spread in patients receiving radiotherapy alone. Inappropriate for this management approach are infants aged younger than 18 months, and infants with metastasized tumor initially or those with significant are of treatment or volume. Treatment option for this group is the use of early intensive chemotherapy (maintenance therapy following a high dose chemotherapy) using new agents. They are treated with surgery followed by chemotherapy with or without delayed radiotherapy.[10]

3) AT/RT

In adults, it has high recurrence rate after surgery. Their prognosis is poor, even after the triple approach of surgery+ radiotherapy+ chemotherapy. Nonetheless, the triple approach is better than other treatment approaches in terms of outcome.[16]

In younger children, giving intensified chemotherapy as an alternate to radiotherapy to avoid the delirious toxic effect of radiotherapy in this age group. The treatment for AT/RT has no specific approved tumor management protocol.[17]

References

1. Maiti & Bidinger. 済無No Title No Title. Journal of Chemical Information and Modeling vol. 53 (1981).

2. Maaz, A. U. R. et al. Presenting symptoms and time to diagnosis for Pediatric Central Nervous System Tumors in Qatar: a report from Pediatric Neuro-Oncology Service in Qatar. Child's Nerv. Syst. ChNS Off. J. Int. Soc. Pediatr. Neurosurg. 37, 465–474 (2021).

3. Sin-Chan, P., Li, B. K., Ho, B., Fonseca, A. & Huang, A. Molecular Classification and Management of Rare Pediatric Embryonal Brain Tumors. Curr. Oncol. Rep. 20, 69 (2018).

4. Choi, S. H. et al. Treatment Outcome and Prognostic Molecular Markers of Supratentorial Primitive Neuroectodermal Tumors. PLoS One 11, e0153443 (2016).

5. Kliot, M., Magistretti, P. J., Friedlander, R. M. & Haglund, M. M. Introduction and General Neurosurgery Oncology Pediatrics. (2017).

6. Kaid, C. et al. Proteome and miRNome profiling of microvesicles derived from medulloblastoma cell lines with stem-like properties reveals biomarkers of poor prognosis. Brain Res. 1730, 146646 (2020).

7. De Braganca, K. C. & Packer, R. J. Treatment Options for Medulloblastoma and CNS Primitive Neuroectodermal Tumor (PNET). Curr. Treat. Options Neurol. 15, 593–606 (2013).

8. Sedano, P. et al. Real-world data for pediatric medulloblastoma: can we improve outcomes? Eur. J. Pediatr. 180, 127–136 (2021).

9. Bouali, S. et al. Embryonal tumor with multilayered rosettes: illustrative case and review of the literature. Child's Nerv. Syst. 34, 2361–2369 (2018).

10. Mayr, L. et al. Potential Importance of Early Focal Radiotherapy Following Gross Total Resection for Long-Term Survival in Children With Embryonal Tumors With Multilayered Rosettes. Front. Oncol. 10, 584681 (2020).

11. Radiopedia. No Title. https://radiopaedia.org/cases/medulloblastoma-55?lang=us (2019).

12. Radiopedia. No Title. https://radiopaedia.org/cases/atypical-teratoid-rhabdoid-tumor-atrt-1?lang=us (2021).

13. Mitchel S. Berger M.D. 1 , Michael S. B. Edwards M.D. 1 , William M. Wara M.D. 1 , Victor A. Levin M.D. 1, and C. B. W. M. D. 1. No Title. J. Neurosurg. 59, (1983).

14. Vikul Kumar1, Anshu Singh2, Vivek Sharma1, M. K. No Title. Asian J. Neurosurg. 12, 351–357 (2017).

15. Shilpa Rao, Saikat Mitra, Harsha Sugur, Vikas Vazhayil, B. Ravi Mohan Rao, Santosh Kumar Annayappa, B. N. Nandeesh, T. C. Y. & V. S. No Title. Springer (2021).

16. Peng, A. J. et al. Atypical teratoid/rhabdoid tumor in adult: case series and an integrated survival analysis. Br. J. Neurosurg. 1–16 (2021) doi:10.1080/02688697.2021.1885620.

17. Ma, X.-J. et al. Overall Survival of Primary Intracranial Atypical Teratoid Rhabdoid Tumor Following Multimodal Treatment: A Pooled Analysis of Individual Patient Data. Neurosurg. Rev. 43, 281–292 (2020).

Article topic: Arachnoid Cyst.

Author: Rania Sanouri.

Editor: Philip Sweidan

Reviewer: Omar Jbarah, Hassan AbuShukair.

Key Words: Brain Cyst, Pediatrics, Seizure, VP Shunt.

Introduction

Arachnoid cysts are benign fluid collections found within the arachnoid mater layer of the meninges (1). The first reported cases of IACs were in 1831, in which the majority (75%) of the cysts were found in children (2). Population studies revealed that arachnoid cysts makeup about 1% of intracranial space-occupying lesions and are found in 1.7% of the adult population and 2.6% in the pediatric population (1). Most arachnoid cysts are incidentally discovered with only a minority of the cysts can become symptomatic and require a neurosurgical intervention (2). The etiology behind their presence is poorly understood and usually seen when workup for headache, increased head circumference, or developmental delay is ordered. Most arachnoid cysts can be found in congenital anomalies. Arachnoid cysts could arise secondary to traumas, hemorrhages, or meningitis. It is infrequent for these cysts to cause cranial neuropathies, seizures, or psychiatric disorders (3)(4)(5).

Epidemiology:

Intracranial arachnoid cysts (IACs) have a male to female predominance of 2:1 to 5:1(2). They can occur in association with many genetic syndromes including AD polycystic kidney disease, Neurofibromatosis, mucopolysaccharidosis, schizencephaly, Down's syndrome, acrocallosal, and Aicardia syndromes (2). Acquired arachnoid cysts represent a smaller number of cases compared to congenital cysts (6). Symptomatic IACs incidence as reported in a large pediatric series is around 6.8% (2).

IACs arise throughout the neuroaxis, and half of the cysts are in the middle temporal fossa (MTF). Other locations are the posterior fossa, the suprasellar region, and rarely intraventricularly (2). Middle fossa or Sylvian fissure cysts are the most common in all age groups (7).

Amongst adults, middle fossa and retro cerebellar cysts show almost similar prevalence (34% and 33%, respectively) (7). Middle fossa cysts in adults were associated with a lower rate of symptoms, whereas cysts located in the cerebellopontine angle,

quadrigeminal cistern (Figure 1), sella, and ambient cisterns, were found to be symptomatic. (7).

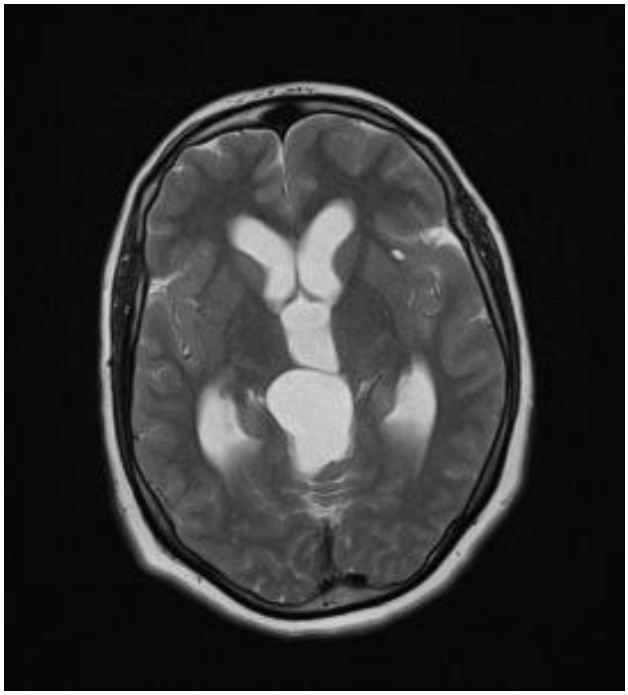


Figure 1: Quadrigeminal cistern, Case courtesy of Dr Farhad Farzam (63)

Pathogenesis:

Since most cases are seen in the pediatric population, a congenital or genetic cause is suspected (8). Various hereditary syndromes, such as Marfan's syndrome, neurofibromatosis, glutamic aciduria type I, autosomal dominant polycystic kidney disease, and tuberous sclerosis, were proved to have a higher incidence of arachnoid cysts than the general population (9). A recent genetic association was defined in a consanguineous family with a high prevalence of arachnoid cysts. A link was found between familial arachnoid cysts to chromosome 6q22.31 -23.2.

Earlier, IACs were thought to result from gestational ischemic, traumatic, or infectious insults; these theories are no longer supported (2). A more recent viewpoint for middle fossa IACs is that it was a failure of the frontal and temporal embryonic meningeal merging, resulting in a duplication within the Sylvian fissure (2). Some suggestions about IACs origination include that it is being achieved by splitting of the arachnoid membrane layers during fetal development, forming a "potential space" for cerebrospinal fluid (CSF) (2).

Embryology:

The origin of arachnoid cysts is still unclear and has many controversies. Their formation is believed to be the result of abnormal embryologic development of the subarachnoid space. (11)

At early normal embryonic development, one layer of connective tissue called the meninx Primitiva, or “the perimedullary mesh” will be the precursor to the pia and arachnoid maters and line the surface of the dura and surround the neural tube. At 15 weeks of gestation, the rhombic roof will rupture, and CSF leaves this mesh, pia and arachnoid matters will incompletely separate, resulting in the cobweb-like appearance of the arachnoid. (11)

The primary hypothesis for arachnoid cysts formation implies that separation of the superficial arachnoid and pia matter is aberrant and that enclosed chambers form and develop into a cystic mass. Instead, the meninx Primitiva formation is aberrant, which may also lead to cyst formation. This hypothesis was found to be accepted, as arachnoid cysts were near an arachnoid cistern in most of the cases. (11)

This embryologic model explains the presence of cysts but lacks an explanation of how and why these cysts expand. Numerous explanations were proposed about why cysts may generate intra-cystic pressure and produce parenchymal compression, though, most were unsatisfactory and no direct evidence of fluid production within the cyst has been found. (10)

According to the size, most cysts remain stable in size and rarely disappear, moreover, a slit valve may exist between the subarachnoid space and the cyst, allowing only entry of CSF. Slit valves are directly being observed with endoscopy and until this time, are the most direct explanation for why the cysts expand. (12) (13) (14)

CT cisternography or cine-phase contrast-enhanced MRI sequences usually show filling or emptying of the arachnoid cyst. On normal CSF pulsation or Valsalva maneuver, in addition to the geometry of the split membrane, the pressure gradient which drives fluid into the cyst can be assessed. (12)(13)(14)

Clinical presentation:

Diagnosis of IAC was found more common in childhood, as the prevalence is most at 1 and 5 years (3.8% and 4.6% respectively) (3). This correlate well with previous studies that found children younger than 2 years had higher prevalence (15).

The clinical presentation for non-incidental paediatric arachnoid cysts is very similar to other childhood mass lesions. The most common indications for work-up and thus treatment of arachnoid cyst involved progressive macrocephaly, intracranial hypertension, headache, hydrocephalus and developmental delay (3)(15).

The most common complaint found in adult patients was headache, However, other complaints in symptomatic arachnoid cysts involved vertigo, ataxia, hearing loss and seizures (also, common) (2).

It was found that arachnoid cysts predispose patients to intracranial hemorrhage for example after mild head trauma (16).

One theory regarded by computational mechanistic study, supports the fact that hemorrhage is attributed to the elevated sheer forces trauma that is delivered to the outer edge of the cyst compared to the normal brain (17).

It also states that larger cysts are more likely to cause hemorrhage. According to Cress and his colleagues, 6% of arachnoid cysts were associated with hemorrhage over a 5-year period. Factors that highly increase the risk for hemorrhage include large maximal diameter of the cyst in addition to history of head trauma (18).

Wester and Helland stated that 4.6% of arachnoid cysts over 17 years and noted that hemorrhages occurred more in temporal cysts (19). In this study group, only 6% with temporal cysts were found to have cyst related hemorrhage. Both studies assume that cyst-related hemorrhages are rare events.

The overwhelming majority of IACs do not change in size from the time of the initial diagnosis. These lesions only rarely expand in the pediatric population; when they do occur, they are primarily found in children under 4 years of age (2).

The following table describes the wide range of presenting symptoms: (Table 1)

Table 1 (2)

Range of presenting symptoms

	Symptoms	**Mechanism/Notes**
Symptoms attributable to mass effect either from the IAC, from cyst rupture, or from cyst hemorrhage	Symptoms of increased ICP (HA, emesis, AMS, vision changes, etc.)	Can be obstructive HCP from compression at a variety of places or nonobstructive HCP presumed to be due to abnormal SCF flow dynamics
	CPA syndrome (tinnitus, hearing loss, facial palsy, nystagmus, and/or vertigo)	CPA IAC
	Parinaud's syndrome	Tectal compression by quadrigeminal plate IAC

	Glacial change (bony remodeling) with or without proptosis	Typically, from MTF IACs resulting in cranial asymmetry ranging from focal skull prominence to disfiguring deformity with distortion of the nearby orbit with proptosis
	Endocrinopathy	Compression of HPA structures by suprasellar IAC
	Seizures	Epileptogenicity localized to affected cortex
Nonspecific symptoms with unclear relationship to IAC	Headache	Headaches unable to be attributed to increased ICP
	Nonlocalized seizures	Seizure foci unable to be precisely localized to affected cortex
	Developmental delay or cognitive deficits	Controversial

IAC=Intracranial arachnoid cysts; ICP=intracranial pressure; CPA=cerebellopontine angle

Supratentorial Arachnoid Cysts

The most common type of intracranial cysts is Sylvian fissure arachnoid cysts or “middle or temporal fossa cysts.” Almost half of the cysts that occur in pediatrics are found in the middle fossa, and predominantly in the male gender on the left side (66%) (3). In adults, IACs are less prevalent (34%) and their distribution on both sides is the same as in children (7) No statistical significance outside the temporal fossa was described in gender differences. (20)

The most common presentation is a unilateral headache in the supraorbital or temporal region that may be increased with physical exertion. The second most common symptoms are Focal, complex-partial, or generalized seizures. These seizures occur in up to one-third of the patients. It is rare to find symptoms of Increased intracranial pressure (ICP) like nausea, vomiting, or papilledema. (21)

Galassi classification (1982) is an extensively used classification for middle temporal fossa (MTF) IACs, which account for half of all IACs. It classifies MTF cysts into 3 significant types based on their sizes and the mass effect they exert. (2) Type 1 cysts are small lens-shaped collections at the anterior pole of the middle fossa, they cause little mass effect and are not associated with calvarial deformities. They freely communicate with CSF on MR-cine or CT-ventriculography. Type I cysts are the most common type, as 68% of the cysts are in this category and rarely require surgery. (2)(3)

Type II cysts are intermediate in size with a rectangular morphology extending to Sylvian fissure they exert a local mass effect on the temporal lobe and cause midline shift, thus requiring surgery. (2)

Type III cysts are large, rounded cysts that involve the entire length of the Sylvian fissure. They usually cause midline shift due to marked mass effect with thinning and expansion of the middle fossa cranial bones (thinning of temporal squama or displacement of the wings of the sphenoid bone) or spreading of cranial sutures in young children. Recent studies found 17% of the arachnoid cysts to be found in this category. They occupy the middle fossa and extend into the anterior fossa compressing the frontal lobe. These cysts do not communicate with the subarachnoid space and usually require surgery. (2)(3)

Parasellar IACs are subdivided into intrasellar and suprasellar cysts according to their relationship to the diaphragma sella. 50% of supraceller cysts were diagnosed in children less than 5 years and 20% less than 1-year-old. Symptomatic supracellar cysts cause hydrocephalus when they reach the third ventricle and obstruct the aqueduct of Sylvius. Other serious symptoms may include visual abnormalities, gait ataxia, opisthotonos and a syndrome called “Bobble-head doll” syndrome.10-60% of suprasellar cases are going to have endocrinopathies including precocious puberty and growth hormone deficiency. (22) (23)

However, according to many MRI studies, a finding of a suprasellar cyst was not significantly associated with the presence of symptoms. (3)

Infratentorial Arachnoid Cysts

Arachnoid cysts in the cerebellopontine angle usually cause symptoms very similar to Meniere’s disease, those include tinnitus, vertigo, facial weakness, hearing loss and ataxia. Other symptoms are trigeminal neuralgia and hemifacial spasm. (24)(25)(26)

One entity of IACs presents as a large posterior fossa cyst in the midline, and usually cause an obstructive hydrocephalus. These cysts should be distinguished from other lesions seen in Dandy-Walker malformation, mega cisterna magna, epidermoid cysts, large cystic tumours. (1)

It is unusual for posterior fossa cysts to present with cerebellar signs like nystagmus, ataxia, and cranial nerve dysfunction or even progressive quadriparesis. (27)(28)(29)

Imaging

Congenital arachnoid cysts on CT or MRI appear as well circumscribed, smoothly marginated, nonenhancing lesions that are isodense and intense to CSF. They have

relatively thin walls that exert mass effect on the surrounding structures, and borders that are difficult to be seen on conventional Imaging. The mass effect on adjacent structures and associated anomalies can best be visualized when combined with contrast imaging to highlight the surrounding vascular anatomy.

Ultrasound often identifies arachnoid cysts in utero or in the neonatal period, but more advanced imaging is usually needed for further characterization.

A noncontrast CT is used to differentiate an arachnoid cyst from other cystic lesions. Communication between the cyst with the basal cistern and the subarachnoid space can be appreciated by CT ventriculography or (cisternography). (27)(28)(29) CT alone is not enough for demonstrating CSF flow dynamics and communication of the arachnoid cyst to the surrounding subarachnoid space.

CT with intrathecal or intraventricular injection of metrizamide can give anatomic detail of the subarachnoid and intraventricular space.

In noncommunicating cysts, it takes 2 to 6 hours for the contrast(metrizamide) to enter inside the cysts, thus the contrast accumulates around the cyst in the cisterns first, creating a halo demarcating the cyst boundary. The contrast then clears from the subarachnoid space and accumulates within the arachnoid cyst.

In communicating arachnoid cysts, the cyst fills with metrizamide, but It's clearance from the cyst is delayed with respect to the surrounding subarachnoid space and basal cistern.

MRI has a high resolution to detect even the smallest cysts and those found near bony structures. 3D relationship of arachnoid cysts to the basal cistern can be seen with multi-planar acquisition of MRI.

MRI can distinguish between CSF-like fluid of most arachnoid cysts and the proteinaceous fluid of other cystic lesions.

MRI sequences can differentiate epidermoids from arachnoid cysts by the hyperintense appearance on proton density–weighted and diffusion-weighted sequences. (30)

Cysts caused by parasitic infections also appear hyperintense on proton density–weighted images. (31)(32)

Treatment

Conservative Management

Natural history tends to favor conservative management for arachnoid cysts. With the increasing demand for central nervous system imaging, it is likely that the incidence of arachnoid cyst diagnosis has increased as well. Although headache is the most common presenting symptom, it is far from the only complaint suggestive of a symptomatic cyst. Additionally, confounding treatment decision making is the observation that even though headache is a common medical complaint, arachnoid cyst is an uncommon finding. Correlation of these common symptoms to pathology does not necessarily imply causation. Therefore, a detailed neurological and psychiatric history is important in the diagnosis and evaluation of patients with arachnoid cysts. It is also worth noting that conservative treatment has been applied successfully to symptomatic cysts or enlarging cysts as well (33)(34).

Although there is considerable controversy about what treatment should constitute the standard of care regarding arachnoid cysts, survey results indicate that most surgeons prefer observation over direct surgical intervention. A study by Tamburrini and associates assessed the practice patterns of the international pediatric neurosurgery community through a case history survey (35). Participants were asked to make recommendations in the case of a pediatric male patient found to have an asymptomatic Galassi type II arachnoid cyst. Most (60%) recommended continued clinical follow-up, and 50% recommended a baseline MRI. A minority (17%) recommended surgery to reduce the lifetime risk for hemorrhage, and 26% recommended avoidance of contact sports for the untreated cyst (3).

Arguments against conservative management tend to rest on the subtlety of symptoms as well as the risk for cyst hemorrhage or expansion. As stated previously, the risk for hemorrhage is minor (approximately 5% of patients), although no prospective trial has assessed the lifetime risk in these patients. The risk for cyst expansion has been similarly shown to be low. In a subgroup analysis of 111 pediatric patients who presented with what were thought to be asymptomatic arachnoid cysts, Al-Holou and colleagues found cyst expansion in 11 patients, decrease in cyst size in 13 patients, and stable cyst size in the remaining (3).

Of those 11, 4 eventually underwent surgery because 3 developed symptoms related to the cyst and 1 had concomitant intractable temporal lobe epilepsy. The authors also noted that cyst expansion seemed to occur exclusively in the very young patients; no patients who were found to have arachnoid cysts after 4 years of age experienced cyst expansion (35).

Surgery

Arguments in favor of surgery tend to cite the improvement in the wide variety of symptoms as the rationale for intervention. Other potential consequences of intracranial mass lesions, such as intracranial hypertension, have been investigated as well, but the

results have not helped to identify those patients who will benefit from surgery (35, 36). Di Rocco and colleagues demonstrated that the 2 patients in the study with Galassi type III cysts had universally elevated ICP on invasive monitoring (35). Half of the patients with Galassi type II cysts had increased ICP, but the implications of this finding were unclear because these patients had cysts that were either asymptomatic or had been diagnosed prenatally. When assessing the effect of elevated intracystic pressure on preoperative symptoms or postoperative results, Helland and Wester found a positive correlation between pressure and the severity of symptoms (36). However, the mean intracystic pressure was within normal limits for all types of temporal cysts. Patients from all groups experienced a postoperative improvement in symptoms, and this improvement was independent of the improvement in cyst size. These studies show that the mechanism of symptomatology may be more complex than simple pressure differentials.

In terms of surgical approaches, several techniques have been shown to be effective for arachnoid cyst treatment. For pediatric patients, a meta-analysis of reported case series revealed similar quality-of-life outcomes for all three types of intervention (37).

Cystoperitoneal Shunt

Some advocate placements of a cystoperitoneal shunt as a first-line treatment to achieve early cyst obliteration while avoiding large fluid shifts associated with microsurgery (37, 38, 39). This practice is controversial, however. Cystoperitoneal shunting may offer the advantage over microsurgical fenestration for improved reduction in postoperative cyst volume (74% versus 58%) (40).

Risks unique to shunt placement include shunt dependency, slit ventricle syndrome, shunt infection, and requirement for shunt revision.

Strategies to avoid these complications include placement of an adjustable pressure valve, attempted removal when cyst obliteration is proved, and avoidance of low-pressure or valveless shunts (41-43). In centers where shunting is the preferred first-line treatment for arachnoid cysts, authors report similar efficacy to microsurgery and similar rates of shunt complication to other pathologies treated by shunting. Placement of a ventriculoperitoneal shunt may be necessary to treat concomitant hydrocephalus before resection of the cyst. Finally, for patients presenting with quadrigeminal cistern or pineal region arachnoid cysts, Torkildsen shunt variation 95 offers the ability for cyst drainage without the risk for overdrainage (44).

Endoscopic Fenestration

Neuroendoscopy has emerged as an effective alternative to microsurgical fenestration and excision. The surgical strategy for cyst fenestration remains the same, but

endoscopy offers several advantages over microsurgery. For midline and intraventricular cysts, endoscopy offers the ability to visualize the boundaries of the cyst as well as critical adjacent structures but reduces the need for extensive dissection. The overall clinical success rate is 83% to 92% (45-53).

Suprasellar, quadrigeminal, and posterior fossa cysts have higher rates of success compared with Sylvian fissure and interhemispheric cysts. Meta-analysis of published case series demonstrated no significant difference in rate of success for endoscopic fenestration of suprasellar, quadrigeminal, and posterior fossa cysts versus open surgery with shunt placement, while the rates of success for sylvian fissure and the interhemispheric fissure cysts is significantly less effective (47).

Some case series report higher rates of recurrence or postoperative complications in patients treated with endoscopy. The most common postoperative complications include subdural hematoma, subdural effusion, and cyst recurrence. However, these numbers are highly variable, and it is not clear what factors are associated with complication development. Several technical modifications can be done to improve outcomes. First, a wide fenestration is recommended to avoid cyst reclosure. Ventriculocystocisternostomy may produce more durable results compared with ventriculocystostomy (55,56).

Spinal Arachnoid Cysts

Arachnoid cysts formed within the spine, can either be found intradurally or extradurally. Those cysts usually involve the thoracic spine and cause subtle symptoms mimicking cord compression. (57,58)

Most patients with spinal arachnoid cysts (SACs) complain of intermittent back pain or radicular pain that is exacerbated by Valsalva manoeuvre. According to Wang & his colleagues, cysts that were found ventral to the spinal cord were more to cause myelopathy and weakness, while dorsal cysts caused more numbness. The cause behind IACs is still unknown but is thought however to be congenital or secondary to infection, trauma, or inflammation. MRI is found to be the most sensitive and specific study for diagnosing SACs. SACs can be found incidental just like the case in IACs (57, 59).

For the purposes of studying fluid dynamics within the cysts, location, and differentiation of SACs from other similar lesions, CT myelography, cine-MRI, or diffusion weighted MRI can be done (58).

Goals of surgical fenestration are similar to IACs. Wide fenestration of the cyst is enough to prevent recurrences. Symptoms of myelopathy and weakness are more likely to resolve after surgery than numbness & pain. Many centers have reported success with

an endoscopic approach, either as primary treatment or to look for cyst wall boundaries (60,61).

Conclusion

Arachnoid cysts are nonneoplastic lesions that can lead to mass effect and obstructive hydrocephalus. Although most cysts produce no symptoms, some cysts however can cause hydrocephalus, epilepsy, cognitive impairments and even cause psychiatric illness. For symptomatic cases, surgical intervention can be especially useful. Microsurgery and endoscopy can aid in decompression of the cysts and CSF circulation restoration, while shunting helps in reducing the size of cysts. Ultimately, Treatment examples are operator dependent and usually give comparable outcomes (62).

External Links

https://www.neurosurgicalatlas.com/volumes/neuroradiology/cranial-disorders/brain-tumors/arachnoid-cyst-ac?texttrack=en-US&highlight=arachn

References

1- Cincu R, Agrawal A, Eiras J. Intracranial arachnoid cysts: current concepts and treatment alternatives. Clin Neurol Neurosurg. 2007;109:837-843.
2- Jafrani R, Raskin JS, Kaufman A, Lam S. Intracranial arachnoid cysts: Pediatric neurosurgery update. Surg Neurol Int. 2019 Feb 6; 10:15. doi: 10.4103/sni.sni_320_18. PMID: 30815323; PMCID: PMC6383341.
3- Al-Holou WN, Yew AY, Boomsaad ZE, et al. Prevalence and natural history of arachnoid cysts in children. J Neurosurg Pediatr. 2010;5:578-585.
4- Handa J, Nakasu S, Kidooka M, et al. Cerebrospinal fluid entrapment cysts with subarachnoid dissemination of medulloblastoma:CT findings. J Comput Assist Tomogr. 1984;8:988-989.
5-Abhinav K, Bradley M, Aquilina K, et al. Spinal arachnoiditis and cyst formation with subarachnoid haemorrhage. Br J Neurosurg. 2012;26:574-575.
6- Rengachary SS, Watanabe I. Ultrastructure and pathogenesis of intracranial arachnoid cysts. J Neuropathol Exp Neurol. 1981;40:61-83.
7- Al-Holou WN, Terman S, Kilburg C, et al. Prevalence and natural history of arachnoid cysts in adults. J Neurosurg. 2013;118:222-231.
8- Ikeda M, Tsuchiya K, Kurosawa T, et al. Marfan's syndrome associated with a frontal arachnoid cyst. Rinsho Shinkeigaku. 1988;28:1076-1078.
9- Boronat S, Caruso P, Auladell M, et al. Arachnoid cysts in tuberous sclerosis complex. Brain Dev. 2014;36:801-806.
10- Pilu G, De Palma L, Romero R, et al. The fetal subarachnoid cisterns: an ultrasound study with report of a case of congenital communicating hydrocephalus. J Ultrasound Med. 1986;5:365-372.
11- McLone DG. The subarachnoid space: a review. Childs Brain. 1980;6:113-130.
12- Santamarta D, Aguas J, Ferrer E. The natural history of arachnoid cysts: endoscopic and cine-mode MRI evidence of a slit-valve mechanism.Minim Invasive Neurosurg. 1995;38:133-137.
13- Halani SH, Safain MG, Heilman CB. Arachnoid cyst slit valves: the mechanism for arachnoid cyst enlargement. J Neurosurg Pediatr. 2013;12:62-66.
14- Schroeder HW, Gaab MR. Endoscopic observation of a slit-valve mechanism in a suprasellar prepontine arachnoid cyst: case report. Neurosurgery. 1997;40:198-200.
15- Oberbauer RW, Haase J, Pucher R. Arachnoid cysts in children: a European co-operative study. Childs Nerv Syst. 1992;8:281-286.
16- Scheel M, Bauknecht HC. Teaching neuroimages: head banging without head trauma: subdural hemorrhage in association with arachnoid cysts. Neurology. 2011;76:e60.
17-Lee CH, Han IS, Lee JY, et al. Analysis of a bleeding mechanism in patients with the sylvian arachnoid cyst using a finite element model. Childs Nerv Syst. 2014;30:1029-1036.

18- Cress M, Kestle JR, Holubkov R, et al. Risk factors for pediatric arachnoid cyst rupture/hemorrhage: a case-control study. Neurosurgery.2013;72:716-722, discussion 22.
19-Wester K, Helland CA. How often do chronic extra-cerebral haematomas occur in patients with intracranial arachnoid cysts?J Neurol Neurosurg Psychiatry. 2008;79:72-75.
20-Helland CA, Lund-Johansen M, Wester K. Location, sidedness, and sex distribution of intracranial arachnoid cysts in a population-based sample. J Neurosurg. 2010;113:934-939.
21-Hanieh A, Simpson DA, North JB. Arachnoid cysts: a critical review of 41 cases. Childs Nerv Syst. 1988;4:92-96.
22- Bhattacharyya KB, Senapati A, Basu S, et al. Bobble-head doll syndrome: some atypical features with a new lesion and review of the literature. Acta Neurol Scand. 2003;108:216-220.
23- Werder EA, Haertel M, Bekier A, et al. Suprasellar arachnoidal cyst as a cause of early puberty. Helv Paediatr Acta. 1984;39:261-264.
24- Jallo GI, Woo HH, Meshki C, et al. Arachnoid cysts of the cerebellopontine angle: diagnosis and surgery. Neurosurgery. 1997;40:31-37, discussion 7-8.
25-Babu R, Murali R. Arachnoid cyst of the cerebellopontine angle manifesting as contralateral trigeminal neuralgia: case report. Neurosurgery. 1991;28:886-887.
26-Ogutcen-Toller M, Uzun E, Incesu L. Clinical and magnetic resonance imaging evaluation of facial pain. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;97:652-658.
27- Galassi E, Tognetti F, Gaist G, et al. CT scan and metrizamide CT cisternography in arachnoid cysts of the middle cranial fossa: classification and pathophysiological aspects. Surg Neurol. 1982;17:
363-369.
28- Hayashi T, Anegawa S, Honda E, et al. Clinical analysis of arachnoid cysts in the middle fossa. Neurochirurgia (Stuttg). 1979;22: 201-210.
29- Handa J, Nakano Y, Aii H. CT cisternography with intracranial arachnoidal cysts. Surg Neurol. 1977;8:451-454.
30- Dutt SN, Mirza S, Chavda SV, et al. Radiologic differentiation of intracranial epidermoids from arachnoid cysts. Otol Neurotol. 2002;23:84-92.
31- Decq P, Brugieres P, Le Guerinel C, et al. Percutaneous endoscopic treatment of suprasellar arachnoid cysts: ventriculocystostomy or ventriculocystocisternostomy? Technical note. J Neurosurg. 1996;84:696-701.
32- Yildiz H, Erdogan C, Yalcin R, et al. evaluation of communication between intracranial arachnoid cysts and cisterns with phasecontrastcine MR imaging. AJNR Am J Neuroradiol. 2005;26:145-151.
33-Russo N, Domenicucci M, Beccaglia MR, et al. Spontaneous reduction of intracranial arachnoid cysts: a complete review. Br J Neurosurg. 2008;22:626-629.
34- Lee JY, Kim JW, Phi JH, et al. Enlarging arachnoid cyst: a false alarm for infants. Childs Nerv Syst. 2012;28:1203-1211
35- Di Rocco C, Tamburrini G, Caldarelli M, et al. Prolonged ICP monitoring in Sylvian arachnoid cysts. Surg Neurol. 2003;60:211-218.
36-Helland CA, Wester K. Intracystic pressure in patients with temporal arachnoid cysts: a prospective study of preoperative complaints and postoperative outcome. J Neurol Neurosurg Psychiatry. 2007;78:620-623.
37-Ali ZS, Lang SS, Bakar D, et al. Pediatric intracranial arachnoid cysts: comparative effectiveness of surgical treatment options. Childs Nerv Syst. 2014;30:461-469.
38-Zhang B, Zhang Y, Ma Z. Long-term results of cystoperitoneal shunt placement for the treatment of arachnoid cysts in children. J Neurosurg Pediatr. 2012;10:302-305.
39-Alexiou GA, Varela M, Sfakianos G, et al. Shunting for the treatment of arachnoid cysts in children. Neurosurgery. 2010;67:1632-1636, discussion 6.
40-Kandenwein JA, Richter HP, Borm W. Surgical therapy of symptomatic arachnoid cysts—an outcome analysis. Acta Neurochir (Wien). 2004;146:1317-1322, discussion 22.
41-Martinez-Lage JF, Ruiz-Espejo AM, Almagro MJ, et al. CSF overdrainage in shunted intracranial arachnoid cysts: a series and review. Childs Nerv Syst. 2009;25:1061-1069.
42-Fang T, Xu J, Wang S, et al. Analysis of therapeutic choices for slit ventricle syndrome after cyst-peritoneal shunting for temporal arachnoid cysts in children. J Neurosurg Pediatr. 2010;6:474-480.
43-Mottolese C, Szathmari A, Simon E, et al. The parallel use of endoscopic fenestration and a cystoperitoneal shunt with programmable valve to treat arachnoid cysts: experience and hypothesis. J Neurosurg Pediatr. 2010;5:408-414.
44-Ohnishi YI, Fujimoto Y, Taniguchi M, et al. Neuroendoscopically assisted cyst-cisternal shunting for a quadrigeminal arachnoid cyst causing typical trigeminal neuralgia. Minim Invasive Neurosurg. 2007;50:124-127.
45-Oertel JM, Wagner W, Mondorf Y, et al. Endoscopic treatment of arachnoid cysts: a detailed account of surgical techniques and results. Neurosurgery. 2010;67:824-836.
46-Spacca B, Kandasamy J, Mallucci CL, et al. Endoscopic treatment of middle fossa arachnoid cysts: a series of 40 patients treated endoscopically in two centres. Childs Nerv Syst. 2010;26:163-172.
47-Gangemi M, Seneca V, Colella G, et al. Endoscopy versus microsurgical cyst excision and shunting for treating intracranial arachnoid cysts. J Neurosurg Pediatr. 2011;8:158-164.
48-Fernandez Molina G. Neuroendoscopic management of middle fossa arachnoid cysts. World Neurosurg. 2013;79:S19-e23.
49-Ersahin Y, Kesikci H, Ruksen M, et al. Endoscopic treatment of suprasellar arachnoid cysts. Childs Nerv Syst. 2008;24:1013-1020.
50-Ersahin Y, Kesikci H. Endoscopic management of quadrigeminal arachnoid cysts. Childs Nerv Syst. 2009;25:569-576.
51- Giannetti AV, Fraga SM, Silva MC, et al. Endoscopic treatment of interhemispheric arachnoid cysts. Pediatr Neurosurg. 2012;48: 157-162.
52-Gui S, Zong X, Li C, et al. Endoscopic treatment of convexity arachnoid cysts. Childs Nerv Syst. 2013;29:505-508.

53- Karabagli H, Etus V. Success of pure neuroendoscopic technique in the treatment of Sylvian arachnoid cysts in children. Childs NervSyst. 2012;28:445-452.
55-Maher CO, Goumnerova L. The effectiveness of ventriculocystocisternostomy for suprasellar arachnoid cysts. J Neurosurg Pediatr.2011;7:64-72.
56- Ellis JA, McCormick PC 2nd, Feldstein NA, et al. Transoccipital endoscopic fenestration of atrial cysts causing ventricular entrapment.J Neurosurg Pediatr. 2015;15:567-572.
57- Hughes G, Ugokwe K, Benzel EC. A review of spinal arachnoid cysts. Cleve Clin J Med. 2008;75:311-315.
58- Qi W, Zhao L, Fang J, et al. Clinical characteristics and treatment strategies for idiopathic spinal extradural arachnoid cysts: a singlecenter experience. Acta Neurochir (Wien). 2015;157:539-545.
59- Yayama T, Kobayashi S, Uchida K, et al. Insidious progression of paraparesis secondary to type III spinal meningeal cyst: a study of six difficult cases. Spinal Cord. 2008;46:159-161.
60- Endo T, Takahashi T, Jokura H, et al. Surgical treatment of spinal intradural arachnoid cysts using endoscopy. J Neurosurg Spine. 2010;12:641-646.
61- Mauer UM, Gottschalk A, Kunz U, et al. Arachnoscopy: a special application of spinal intradural endoscopy. Neurosurg Focus. 2011; 30:E7.
62- H.Richard WInn. (1996). Youman and Winn Neurology. 7.
63-Radiopedia. (n.d.). *quadrigeminal-cistern-arachnoid-cyst (1)*. https://radiopaedia.org/cases/68172%22%3ErID: 68172%3C/a%3E

Article topic: Craniopagus Twins.

Author: Ghayda'a Netham Al-Majali.

Editor: Philib Sweidan.

Reviewer: Omar Jbarah, Hassan AbuShukair.

Keywords: ***congenital anomaly, newborn, Obstetrics.***

Overview

Craniopagus twins (CPT) are a rare congenital malformation or dysmorphism in which twins are conjoined and fused at the cranium (Head), accounting for only 2%–6% of conjoined twins, with an incidence once in every 0.6 to 2.5 million lives births (1)(2). CPT is predisposed more in females than males with a ratio of 3:1 although this has not been correlated with any cause of the condition (3). Mortality rate of CPT is 40% stillborn and 33% die in perinatal period (4).

The skulls are often joined in homogeneous regions on each twin in both vertical and angular directions (5). Conjoined brain tissue connected arteries and veins, and defects in the skull and Dura make surgery technically challenging and difficult (6). Although there is high prenatal and postnatal mortality for CPT, successful separation has become more common due to advances and improvements in neuroimaging, neuro-anesthesia, and neurosurgical techniques (7)(8).

Neuroimaging, including CT, MRI, and conventional angiography, plays a key role in mapping the connected arterial and venous structures, brain parenchyma, calvaria, and Dura (9)(10).

Digital and physical 3D models arised from CT and MRI data are important tools for operative planning and as a guide in the operating room (6).

Understanding the shared vascular anatomy is important for surgical planning because separating common vessels is associated with complications and manifestations such as thrombosis, pulmonary embolism, infarction, and hemorrhage (11).

Separation can take place in single or multistage procedures and has improved as the understanding of the physiology, surgical techniques, and technology of CPT have evolved (12).

So, the preoperative radiologic evaluation of CPT, including the anatomy, classification systems, and surgical management should be all reviewed, that is important for the radiologist to understand in addition to consultation for multiple successful CPT separations with an experienced neurosurgical specialist in CPT (2).

Moreover, Separation of conjoined twins poses several technical, legal, religious, moral, and ethical issues (13).

Etiology

The cause of the conjoined Twins is unclear; incomplete fission and fusion have been proposed by embryologists and there are no known environmental or genetic factors (4).

Embryology

The monoamniotic, monochorionic type of monozygotic twinning has the highest potential for leading to conjoined twins (Kaufman, 2004), The two main theories of how monoamniotic monozygotic twins conjoin are the "fission" and "fusion" theories (14).

Fission theory proposes an incomplete cleavage or cleavage of the embryo at the primitive streak stage, resulting in conjoined embryos, this theory explains the apparent increase in the incidence of inversion and mirror imaging in conjoined twins, because a dividing cell or cell mass maintains mirror imaging (15).

The fusion theory suggests that embryos return to and rejoin at vulnerable sites after complete initial separation, this theory explains the different angles at which conjoined twins can be fused, along the dorso-ventral or rostro-caudal axis (14).

Anatomy

CPT are conjoined only at the calvaria, without involvement of the foramen magnum, skull base, vertebrae, or face. Other conjoined twins' variations involving the head include cephalopagus (which involve the brain, face, thorax, and upper abdomen), parapagus diprosopus (which involve 2 faces on 1 head with 1 body), and rachipagus (which means joined dorsally along the vertebra and occasionally along the occiput) (2).

Conjunction is rarely symmetric, and it may involve any portion of the head, including underlying structures such as meninges, venous sinuses, or cortex. Configuration can vary on the basis of the attachment location, degree of rotation and angulation between the 2 twins, which will determine the anatomy and difficulty of separation (2).

Classification System

The first classification system was developed by O'Connell, in which CPT were classified as partial or total (16).

Total CPT share an extensive surface area with widely connected cranial cavities (In which two brains can be thought of as being located within one skull and a series of gross intracranial malformations and abnormalities develop) (16).

There are 3 varieties can be recognized in the total form, these include: (16)

- Deformity of the skull base,
- Deformity and displacement of the cerebrum,
- And a gross circulatory abnormality.

While in Partial CPT, the union is of limited extent, particularly regarding its depth and only superficial surface area is affected (In which separation can be expected to follow the survival and leading a normal life for both children) (16).

O'Connell subdivided partial form on the basis of the degree of rotation of one head in relation to the other, with different abnormalities and deformities of the brain and abnormal circulation for each: (16)

- Type I vertical CPT face the same direction (in which rotation is less than 40 degrees)
- Type II CPT face opposite sides (in which rotation is between 140 and 180 degrees)
- And type III twins have an intermediate angle of rotation (in which rotation ranges from 40 to less than 140 degrees)

Then, Stone and Goodrich defined partial CPT as lacking substantial shared dural venous sinuses, whereas total CPT share a large portion of their dural venous sinuses and present with clear brain compression, which leads to distortion within the cranium (17). So, they are in an effort to evaluate outcomes among different types of twins, used the partial and total divisions which described by O'Connell and defined 2 main subtypes based on the long-axis angle between twins: angular and vertical (4).

Angular CPT have an inter-twin longitudinal angle of less than 140 degrees, regardless of axial rotation (17)(4), while Vertical CPT display a continuous longitudinal cranium, and this type is further subdivided according to the degree of inter-twin axial facial rotation similar to the O'Connell classification (17)(2).

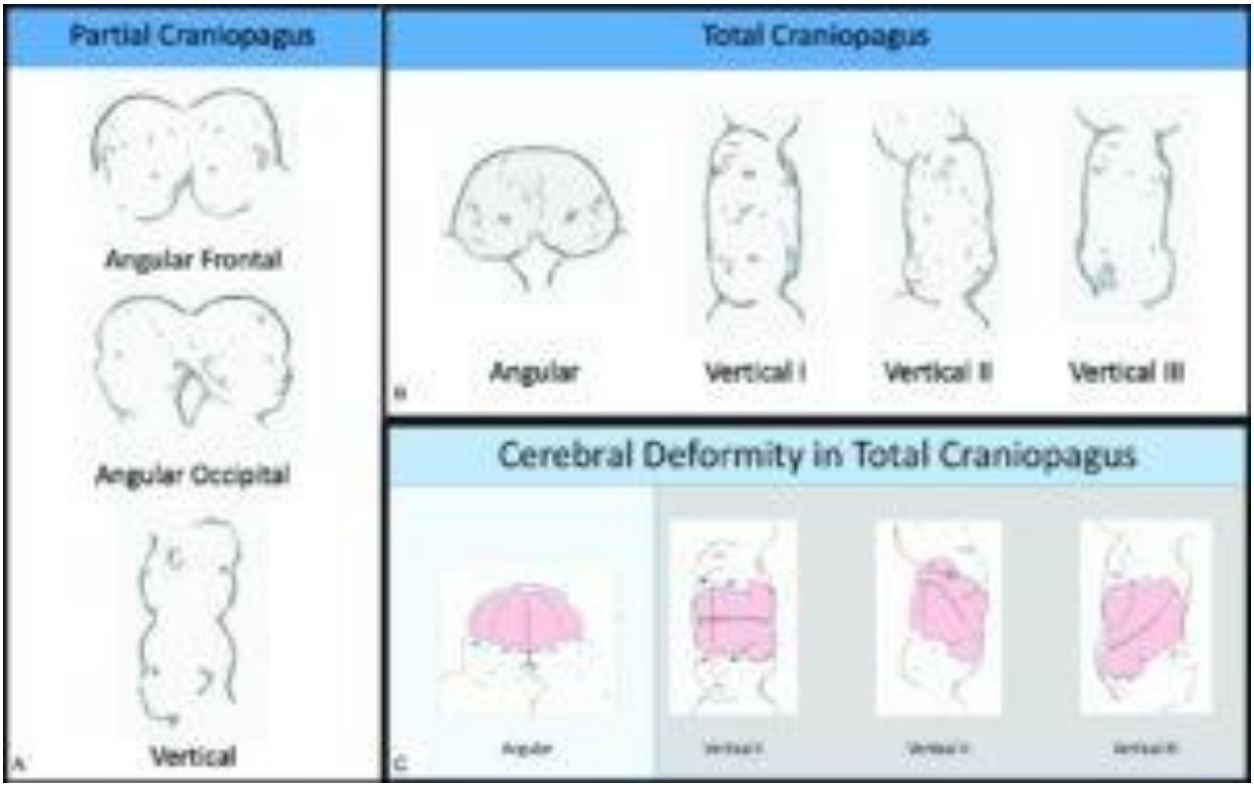


Figure 1: Stone and Goodrich classification for Craniopagus Twins. Partial CPT lack substantial shared dural venous sinuses. Total CPT share a large portion of dural venous sinuses and present with pronounced brain compression, leading to distortion within the cranium. The two main subtypes are based on the long-axis angle between twins: angular and vertical. Shared calvaria causes deformity of each twin's brain. Reproduced with permission from Stone and Goodrich, 2006 (17)(2).

Surgical Separation / Operative Management

The decision to separate CPT is obviously fraught with serious and dangerous considerations, the preoperative evaluation and assessment of patients before a separation procedure is critical, and planning takes months of clinical monitoring, imaging, and modeling. Consultation among experts in multiple specialties is crucial and must involve surgeons, anesthesiologists, nursing teams, and other care providers. In addition to cranial considerations, cardiac, pulmonary, and renal function determine the feasibility of the prolonged surgical procedure of separation. Separation cannot be done until the patients have reached the age and body weight which allow them to tolerate the potentially significant blood loss that can occur during surgery (4).

The goal of surgical separation of craniopagus twins involves separating shared structures, including cerebral vasculature and interdigitating brain, and reconstructing cranial structures for each twin. Single and multistage approaches have been used (2).

In the single-stage procedure, one twin receives the circumferential venous sinus, while the other twin develops a deep venous drainage system through several months by serial

ligation of draining veins (2). There has been limited success with this approach of separation. In general, the length of procedures often exceeds 20-30 hours. Unfortunately, these efforts are rarely successful because of the complexity of this procedure and the instant change in hemodynamic forces and stresses that occur when the surgeon tries to bypass the entire cerebral venous outflow. So due to the complexity of these cases and the difficulty of predicting the suitability of individual venous outflow, which must function immediately on separation, we favor or prefer a multistaged surgical approach (4).

Multistage procedures are often not required for partial CPT. Reconstruction involves adequate dural, cranial, and soft-tissue coverage.

The dominant twin will have a thriving and more strong clinical presentation, and the non-dominant twin may experience the effects of hypotension and low cardiac output, including oliguria, low weight, aspiration pneumonia, and failure to thrive. Most midline structures, including the circumferential venous sinus will be given to the dominant twin, with the plane of division on the side of the non-dominant twin (2).

Despite multiple previous unsuccessful attempts, the first successful separation of Craniopagus Twins occurred in 1953, only one child survived, when a multistaged approach was used (18). As techniques improved, single-stage approach became the standard for total CPT separation, in which the surviving twin received the bulk of the superior dural venous sinuses, usually surviving with severe disability, with operations often lasting as long as 22–100 hours (5)(17)(19)(20). Although surgical results for total CPT have been gradually improving through decades, single-staged results were likely no better than the earlier developed multistaged separation procedures (17).

Multistaged surgical separation is the preferred current management of choice in total CPT (21). Gradually dividing bridging veins increases collateral formation and dilation of shared or communicating veins in the non-dominant twin, who does not receive the superior sagittal sinus. This improves venous drainage, leading to decrease the risk of cerebral edema and CSF leak. Additionally, the cardiac and renal issues and number of medications needed get better by the end of the third stage (2).

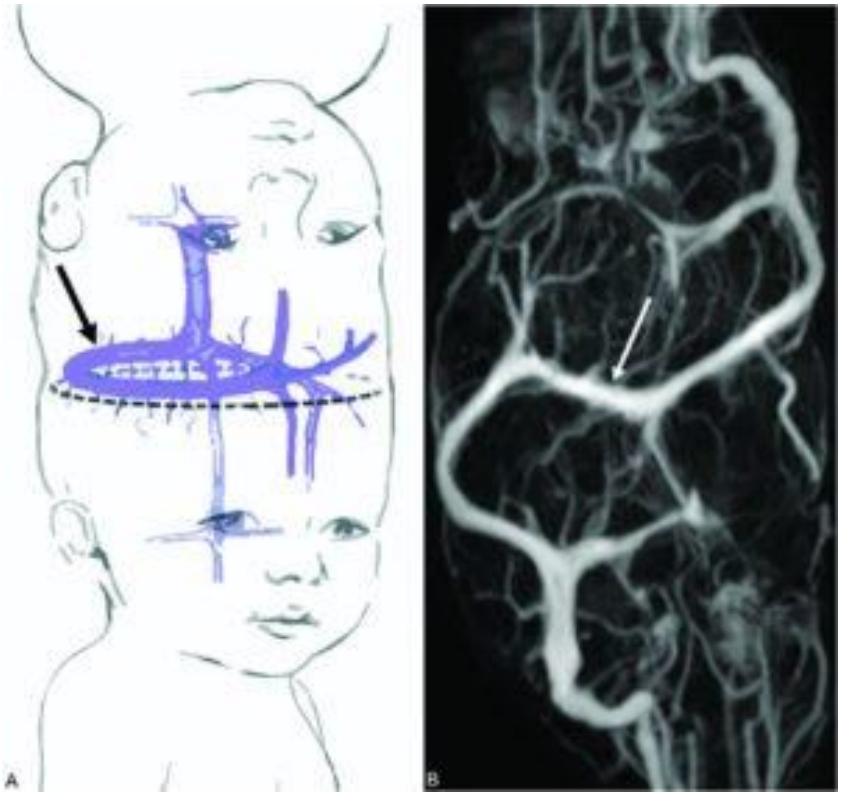


Figure 2: A, Surgical-separation strategy may require sequential division of venous sinus branches from the non-dominant twin (dashed line), allowing the anatomically predisposed dominant twin to keep the CVS (black arrow) and associated dura. In the non-dominant twin, subsequent reversal of venous drainage to collateral basal channels may be induced (Reproduced, with permission, from Stone and Goodrich, 2006). B, Postcontrast MR venography demonstrates the CVS (white arrow) (17)(2).

Conclusion

Separation of Craniopagus twins must be a well-organised multidisciplinary effort. The care of these children includes critical care time, nursing, social support, travel, anesthesia, neurosurgery, diagnostic and interventional neuroradiology, and the administrative support. The neuroradiologist plays a critical role in the care team of CPT, from initial evaluation through the operation and follow-up, using conventional imaging techniques CT scan, MRI, angiography, endovascular therapies and creating 3D models. Technologic advances that can greatly improve this field will include 3D virtual reality navigation to improve the knowledge of what lies behind a “wall” of fused brain in the operating room, keeping loss of brain tissue to a minimum. The combination of high-resolution MR images and virtual reality 3D systems is already in use. Embolizing vessels will become even more precise due to availability of new endovascular devices and embolic materials, decreasing operative time needed for vascular ligation, providing a roadmap for surgeons when they divide veins and further mitigating blood loss. Also, diagnostic, and interventional neuroradiology plays an increasingly key role in the care of craniopagus twins (2).

References

1. Spitz, L., & Kiely, E. M. (2003). Conjoined twins. *JAMA*, *289*(10), 1307–1310. https://doi.org/10.1001/jama.289.10.1307
2. Goldman-Yassen, A. E., Goodrich, J. T., Miller, T. S., & Farinhas, J. M. (2020). Preoperative Evaluation of Craniopagus Twins: Anatomy, Imaging Techniques, and Surgical Management. *American Journal of Neuroradiology*, *41*(6), 951–959. https://doi.org/10.3174/ajnr.A6571
3. Mian, A., Gabra, N. I., Sharma, T., Topale, N., Gielecki, J., Tubbs, R. S., & Loukas, M. (2017). Conjoined twins: From conception to separation, a review. *Clinical Anatomy (New York, N.Y.)*, *30*(3), 385–396. https://doi.org/10.1002/ca.22839
4. Surgery, youmans and winn neurological. (n.d.). *Youmans and Winn Neurological Surgery 7*. https://drive.google.com/file/d/1hDvJTMdpuZAMXXgiW1SOECjU5Pizzpr7/view?fbclid=IwAR365UiQNEPZsNewUoS4vh8rrohzvoGfoRAdvRRAIiUuzBQ3_xgiIpf4RjI
5. Winston, K. R., Rockoff, M. A., Mulliken, J. B., Strand, R. D., & Murray, J. E. (1987). Surgical division of craniopagi. *Neurosurgery*, *21*(6), 782–791. https://doi.org/10.1227/00006123-198712000-00002
6. Browd, S. R., Goodrich, J. T., & Walker, M. L. (2008). Craniopagus twins. *Journal of Neurosurgery. Pediatrics*, *1*(1), 1–20. https://doi.org/10.3171/PED-08/01/001
7. Walker, M., & Browd, S. R. (2004). Craniopagus twins: embryology, classification, surgical anatomy, and separation. *Child's Nervous System : ChNS : Official Journal of the International Society for Pediatric Neurosurgery*, *20*(8–9), 554–566. https://doi.org/10.1007/s00381-004-0991-6
8. Pai K, M., Naidu, R. C., Raja, A., Rai, Y. S., Kumar, N., Kini, A., Joseph, S., Hegde, V., Ballal, H. S., Rao, R., Sharma, S. V, & Valakatte, V. K. (2018). Surgical nuances in the separation of craniopagus twins - Our experience and a follow up of 15 years. In *Neurology India* (Vol. 66, Issue 2, pp. 426–433). https://doi.org/10.4103/0028-3886.227289
9. Schindler, E., & Hajek, P. (1988). Craniopagus twins: neuroradiological findings (CT, angiography, MRI). *Neuroradiology*, *30*(1), 11–16. https://doi.org/10.1007/BF00341936
10. Alokaili, R. N., Ahmed, M. E., Al Feryan, A., Goodrich, J. T., & Aloraidi, A. (2015). Neurointerventional participation in craniopagus separation. *Interventional Neuroradiology : Journal of Peritherapeutic Neuroradiology, Surgical Procedures and Related Neurosciences*, *21*(4), 552–557. https://doi.org/10.1177/1591019915590313
11. Bucholz, R. D., Yoon, K. W., & Shively, R. E. (1987). Temporoparietal craniopagus. Case report and review of the literature. *Journal of Neurosurgery*, *66*(1), 72–79. https://doi.org/10.3171/jns.1987.66.1.0072
12. Staffenberg, D. A., & Goodrich, J. T. (2012). Separation of craniopagus conjoined twins with a staged approach. *The Journal of Craniofacial Surgery*, *23*(7 Suppl 1), 2004–2010. https://doi.org/10.1097/SCS.0b013e318262d3f7
13. Annas, G. J. (2001). Conjoined twins--the limits of law at the limits of life. *The New England Journal of Medicine*, *344*(14), 1104–1108. https://doi.org/10.1056/NEJM200104053441419
14. Spencer, R. (2000). Theoretical and analytical embryology of conjoined twins: part I: embryogenesis. *Clinical Anatomy (New York, N.Y.)*, *13*(1), 36–53. https://doi.org/10.1002/(SICI)1098-2353(2000)13:1<36::AID-CA5>3.0.CO;2-3
15. Kaufman, M. H. (2004). The embryology of conjoined twins. *Child's Nervous System : ChNS : Official Journal of the International Society for Pediatric Neurosurgery*, *20*(8–9), 508–525. https://doi.org/10.1007/s00381-004-0985-4
16. O'Connell, J. E. (1976). Craniopagus twins: surgical anatomy and embryology and their implications. *Journal of Neurology, Neurosurgery, and Psychiatry*, *39*(1), 1–22. https://doi.org/10.1136/jnnp.39.1.1
17. Stone, J. L., & Goodrich, J. T. (2006). The craniopagus malformation: classification and implications for surgical *Brain : A Journal of Neurology*, *129*(Pt 5), 1084–1095. https://doi.org/10.1093/brain/awl065
18. SUGAR, O., GROSSMAN, H., GREELEY, P., & DESTRO, V. (1953). The Brodie craniopagus twins. *Transactions of the American Neurological Association*, *3*(78th Meeting), 198–199.
19. Campbell, S. (2004). Separation of craniopagus twins: the Brisbane experience. *Child's Nervous System : ChNS : Official Journal of the International Society for Pediatric Neurosurgery*, *20*(8–9), 601–606. https://doi.org/10.1007/s00381-004-0990-7
20. Huang, W. Q., Fang, J. Y., Xiao, L. C., Jiang, X. P., Xia, J. H., Feng, X., & Jiang, N. (2004). Anesthetic management for separation of craniopagus twins. *Acta Anaesthesiologica Scandinavica*, *48*(7), 919–921. https://doi.org/10.1111/j.0001-5172.2004.00444.x
21. Harvey, D. J., Totonchi, A., & Gosain, A. K. (2016). Separation of Craniopagus Twins over the Past 20 Years: A Systematic Review of the Variables That Lead to Successful Separation. *Plastic and Reconstructive Surgery*, *138*(1), 190–200. https://doi.org/10.1097/PRS.0000000000002269

Article topic: High-Grade Glioma (Anaplastic Astrocytoma).

Author: Shroug Naser Al Hamdan.

Editor: Philip Sweidan**.**

Reviwer: Ethar Hazaimeh.

Keywords: anaplastic astrocytoma, malignant astrocytoma.

Overview

Anaplastic astrocytoma (AA) is a diffusely infiltrating, malignant, astrocytic, primary brain malignant tumor with a median age of onset of 41 years [1]. Presently, an anaplastic astrocytoma is defined by the histologic characteristics of nuclear atypia, increased cellularity, significant proliferative activity as manifested by mitoses, and lacking either endothelial proliferation or necrosis [1].

Nearly, a quarter of anaplastic astrocytoma (AA) arise as a de novo tumor, whereas it is estimated that three quarters are a consequence of transformation from a lower-grade astrocytoma [2].

AA accounts for 4% of all malignant CNS tumors and 10% of all gliomas [3]. The survival of patients with AA varies depending on molecular pathology. With conventional treatment, median overall survival and 5-year survival rates are 3 years and 28% [[3][4]].

Risk factors

Exposure to ionizing radiation and rare genetic syndromes such as neurofibromatosis type 1 and neurofibromatosis type 2, tuberous sclerosis, and the Li-Fraumeni syndrome is the only established risk factors.

Clinical presentation

Patients with AA mainly present with focal or generalized neurologic symptoms. The specific focal symptom depends upon the anatomic localization of this tumor and includes weakness, sensory loss, visual impairment, language dysfunction, and gait disorder. Generalized symptoms such as personality changes, seizures, and headaches. Compared to low-grade astrocytoma, seizure at presentation is less common [5].

Imaging

MRI with the administration of gadolinium contrast is the best imaging modality for diagnosis and management of Anaplastic astrocytoma. MRI helps in establishing a differential diagnosis, guides biopsy or resection is fundamental for treatment (i.e., radiotherapy) planning, monitoring response to treatment determines disease progression. MRI shows AA as an ill-defined, T1-weighted hypointense and T2-weighted hyperintense mass with surrounding vasogenic edema. Nodular areas of enhancement are usually observed, although nearly one-third of anaplastic astrocytoma display no contrast enhancement [2].

Contrast enhancement usually indicates the presence of a higher-grade component notwithstanding if a biopsy indicates a low-grade tumor as sampling error may occur. Advanced imaging includes diffusion-weighted MRI imaging, MR spectroscopy, MR perfusion, and amino acid positron emission tomography imaging may also help in the diagnosis and management of AA [[2]].

Figure (1): CT of anaplastic astrocytoma, Case courtesy of Dr. Bruno Di Muzio,[6].

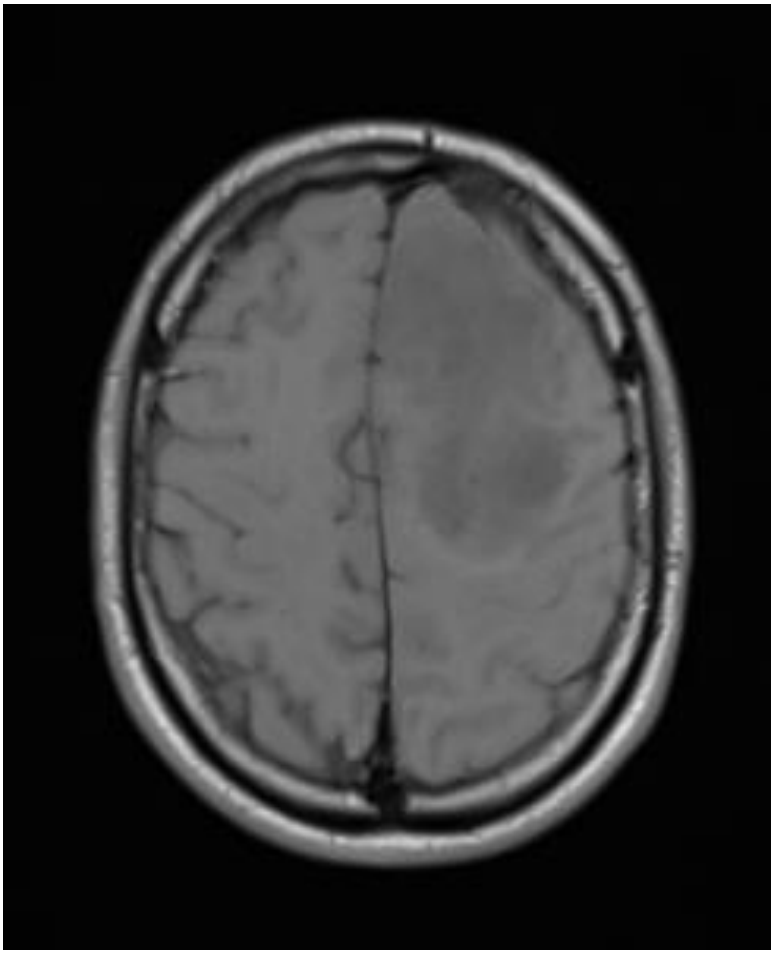


Figure (2): MRI of anaplastic astrocytoma, Case courtesy of Dr. Bruno Di Muzio,[7].

Histology

AA frequently shows heterogeneous histology consisting of areas of low- and high-grade tumor that is thought to indicate progression from a lower grade tumor precursor. The diagnosis of AA is sometimes established from biopsy in which sampling error may occur. AA, defined by WHO as a grade III anaplastic glioma, characterized by mitotic activity, increased cellularity, presence of glial makers (e.g., GFAP), absence of neuronal markers, and nuclear atypia [1]. The MIB-1 labeling index in AA is 5–10% but may overlap with both low-grade astrocytoma and may show considerable variation within a given tumor [8]. The histologic classification and grading of anaplastic gliomas have poor benefit among pathologists and often poorly predicts clinical outcome [9]. NOW, clinicians are utilizing the molecular classification of gliomas to guide clinical decision-making [10].

Types depending on molecular abnormalities

Anaplastic astrocytomas can be classified into more specific subtypes based on genetic characteristics. anaplastic astrocytomas can have abnormal genetic abnormalities,

including mutations in the IDH1 or IDH2 genes. The presence of these genetic differences can affect prognosis and treatment, and are classified as:

- Anaplastic astrocytoma, IDH-mutant (if a mutation in either IDH1 or IDH2)
- Anaplastic astrocytoma, IDH-wildtype (if no IDH mutations)
- Anaplastic astrocytoma, not otherwise specified NOS (if the tumor has not been tested) [11].

Treatment

A personalized treatment plan will consider various factors, including size, location, and extent of surgical removal, among others.

Surgery

Surgery is the first step in treating an anaplastic astrocytoma. The main objective is to remove as much of the tumor as possible while protecting critical brain function – this is called "maximal safe resection," In some cases, doctors may be able to remove all the tumor or most of it [5]. However, anaplastic astrocytomas grow quickly, so doctors may only be able to safely remove part of the tumor, anaplastic astrocytomas can occur in near locations of the brain that control and manage body movement, sensation, language, or vision, specific measures may be taken to protect these functions [11].

Awake surgery with brain mapping is commonly used when tumors are located in the brain areas that control language or movement. This technique helps surgeons safely identify and preserve critical brain regions [5][11].

Chemotherapy and radiation therapy

If the tumor cannot be removed with surgery, or only part of it was removed, it may need radiation therapy. Radiation therapy destroys rapidly dividing cells (cancerous cells). This will aid to shrink the tumor or destroy any parts that were not removed during surgery [11]. Radiation may be suggested to treat residual tumor cells. Certain radiotherapy techniques such as Gamma Knife and IMRT offer the ability to specifically target tumor cells while reducing radiation exposure to healthy tissue, Chemotherapy may also be used to continue treatment after surgery, such as temozolomide (Temodar), during or after radiation therapy may be beneficial [5][11].

External links

https://www.neurosurgicalatlas.com/cases?query=anaplast

https://www.neurosurgicalatlas.com/volumes/neuroradiology/cranial-disorders/brain-tumors/anaplastic-astrocytoma-aa

References

[1] D. N. Louis *et al.*, "The 2007 WHO classification of tumours of the central nervous system," *Acta Neuropathologica*, vol. 114, no. 2. pp. 97–109, Aug. 2007, doi: 10.1007/s00401-007-0243-4.

[2] L. Mechtler, "Neuroimaging in Neuro-Oncology," *Neurologic Clinics*, vol. 27, no. 1. pp. 171–201, Feb. 2009, doi: 10.1016/j.ncl.2008.09.015.

[3] Q. T. Ostrom *et al.*, "CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2007–2011," *Neuro-Oncology*, vol. 16, pp. iv1–iv63, Oct. 2014, doi: 10.1093/neuonc/nou223.

[4] M. D. Prados *et al.*, "0 Clinical Original Contribution HIGHLY ANAPLASTIC ASTROCYTOMA: A REVIEW OF 357 PATIENTS TREATED BETWEEN 1977 AND 1989," 1992.

[5] S. A. Grimm and M. C. Chamberlain, "Anaplastic astrocytoma," *CNS oncology*, vol. 5, no. 3. pp. 145–157, Jul. 01, 2016, doi: 10.2217/cns-2016-0002.

[6] radiopaedia, "anaplastice astrocytoma." . Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org. From the case rID: 57768

[7] radiopaedia, "anaplastic astrocytoma." . Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org. From the case rID: 57768

[8] E. Karamitopoulou, E. Perentes, I. Diamantis, T. Maraziotis, E. Karamitopoulou, and E. Perentes, "Ki-67 immunoreactivity in human central nervous system tumors: a study with MIB 1 monoclonal antibody on archival material," Springer-Verlag, 1994.

[9] "Improving Diagnostic Accuracy and Interobserver Concordance in the Classification and Grading of Primary Gliomas."

[10] B. J. Theeler, W. K. A. Yung, G. N. Fuller, and J. F. de Groot, "Moving toward molecular classification of diffuse gliomas in adults VIEWS & REVIEWS," 2012.

[11] Q. T. Ostrom *et al.*, "CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014," *Neuro-oncology*, vol. 19, no. 5, pp. v1–v88, Nov. 2017, doi: 10.1093/neuonc/nox158.

Article Topic: Optic Pathway Glioma.

Author: Rahaf Naser Aldeen.

Editor: Ethar Hazaimeh

Reviewer: Omar Jbarah.

Keywords: low-grade glioma, neurofibromatosis type 1, optic pathway glioma, pilocytic astrocytoma.

Introduction

Optic pathway glioma (OPG) is one of the central nervous system tumors which represents 1% of all intracranial tumors [1], and 2-5% of intracranial tumors in the pediatric population.[2] OPG has variant growing patterns, ranging from slow-growing tumors (indolent) to higher-grade malignant lesions (proliferative).[3] slow-growing tumors labeled as WHO grade 1 tumor, arising in young patients, which are characterized by expansion and rare metastasize. whereas higher-grade tumors are present in adults and characterized by directly invading near structures, such as basal ganglia, internal capsule, and hypothalamus. [4] These tumors can develop in any part of the optic pathway including the optic nerve, optic chiasm[5], and many reported retro geniculate lesions development.[4]

the mean age of tumors detection ranges from three to six years, with rare growth after the age of 10.[6] Erin et al.[7] estimated the racial and ethnic variations in the incidence of OPG using data from the surveillance, epidemiology, and end results (SEER) program of the national cancer institute in the United States (US). they found that white children have the highest OPGs incidence compared to blacks, Asians, and Latinos. the 5-year survival rate of OPG is above 95%,[8]nevertheless severe visual impairment has a high prevalence among patients, which is estimated over 75% [9,10], and can progress to persistent blindness.[11]

Pathogenesis and Etiology

for the pathological evaluation, low-grade OPG is classified into infiltrative (diffuse astrocytoma) and circumscribed (pilocytic astrocytoma). these two groups have different histopathological features which need to be considered apart for behavior and treatment response.[12] Moreover, malignant optic nerve glioma counts as high-grade astrocytomas or glioblastomas multi forme.[13]

Pilocytic Astrocytomas

the WHO grade 1 is the general classification for pilocytic astrocytoma (PA), which is considered the most popular brain tumor in the pediatric population.[14,15] furthermore, WHO grade 2 is a special term assigned for pilocytic astrocytomas, manifest in the hypothalamus/chiasmatic region in infants (0-1 year of age).[16] more in-depth, PAs are classified into sporadic and syndromic cases, which are associated with K1AA1549: BRAF fusion rearrangement, and neurofibromatosis NF-1 syndrome, respectively. [17]the neurofibromatosis 1 syndrome also termed von Recklinghausen disease or peripheral NF [18], is mostly linked with OPG in children.[19]

the OPGs have two constructional features of growth patterns, which are perineural and intraneural growth.[20] perineural tumors are mostly linked with NF-1 and manifest as circumferential growth of astrocytes. this growth manner leads to parenchymal expansion and epidural-subarachnoid space widening. additionally, the tumor may penetrate the pia-arachnoid layer to plug both subarachnoid and subdural spaces. nevertheless, the extension of the tumor posts the orbit, and optic canal remains within the Dural sheath confines.[20,21] while, the intraneural tumor growth is frequently observed in sporadic cases, which are produced by fibrovascular trabeculae expansion and have little cystic degeneration.[20]

the macroscopic appearance of PAs is described as well-defined soft texture and gray in the section of fixed specimens. the cysts manifest within and around the tumor. additionally, calcium sediments and hemosiderin exist because of small bleeds into the tumor tissue. however, it is exceedingly rare to present the PAs with extensive leptomeningeal involvement in absence of parenchymal association.[16] precisely, PA of the optic nerve develops inside the cylindrical confines of the optic nerve sheath, [22] but the hypothalamic/ chiasmatic PA tumors are larger, soft, and have more cysts.[23]

microscopic characteristics of PAs have biphasic structure, accompanied by loose and dense areas. [23] the tumors are made up of bipolar spindle cells, and often hold within them Rosenthal fibers. Rosenthal fibers origin till has opposing arguments, but these fibers represent degenerated glial fibers.[24] Beside that, PAs are strongly positive to glial fibrillary acid protein expression (GFAP), transcription factor oligo-2, and synaptophysin (neural marker). the complete lack of neurofilament protein staining can be used as proof of a non-infiltrating tumor.[25]

Diffuse Astrocytoma

diffuse astrocytomas can be alternatively termed as "fibrillary astrocytoma", and pediatric OPGs from the diffuse category accounts for a minority of the cases. [8] historically, diffuse astrocytomas are characterized by highly infiltrative lesions and are

well-differentiated. the most useful stain is the neurofilament protein, which shows the remarkable infiltrative pattern of the tumor. furthermore, IDH-1 antibody expression is positive in the adult group.[26]

Malignant Optic Nerve Glioma

as mentioned before, it is a high-grade astrocytomas or glioblastomas multiforme. [13] in most of the cases, it was masked as optic nerve neuritis in the initial investigation, with a rapidly fatal optical pathway tumor. this type of gliomas is a rare cause of sightlessness. [27] malignant OPGs are an extremely rare case, and commonly observed in the 20s to 80s of age, with no specific tumor tendency in gender groups.[13,28,29]

the macroscopic features of malignant OPGs have a similar appearance with other central nervous system malignant gliomas and have a variegated, yellow, and centrally hemorrhagic cut surface with focal necrosis. Microscopically, malignant OPGs are highly cellular with increasing mitoses and show the usual characteristic features of high-grade tumors.[13]

Clinical Presentation

Most NF-1 syndrome patients have asymptomatic OPGs, precisely in children who are younger than 10 years old. This is frequently reduced with increasing age until adulthood.[30] Most of the asymptomatic OPGs with NF-1 syndrome are detected accidentally while screening brain images.[31]

The most common symptom manifest in OPG patients is vision loss, and there is no association between tumor size and visual loss. other OPG symptoms are decreased visual acuity, visual field defects; like central scotoma, bitemporal hemianopia, and peripheral contraction. relative afferent pupillary defect (RAPD) may be found in up to 75% of cases.[32]

optical coherence tomography (OCT) abnormalities reflected by retinal nerve fiber layers' loss (RNFL).[33] Additionally, symptoms like proptosis, visual evoked potential alterations (VEP), strabismus, nystagmus, precious puberty, and various neurological signs may be present. [19,34,35] In a study conducted to evaluate the neuropsychological outcomes of children with OPG [36]. It found out that this population has a moderate risk of neuropsychological impairment, particularly visual perception, and cognitive ability.

More in-depth, clinical presentation relies on the tumor location, which can appear anywhere along the optic pathway. [37] Symptomatic optic nerve gliomas present with unilateral vision loss [21,38,39], decreased visual acuity [40], visual field defect[40], dyschromatopsia, RAPD[21,39,40], optic disc swelling or atrophy[21,39], and strabismus[21,38–40],

which correlates with large tumor size, manifest as exotropia and hypertropia.[40] proptosis is the most common presenting sign of NF-1 associated with optic nerve glioma,[38,41,42] which results in secondary complications of corneal ulcers because of incomplete eyelid closure.[38]

Chiasmal glioma patients present with slow bilateral vision loss, with bitemporal visual field defect, as well as optic disc alterations, strabismus, chiasmal apoplexy, and nystagmus.[2,6,38] Nystagmus in chiasmal glioma is characterized by high frequency, asymmetric horizontal direction, it can be present separately or in combination with head nodding or torticollis.[40]

The extension of the tumor to the hypothalamus region can contribute to the manifestation of hydrocephalus, diencephalic syndrome, precocious puberty, and endocrinological defects.[38] Large chiasmal and hypothalamic lesions can compress the third ventricle leading to elevated intracranial pressure, headache, and papilledema.[2,6,8,13,38,40,43]

Malignant OPGs in adults manifest with sudden acute vision loss in 70% to 80% of cases[29,44], with development of central retinal vein occlusion, venous stasis retinopathy, iris rubeosis associated with neovascular glaucoma, or ocular ischaemic syndrome[21,22]. In contrast to OPG in the pediatric population, the presence of proptosis is rare in malignant OPGs.[45]

Work up and Diagnosis

the most vital aspect of OPG patient's management is vision protection, for this reason, ophthalmologic assessment is a priority. ophthalmologic assessment usually includes a variety of visual parameters such as visual acuity, visual field, fundoscopy[6], and eye segments examination with the slit lamp.[6,34]

for asymptomatic NF-1 children, the follow-up screening routine is recommended to occur annually until the age of 7 or 8, which is the greatest risk period for the tumor development, then the follow-up expanded to every two years till the age of 18-25 years old.[6,22,40]

Visual assessment

Visual acuity

visual acuity (VA) assessment is the first test that should be accomplished prior to other eye screening tests. [46,47] visual acuity has different types of tests for each age group, such as teller acuity cards used with 0 to 2 years old, Lea symbols for 2 to 6 years old, and HOTV cards for 6 to 15 years old children.[47] some children are preverbal or

uncooperative and their VA examination can be challenging. preverbal infants or toddlers undergo visual acuity measurements by tracking eye movement by preferential looking test or observing children's response while watching TV.[48]

age-appropriate evaluation of VA is crucial for monitoring NF-1 associated with OPG patients and must be performed by professional pediatric ophthalmologists,[46,47] and the results should correspond to normal age values[49,50]. importantly, in the VA follow-up assessment, the same optotype was used for standardization[40].

when a physician detects increasing visual loss, other causes should be excluded, like nonorganic vision loss, lack of cooperation, or refractive errors before attributing the finding to tumor progression[51]. moreover. for confirmation, the patient should be reassessed within 1 to 2 weeks before deciding on treatment.[40,51] Accordingly, ophthalmologists proposed clinical progression criteria as the following: (1) a 2-line change in lea, HOTV, or Snellen VA compared with the former examination, or (2) a 2-line decrease in teller visual acuity test[34]. according to age-based values comparison, if there is a confirmed reduction in VA, then MRI is recommended.[6]

nonetheless, children with symptomatic OPG with NF-1 syndrome may experience ophthalmological abnormalities and moderate to severe cognitive impairment, accompanied by attention difficulties, leading to reducing visual acuity examination reliability[33]. alternatively, other morphological and functional examinations have been suggested,[33,47] such as OCT[48], as full replacement of the VA test.

Visual field test

the visual field test has been suggested as complementary to the VA test. on one hand, it defines the loss of VA in OPG associated with NF-1. On the other hand, attention defects in NF-1 patients can cause biased results, especially in children[6,33], thus, the results of visual field examinations can be considered unreliable for ages lower than 7.[52]

3.1.3. Optical coherence tomography (OCT)

OCT has been used as an objective measurement for the diagnosis and follow-up of OPGs with NF-1 syndrome.[33,53] Objective measurements have been used as a useful tool for accurate vision assessment in NF-1 children who have a comorbidity of attention, cognitive impairment,[6,34] and who cannot cooperate for visual acuity or visual field testing.[48]

OCT under sedation measures the retinal nerve fiber layer thickness (RNFL)[48], which reports the loss of optic nerve fibers and visual loss.[33,53] The thickness of RNFL is a marker of damages in the visual pathway, in which there is proof of a negative relationship between the volumetric measurements of the entire visual pathway and the total volume of the brain.[54] Therefore, it has higher sensitivity, specificity, and positive

and negative predictive values, in comparison with VA and optic disc evaluation.[33] in addition to RNFL analysis, Mustafa Hepokur [55] found out there are other measurements such as macular thickness and GCL-IPL thickness that can be used to monitor suspected OPG patients.

Visual evoked potential (VEP)

VEP is one of the suggested screening tests, which measures the critical activity in response to a visual stimulus, by implementing electrodes over the scalp[46]. For presymptomatic OPGs with NF-1, some researchers proposed the sweap visual evoked potential as an alternative to conventional visual evoked potential.[56]

VEP indicates visual pathway damages by prolonged latency or decreased amplitude. this screening tool is characterized by high OPG identifying sensitivity (70-90%). However, VEP has low specificity (58-69%), which cannot differentiate between symptomatic and asymptomatic OPG, and its results do not correlate with visual acuity.[46,57] Furthermore, the test time duration takes up to 30 minutes which is considered bothersome to children.[6,33,58]

Other diagnostic tools

magnetic resonance image (MRI) of the brain and orbit is the gold standard neuroimaging screening for symptomatic OPG with NF-1 diagnosis.[59,60] some authors support the routine MRI examination especially in children less than 15 months of age, for identifying the risk of chiasmal or post-chiasmal OPG with a high tendency to cause visual dysfunction.[61–63] through MRI, The T1-weighted sequence shows pilocytic astrocytomas (PAs) as hypo- or iso-intense, and the T2-weighted or FLAIR shows PAs as hyper-intense images, with strong and diffuse enhancement. in addition, it consists of cysts or tumor nodules in a cyst.[64]

figure (1): Optic nerve glioma, MRI scan, Case courtesy of Dr. Ammar Haouimi.[65]

Computed tomography (CT) scanning can show pilocytic astrocytomas as round/ oval lesions will be well-characterized iso- or slightly hypo- dense and enhanced with contrast media.[64] Calcification is uncommon and can be used as differentiating sign between OPG and optic nerve meningiomas that commonly calcify. Exceptionally, chiasmatic glioma is more likely to have calcifications rather than optic nerve glioma.[66] Further imaging techniques recommended for OPG management is Positron emission tomography (PET). PET has accuracy in predicting tumor progression that is evaluated in many studies.[67]

Management and treatment

OPG has many management and treatment approaches, including observation, surgery, radiotherapy, and chemotherapy.[58] The main goal of these approaches is to preserve crucial functions from loss (such as vision), prevent the growth of the tumor, and keep in mind the main rule is long-term survival. Accordingly, it is important to balance the main goals of treatment with treatment side effects and consider it as an essential part of the process of decision-making.[68]

Observations

A vast number of OPG patients require observation as a primary management option for non-progressive, non-surgical lesions. for the pediatric OPG population, ophthalmological follow-ups must be performed at three months intervals after the detection of the tumor for one year, followed by expanded follow-up intervals.[6]

Surgery

For OPG treatment, surgery procedure plays a minor role.[39] It is used when the tumor size is large enough to cause symptoms and morbidities.[6,69] indications of the surgical procedure include hydrocephalus obstruction, cosmetic configurations because of proptosis which is also associated with corneal exposure, in addition to irreversible and severe vision loss.[6,69–71]

Complete resection surgeries are indicated when the tumor is restricted inside the optic nerve and associated with complete blindness,[72] in this case, resection can be curative.[69,73] However, this surgical option is associated with considerable neuroophthalmological morbidity [6,69] and most clinicians would not suggest it in the sighted eye.[20,71] surgical debulking is an option when the tumor's exophytic parts compress the optic nerve, chiasm, or other structures.[74]

Radiotherapy

Historically, radiotherapy has been used to monitor the growth of tumors and has been applied as primary or post-surgical adjuvant therapy in patients who's older than 5 years for both syndromic and sporadic OPG.[38,69]

There are many radiation therapy techniques with different properties and effects on OPG patients. Stereotactic conformal techniques showed better results than conventional techniques in terms of reducing side-effect risks, controlling the tumor, and protecting healthy tissue. Studies conducted on proton therapy proved to focus the treatment on the tumor itself and minimizing the dosage on healthy tissue which is considered more effective.[75] In a comparison study between proton and photon therapy, conducted by Merchant et al.[76] to determine the clinical advantage superiority. The study concludes that proton therapy has long-term clinical benefits especially in cognitive functions for OPG pediatric patients.

On one hand, radiotherapy has been proven to be most effective in obtaining functional improvement and cancer stability.[1] On the other hand, radiotherapy has critical late side effects,[77] and its toxicity must be considered. commonly, cerebral radiotherapy in the pediatric population raises the risk for developmental anomalies in the brain, such as visual and hearing loss, and second cancers late in life,[78] in addition to neurocognitive deficits and endocrinopathies.[79] Vasculopathy is also termed moyamoya disease.[80] It is a crucial complication of radiotherapy in OPG patients, which is due to the proximity of the therapy to the circle of wills, and the modern techniques of radiotherapy, even proton therapy, cannot eliminate the risk of vasculopathy.[81,82]

Chemotherapy

since 2000, chemotherapy has been chosen as the first-line treatment for all ages of cancer patients to avoid radiotherapy side effects[22]. Chemotherapy management begins with the detection of declined visual acuity. However, waiting for the patients to observe changes in their visual acuity may result in more threatening visual acuity issues. Therefore, the presence of optic disc pallor throughout the management period may indicate worsening the visual acuity in patients.[83]

Several regimens are used to control the progression of cancers, and the most common effective regimen is carboplatin/vincristine combination therapy, and it can be considered first-line treatment for non-surgical OPG associated with NF-1[84]. The carboplatin regimen is well tolerated and not linked with major toxicity. However, a number of side effects may be observed such as neutropenia, allergic reactions, and thrombocytopenia.[85,86] Temozolomide is another effective regimen, but in comparison with vineristin/carboplatin combination may not show the same advantages and effectiveness[12]. Falsini et al[87] conducted a randomized trial in 13 patients with OPG associated with NF-1 syndrome who received nerve growth factor (NGF) eye drops after the end of chemotherapy. Thier results show improvement in the visual field and electrophysiological parameters.

The following is treatment recommendation algorithms for each age group[5]:

1. Children under the age of 1 year: instantaneous chemotherapy should be considered in nearly all cases. surgery to be discussed individually depending on clinical presentation (presence/absence of hydrocephalus). no observation duration and radiotherapy.
2. Children 1-5 years old: observation in the case of a small cancer size without visual impairment. about the bulky tumor, a biopsy is suggested, debulking cases to be discussed individually. whether surgery/biopsy is achieved or not, chemotherapy is to be considered if there is proof of radiological progression or visual worsening.
3. Children 6-10 years old: observation in the case of a small cancer size without visual impairment. about the bulky tumor, a biopsy is suggested, debulking cases to be discussed individually. chemotherapy be considered after a duration of observation if there is proof of radiological progression or visual deterioration. conformal radiation therapy is a replacement for chemotherapy in non-nf1 patients.
4. Children > 10 years old: observation in the case of a small cancer size without visual impairment. about the bulky tumor, a biopsy is suggested, debulking cases

to be discussed individually. Chemotherapy or conformal radiation treatment to be considered if there is proof of radiological progression or visual worsening.

For Surgical Approach (Video)

https://www.neurosurgicalatlas.com/cases/optic-nerve-glioma?texttrack=en-US&highlight=optic%20nerve%20glioma

References

1. Kortmann, R.-D. *et al.* Current and future strategies in radiotherapy of childhood low-grade glioma of the brain. Part I: Treatment modalities of radiation therapy. *Strahlenther. Onkol.* **179**, 509–520 (2003).
2. Czyzyk, E., Jóźwiak, S., Roszkowski, M. & Schwartz, R. A. Optic pathway gliomas in children with and without neurofibromatosis 1. *J. Child Neurol.* **18**, 471–478 (2003).
3. Reis, G. F. *et al.* Pilocytic astrocytomas of the optic nerve and their relation to pilocytic astrocytomas elsewhere in the central nervous system. *Mod. Pathol. an Off. J. United States Can. Acad. Pathol. Inc* **26**, 1279–1287 (2013).
4. Liu, G. T. *et al.* Optic radiation involvement in optic pathway gliomas in neurofibromatosis. *Am. J. Ophthalmol.* **137**, 407–414 (2004).
5. Opocher, E. *et al.* Prognostic factors for progression of childhood optic pathway glioma: a systematic review. *Eur. J. Cancer* **42**, 1807–1816 (2006).
6. Listernick, R., Ferner, R. E., Liu, G. T. & Gutmann, D. H. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Ann. Neurol.* **61**, 189–198 (2007).
7. Peckham-Gregory, E. C. *et al.* Evaluation of racial disparities in pediatric optic pathway glioma incidence: Results from the Surveillance, Epidemiology, and End Results Program, 2000-2014. *Cancer Epidemiol.* **54**, 90–94 (2018).
8. Nicolin, G. *et al.* Natural history and outcome of optic pathway gliomas in children. *Pediatr. Blood Cancer* **53**, 1231–1237 (2009).
9. Ertiaei, A., Hanaei, S., Habibi, Z., Moradi, E. & Nejat, F. Optic Pathway Gliomas: Clinical Manifestation, Treatment, and Follow-Up. *Pediatr. Neurosurg.* **51**, 223–228 (2016).
10. Kalin-Hajdu, E., Décarie, J.-C., Marzouki, M., Carret, A.-S. & Ospina, L. H. Visual acuity of children treated with chemotherapy for optic pathway gliomas. *Pediatr. Blood Cancer* **61**, 223–227 (2014).
11. Shofty, B. *et al.* Visual outcome following chemotherapy for progressive optic pathway gliomas. *Pediatr. Blood Cancer* **57**, 481–485 (2011).
12. Gururangan, S. *et al.* Temozolomide in children with progressive low-grade glioma. *Neuro. Oncol.* **9**, 161–168 (2007).
13. Shapey, J., Danesh-Meyer, H. V & Kaye, A. H. Diagnosis and management of optic nerve glioma. *J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas.* **18**, 1585–1591 (2011).
14. Dolecek, T. A., Propp, J. M., Stroup, N. E. & Kruchko, C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro. Oncol.* **14 Suppl 5**, v1-49 (2012).
15. Pfister, S. & Witt, O. Pediatric gliomas. *Recent results cancer Res. Fortschritte der Krebsforsch. Prog. dans les Rech. sur le cancer* **171**, 67–81 (2009).
16. Louis, D. N. *et al.* The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol.* **114**, 97–109 (2007).
17. Chen, Y.-H. & Gutmann, D. H. The molecular and cell biology of pediatric low-grade gliomas. *Oncogene* **33**, 2019–2026 (2014).
18. Lewis, R. A., Gerson, L. P., Axelson, K. A., Riccardi, V. M. & Whitford, R. P. von Recklinghausen neurofibromatosis. II. Incidence of optic gliomata. *Ophthalmology* **91**, 929–935 (1984).
19. Trevisson, E. *et al.* Natural history of optic pathway gliomas in a cohort of unselected patients affected by Neurofibromatosis 1. *J. Neurooncol.* **134**, 279–287 (2017).
20. Dutton, J. J. Gliomas of the anterior visual pathway. *Surv. Ophthalmol.* **38**, 427–452 (1994).
21. Miller, N. R. Primary tumours of the optic nerve and its sheath. *Eye (Lond).* **18**, 1026–1037 (2004).
22. Liu, G. T. Optic gliomas of the anterior visual pathway. *Curr. Opin. Ophthalmol.* **17**, 427–431 (2006).
23. Koeller, K. K. & Rushing, E. J. From the archives of the AFIP: pilocytic astrocytoma: radiologic-pathologic correlation. *Radiogr. a Rev. Publ. Radiol. Soc. North Am. Inc* **24**, 1693–1708 (2004).
24. Wippold, F. J. 2nd, Perry, A. & Lennerz, J. Neuropathology for the neuroradiologist: Rosenthal fibers. *AJNR. Am. J. Neuroradiol.* **27**, 958–961 (2006).
25. Korshunov, A. *et al.* Combined molecular analysis of BRAF and IDH1 distinguishes pilocytic astrocytoma from diffuse astrocytoma. *Acta Neuropathol.* **118**, 401–405 (2009).
26. Jones, D. T. W. *et al.* Adult grade II diffuse astrocytomas are genetically distinct from and more aggressive than their paediatric counterparts. *Acta Neuropathol.* **121**, 753–761 (2011).

27. Hoyt, W. F., Meshel, L. G., Lessell, S., Schatz, N. J. & Suckling, R. D. Malignant optic glioma of adulthood. *Brain* **96**, 121–132 (1973).
28. Nagaishi, M. *et al.* Clinicopathological and molecular features of malignant optic pathway glioma in an adult. *J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas.* **22**, 207–209 (2015).
29. Wabbels, B. *et al.* Unilateral adult malignant optic nerve glioma. *Graefe's Arch. Clin. Exp. Ophthalmol. = Albr. von Graefes Arch. fur Klin. und Exp. Ophthalmol.* **242**, 741–748 (2004).
30. Sellmer, L. *et al.* Serial MRIs provide novel insight into natural history of optic pathway gliomas in patients with neurofibromatosis 1. *Orphanet J. Rare Dis.* **13**, 62 (2018).
31. King, A., Listernick, R., Charrow, J., Piersall, L. & Gutmann, D. H. Optic pathway gliomas in neurofibromatosis type 1: the effect of presenting symptoms on outcome. *Am. J. Med. Genet. A* **122A**, 95–99 (2003).
32. Thiagalingam, S., Flaherty, M., Billson, F. & North, K. Neurofibromatosis type 1 and optic pathway gliomas: follow-up of 54 patients. *Ophthalmology* **111**, 568–577 (2004).
33. Parrozzani, R. *et al.* Optical coherence tomography in the diagnosis of optic pathway gliomas. *Invest. Ophthalmol. Vis. Sci.* **54**, 8112–8118 (2013).
34. Campen, C. J. & Gutmann, D. H. Optic Pathway Gliomas in Neurofibromatosis Type 1. *J. Child Neurol.* **33**, 73–81 (2018).
35. Fisher, M. J. *et al.* Functional outcome measures for NF1-associated optic pathway glioma clinical trials. *Neurology* **81**, S15-24 (2013).
36. Papini, C., Dineen, R. A., Walker, D. A., Thomas, S. & Pitchford, N. J. Neuropsychological outcomes of children with Optic Pathway Glioma. *Sci. Rep.* **10**, 3344 (2020).
37. Taylor, T. *et al.* Radiological classification of optic pathway gliomas: experience of a modified functional classification system. *Br. J. Radiol.* **81**, 761–766 (2008).
38. Grill, J. *et al.* When do children with optic pathway tumours need treatment? An oncological perspective in 106 patients treated in a single centre. *Eur. J. Pediatr.* **159**, 692–696 (2000).
39. Wilhelm, H. Primary optic nerve tumours. *Curr. Opin. Neurol.* **22**, 11–18 (2009).
40. Avery, R. A., Fisher, M. J. & Liu, G. T. Optic pathway gliomas. *J. neuro-ophthalmology Off. J. North Am. Neuro-Ophthalmology Soc.* **31**, 269–278 (2011).
41. Guillamo, J.-S. *et al.* Prognostic factors of CNS tumours in Neurofibromatosis 1 (NF1): a retrospective study of 104 patients. *Brain* **126**, 152–160 (2003).
42. Zeid, J. L., Charrow, J., Sandu, M., Goldman, S. & Listernick, R. Orbital optic nerve gliomas in children with neurofibromatosis type 1. *J. AAPOS Off. Publ. Am. Assoc. Pediatr. Ophthalmol. Strabismus* **10**, 534–539 (2006).
43. Habiby, R., Silverman, B., Listernick, R. & Charrow, J. Precocious puberty in children with neurofibromatosis type 1. *J. Pediatr.* **126**, 364–367 (1995).
44. Hartel, P. H., Rosen, C., Larzo, C. & Nestor, S. Malignant optic nerve glioma (glioblastoma multiforme): A case report and literature review. *W. V. Med. J.* **102**, 29–31 (2006).
45. Dinh, T. T., Wang, Y. Y., Rosenfeld, J. V & Cherny, M. Glioblastoma of the optic chiasm. *J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas.* **14**, 502–505 (2007).
46. de Blank, P. M. K. *et al.* Optic Pathway Gliomas in Neurofibromatosis Type 1: An Update: Surveillance, Treatment Indications, and Biomarkers of Vision. *J. neuro-ophthalmology Off. J. North Am. Neuro-Ophthalmology Soc.* **37 Suppl 1**, S23–S32 (2017).
47. Avery, R. A., Bouffet, E., Packer, R. J. & Reginald, A. Feasibility and comparison of visual acuity testing methods in children with neurofibromatosis type 1 and/or optic pathway gliomas. *Invest. Ophthalmol. Vis. Sci.* **54**, 1034–1038 (2013).
48. Avery, R. A. *et al.* Handheld optical coherence tomography during sedation in young children with optic pathway gliomas. *JAMA Ophthalmol.* **132**, 265–271 (2014).
49. Anstice, N. S. & Thompson, B. The measurement of visual acuity in children: an evidence-based update. *Clin. Exp. Optom.* **97**, 3–11 (2014).
50. Campagna, M. *et al.* Optic pathway glioma: long-term visual outcome in children without neurofibromatosis type-1. *Pediatr. Blood Cancer* **55**, 1083–1088 (2010).
51. Cassiman, C. *et al.* Ophthalmological examination in neurofibromatosis type 1: a long-term retrospective analysis. *Acta ophthalmologica* vol. 96 e1044–e1046 (2018).
52. Beres, S. J. Optic Pathway Gliomas in Neurofibromatosis Type 1: Imaging and Monitoring. *Int. Ophthalmol. Clin.* **58**, 97–112 (2018).
53. Parrozzani, R. *et al.* Correlation of peripapillary retinal nerve fibre layer thickness with visual acuity in paediatric patients affected by optic pathway glioma. *Acta Ophthalmol.* **96**, e1004–e1009 (2018).
54. Avery, R. A. *et al.* Optic pathway glioma volume predicts retinal axon degeneration in neurofibromatosis type 1. *Neurology* **87**, 2403–2407 (2016).
55. Hepokur, M. & Sarici, A. M. Investigation of retinal nerve fiber layer thickness and ganglion cell layer-inner plexiform layer thickness in patients with optic pathway gliomas. *Graefe's Arch. Clin. Exp. Ophthalmol. = Albr. von Graefes Arch. fur Klin. und Exp. Ophthalmol.* **256**, 1757–1765 (2018).
56. Chang, B. C. M. *et al.* Screening and diagnosis of optic pathway gliomas in children with neurofibromatosis type 1 by using sweep visual evoked potentials. *Invest. Ophthalmol. Vis. Sci.* **48**, 2895–2902 (2007).
57. Kelly, J. P. & Weiss, A. H. Detection of tumor progression in optic pathway glioma with and without neurofibromatosis type 1. *Neuro. Oncol.* **15**, 1560–1567 (2013).
58. Fried, I., Tabori, U., Tihan, T., Reginald, A. & Bouffet, E. Optic pathway gliomas: a review. *CNS Oncol.* **2**, 143–159 (2013).

59. Listernick, R., Charrow, J., Greenwald, M. & Mets, M. Natural history of optic pathway tumors in children with neurofibromatosis type 1: a longitudinal study. *J. Pediatr.* **125**, 63–66 (1994).
60. Listernick, R., Louis, D. N., Packer, R. J. & Gutmann, D. H. Optic pathway gliomas in children with neurofibromatosis 1: consensus statement from the NF1 Optic Pathway Glioma Task Force. *Ann. Neurol.* **41**, 143–149 (1997).
61. Blazo, M. A. *et al.* Outcomes of systematic screening for optic pathway tumors in children with Neurofibromatosis Type 1. *Am. J. Med. Genet. A* **127A**, 224–229 (2004).
62. Prada, C. E. *et al.* The Use of Magnetic Resonance Imaging Screening for Optic Pathway Gliomas in Children with Neurofibromatosis Type 1. *J. Pediatr.* **167**, 851-856.e1 (2015).
63. Balcer, L. J. *et al.* Visual loss in children with neurofibromatosis type 1 and optic pathway gliomas: relation to tumor location by magnetic resonance imaging. *Am. J. Ophthalmol.* **131**, 442–445 (2001).
64. Fisher, P. G. *et al.* A clinicopathologic reappraisal of brain stem tumor classification. Identification of pilocystic astrocytoma and fibrillary astrocytoma as distinct entities. *Cancer* **89**, 1569–1576 (2000).
65. Radiopedia. optic nerve glioma.
66. Pepin, S. M. & Lessell, S. Anterior visual pathway gliomas: The last 30 years. *Semin. Ophthalmol.* **21**, 117–124 (2006).
67. Kruer, M. C. *et al.* The value of positron emission tomography and proliferation index in predicting progression in low-grade astrocytomas of childhood. *J. Neurooncol.* **95**, 239–245 (2009).
68. Parsa, C. F. *et al.* Spontaneous regression of optic gliomas: thirteen cases documented by serial neuroimaging. *Arch. Ophthalmol. (Chicago, Ill. 1960)* **119**, 516–529 (2001).
69. Astrup, J. Natural history and clinical management of optic pathway glioma. *Br. J. Neurosurg.* **17**, 327–335 (2003).
70. Massimi, L., Tufo, T. & Di Rocco, C. Management of optic-hypothalamic gliomas in children: still a challenging problem. *Expert Rev. Anticancer Ther.* **7**, 1591–1610 (2007).
71. Lee, A. G. Neuroophthalmological management of optic pathway gliomas. *Neurosurg. Focus* **23**, E1 (2007).
72. Hoffman, H. J. *et al.* Optic pathway/hypothalamic gliomas: a dilemma in management. *Pediatr. Neurosurg.* **19**, 186–195 (1993).
73. Kaufman, L. M. & Doroftei, O. Optic glioma warranting treatment in children. *Eye (Lond).* **20**, 1149–1164 (2006).
74. Tong, Z., Wanibuchi, M., Uede, T., Tanabe, S. & Hashi, K. Significant improvement of visual functions after removal of an intracranial giant optic nerve glioma revealing exophytic growth: case report. *Neurosurgery* **58**, E792; discussion E792 (2006).
75. Jahraus, C. D. & Tarbell, N. J. Optic pathway gliomas. *Pediatr. Blood Cancer* **46**, 586–596 (2006).
76. Merchant, T. E. *et al.* Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr. Blood Cancer* **51**, 110–117 (2008).
77. Kortmann, R.-D. *et al.* Current and future strategies in radiotherapy of childhood low-grade glioma of the brain. Part II: Treatment-related late toxicity. *Strahlenther. Onkol.* **179**, 585–597 (2003).
78. Packer, R. J. *et al.* Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **21**, 3255–3261 (2003).
79. Mulhern, R. K., Merchant, T. E., Gajjar, A., Reddick, W. E. & Kun, L. E. Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet. Oncol.* **5**, 399–408 (2004).
80. Ullrich, N. J. *et al.* Moyamoya following cranial irradiation for primary brain tumors in children. *Neurology* **68**, 932–938 (2007).
81. Bowers, D. C. *et al.* Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **24**, 5277–5282 (2006).
82. Bowers, D. C. *et al.* Nonperioperative strokes in children with central nervous system tumors. *Cancer* **94**, 1094–1101 (2002).
83. Fisher, M. J. *et al.* Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. *Neuro. Oncol.* **14**, 790–797 (2012).
84. Packer, R. J. *et al.* Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. *J. Neurosurg.* **86**, 747–754 (1997).
85. Aquino, V. M., Fort, D. W. & Kamen, B. A. Carboplatin for the treatment of children with newly diagnosed optic chiasm gliomas: a phase II study. *J. Neurooncol.* **41**, 255–259 (1999).
86. Mahoney, D. H. J. *et al.* Carboplatin is effective therapy for young children with progressive optic pathway tumors: a Pediatric Oncology Group phase II study. *Neuro. Oncol.* **2**, 213–220 (2000).
87. Falsini, B. *et al.* Nerve growth factor improves visual loss in childhood optic gliomas: a randomized, double-blind, phase II clinical trial. *Brain* **139**, 404–414 (2016).

Article topic: Brown Sequard Syndrome.

Author: Zuhdi Badwan.

Editor: Aseel Rabadi.

Reviwer: Omar Jbarah.

Keywords: *Brown Sequard Syndrome, incomplete spinal cord injury, spinal cord syndrome, Spine, neurosurgery.*

History

Brown-Sequard syndrome (BSS) is classified as an incomplete spinal cord injury, where sensory and motor functions are not completely lost below the level of damage.

Brown-Sequard syndrome, named after the physiologist Charles-Edouard Brown-Séquard (1817–1894), was famous for his contributions to the fields of neurology and endocrinology [1]. He first published this condition in (1849) and discussed it later other occasions: one was a case about a sea captain who developed the syndrome after getting stabbed in the neck. Also, in The Lancet (1869), he defined the syndrome as we know it today [1].

Epidemiology

There is no reliable estimate of the global prevalence or incidence of Brown-Sequard syndrome. However, spinal cord injuries, in general have a global incidence from 8 to 246 cases per million per year and a global prevalence from 236 to 1,298 cases per million per year [2]. Given that, the National Organization for Rare Diseases (NORD) estimated that around 2% of spinal cord injury cases are Brown-Sequard syndrome cases [3].

Etiology and pathogenesis

In The Lancet (1869): the physiologist Brown Sequard described his syndrome based on three findings: “A lesion in one of the lateral halves of the spinal cord that produces: firstly, paralysis of voluntary movements in the same side; secondly, anesthesia to touch, tickling, painful impressions, and changes of temperature in the opposite side; thirdly, paralysis of muscular senses in the same side”[1].

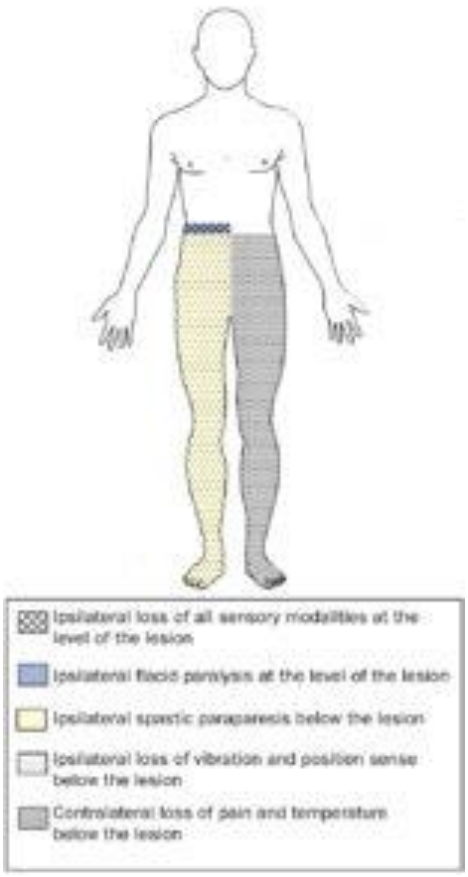


Figure 1: Features of Brown Sequard syndrome.

To understand these findings, we must look at the spinal cord: it has a lot of tracts, but BSS is only concerned with three of them: the spinothalamic tract, the lateral corticospinal tract, and the medial lemniscus tract.

Spinothalamic tract

The spinothalamic tract mediates the sensation of pain and temperature. Sensory modalities enter the cord via the dorsal root entry zone and synapse in the dorsal horn. At the level of synapses, the postsynaptic fibers directly cross to the opposite side. After that, they ascend within the anterolateral funiculus. These fibers continue to the thalamus to synapse with ventral posterolateral and intralaminar thalamic nuclei, continuing from the thalamic nuclei to the primary somatosensory cortex [4].

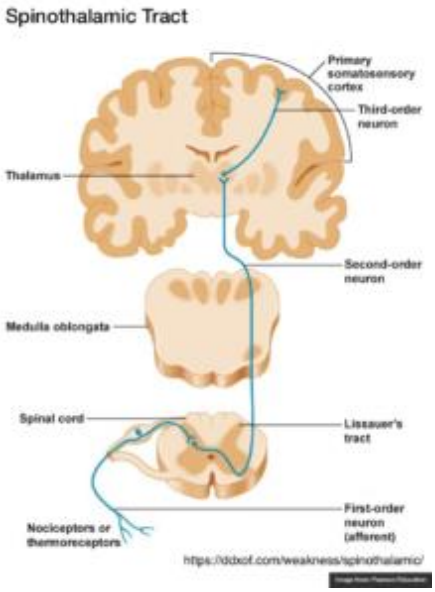


Figure 2: the spinothalamic tract.

Lateral corticospinal tract

The lateral corticospinal tract on the other hand, mediates axial body and limb movements. It descends from the precentral motor cortex to decussate at the level of the lower medulla to the contralateral side. Then it continues down to synapse with neurons in the anterior gray horn at each ventral root. Lastly, the postsynaptic neurons exit via the ventral root to innervate the muscles [4].

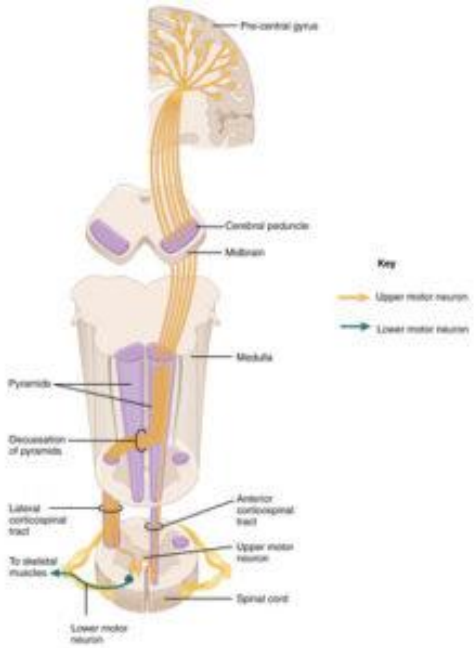


Figure 3: The lateral corticospinal tract.

Dorsal/Medial lemniscus tract

The medial lemniscus tract mediates the sensations of vibration, proprioception (position sense), and 2-point discrimination from the skin and joints. Sensory modalities enter the spinal cord via the dorsal root. Nerve fibers ascend on the same side of their entry until they reach the gracile and cuneate nuclei in the lower medulla where they synapse. Postsynaptic fibers leave the nuclei and decussate to the contralateral side. Then travel upward to the ventral posterolateral thalamic nucleus to new synapses point which eventually leads to the primary somatosensory cortex [4].

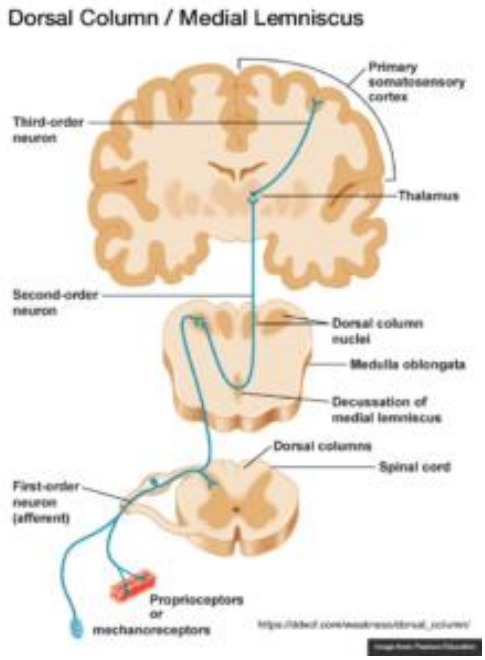


Figure 4: The medial lemniscus tract.

To sum up, if the spinal cord is injured in a way that affects the three tracts on the same lateral half, the signal transmission is disrupted and as a result Brown Sequard syndrome will manifest accordingly.

Overall, three main mechanisms cause a spinal cord injury and can develop a case of Brown Sequard syndrome: First, direct physical damage causing physical spinal cord damage. Second, when the cord vascular supply is compromised causing ischemia. Third, due to spinal cord contusion and innate problems in the nervous tissue [5].

Most BSS cases are of a traumatic etiology: car accidents, violent acts (stabbing, gunshot, etc.), and falls. Non-traumatic causes are less prevalent but have many variations in the literature, like tumors, degenerative diseases, disk herniation, ischemia, inflammation or infections of the spinal cord, epidural hematoma, decompression sickness, cervical synovial cyst, and ruptured pheochromocytoma [5-8].

Diagnosis and Management

Diagnosis is reached based on extensive neurological clinical exams that show the features of BSS. In addition to MRI and CT imaging, other investigations such as spinal angiography and nuclear medicine can help identify vascular malformations and infectious or inflammatory causes.

BSS treatment can be conservative (medical treatment, physiotherapy, and rehabilitation) or surgical management, from which to choose depending on the patient's neurological status and radiological findings.

Surgical interventions are necessary to reduce pressure on the spinal cord and increase its stability. For instance, in cases of traumatic injury, disc herniation, spinal hematoma to evacuate, or a foreign object or bony elements to remove. Used Surgical interventions include laminoplasty, laminectomy, and discectomy. Whilst medical management is chosen over surgical interventions in cases of infective, inflammatory, or demyelinating causes of BSS. Corticosteroids, antibiotics, antispasmodics, and analgesics are often used [9-12].

Complications

Published literature did not point out specific complications following BSS. However, spinal cord injuries collectively have certain complications which can involve many systems, and they depend on the location of the injury. For example:

- Cardiovascular complications are the most common cause of death in SCI. Manifest as a neurogenic shock. A neurogenic shock: involves bradycardia and hypotension, it happens due to loss of sympathetic drive because of injuries at T6 vertebrae level and above.
- Pulmonary complications are the most common complications in SCI. Including Diaphragmatic and intercostal muscles dysfunctions, caused by injuries at T1 vertebrae level and above. Whereas injuries at C3 vertebrae level and above are more severe and could lead to diaphragmatic paralysis. Added pulmonary complications include pneumonia, pulmonary embolism, pleural effusion, pneumothorax, and mucus plug.
- Gastrointestinal Complications include ileus, constipation, pancreatitis, abdominal rigidity, and stress ulceration.
- Genitourinary Complications include neurogenic bladder and urinary tract infections.
- Autonomic dysreflexia happens due to an injury in high thoracic and cervical levels. Opposite to what happens in a neurogenic shock: the lesion blocks

sympathetic inhibitory outflow which leads to a sympathetic overdrive, that causes cardiac, bladder, bowel, temperature, and sexual dysfunctions [13].

Prognosis

BSS demonstrates a bright prognosis after rehabilitation. Shortly after it, patients can independently perform functional skills at discharge and could even regain employment.

It is important to mention that patients with predominant upper limb weakness show better outcomes than those with predominant lower limb weakness. Also, BSS has a better prognosis than all the other spinal cord injuries [14,15].

References

1: Tattersall R, Turner B. Brown-Séquard and his syndrome. The Lancet. 2000 Jul 1;356(9223):61-3.
2: Furlan JC, Sakakibara BM, Miller WC, Krassioukov AV. Global incidence and prevalence of traumatic spinal cord injury. Canadian journal of neurological sciences. 2013 Jul;40(4):456-64.
3: https://rarediseases.org/rare-diseases/brown-sequard-syndrome/#:~:text=The%20incidence%20of%20Brown%2DS%C3%A9quard,30%2D40%20per%201%2C000%2C000%20people.
4: Bican O, Minagar A, Pruitt AA. The spinal cord: a review of functional neuroanatomy. Neurologic clinics. 2013 Feb 1;31(1):1-8
5: Moskowitz E, Schroeppel T. Brown-sequard syndrome. Trauma surgery & acute care open. 2018 Feb 1;3(1):e000169.
6: (2017) SCI Facts and Figures, The Journal of Spinal Cord Medicine, 40:1, 126-127, DOI: 10.1080/10790268.2017.1294349
7: William McKinley MD, Katia Santos MD, Michelle Meade PhD & Karen Brooke MT (2007) Incidence and Outcomes of Spinal Cord Injury Clinical Syndromes, The Journal of Spinal Cord Medicine, 30:3, 215-224, DOI: 10.1080/10790268.2007.11753929
8: Koehler PJ, Endtz LJ. The Brown-Séquard syndrome: true or false?. Archives of neurology. 1986 Sep 1;43(9):921-4.
9: Abouhashem S, Ammar M, Barakat M, Abdelhameed E. Management of Brown-Sequard syndrome in cervical disc diseases. Turkish neurosurgery. 2013 Jan 1;23(4):470-5.
10: Ranga U, Aiyappan S. Brown-Séquard syndrome. The Indian journal of medical research. 2014 Oct 1;140(4):572-3.
11: Alrabiah AA, Alskait GA, Alwakeel TS, Zekry AH, Yousef AA. Conservative Management of Traumatic Brown-Séquard Syndrome: A Case Report. The American journal of case reports. 2021;22:e930036-1.
12: Kulkarni AG, Nag K, Shah S. Cervical epidural haematoma causing Brown-Sequard syndrome: a case report. Journal of Orthopaedic Surgery. 2013 Dec;21(3):372-4.
13: Sweis R, Biller J. Systemic complications of spinal cord injury. Current neurology and neuroscience reports. 2017 Jan;17(1):1-8.
14: Roth EJ, Park T, Pang T, Yarkony GM, Lee MY. Traumatic cervical Brown-Sequard and Brown-Sequard-plus syndromes: the spectrum of presentations and outcomes. Spinal Cord. 1991 Nov;29(9):582-9.
15: Bosch A, Stauffer ES, Nickel VL. Incomplete traumatic quadriplegia: a ten-year review. Jama. 1971 Apr 19;216(3):473-8.
Figure 1: Tattersall R, Turner B. Brown-Séquard and his syndrome. The Lancet. 2000 Jul 1;356(9223):61-3.
Figure 2: https://ddxof.com/weakness/spinothalamic/
Figure 3: Case courtesy of OpenStax College, Radiopaedia.org. From the case rID: 53266
Figure 4: https://ddxof.com/weakness/dorsal_column/

Article topic: Brain abscess.

Authors: Qusay Fadel, Rand Al-Qaseer.

Editor: Sia Sawan.

Reviewer: Omar Jbarah.

***Keywords**: Cerebral abscess, Neuro infection, Hypodense lesion.*

Overview

Brain abscess (BA or Cerebral abscess) is a circumscribed collection of purulent exudates in the brain that develops in response to an infection or trauma. Most cases are caused by the spread of infected material from a focus of suppuration elsewhere in the body, notably the paranasal sinuses, middle ear, heart, and lungs. Penetrating craniocerebral trauma and neurosurgical procedures may also be associated with this condition. Clinical manifestations include headache; seizures; focal neurologic deficits; and alterations of consciousness.

Brain abscesses are potentially serious, life-threatening diseases that pose a complex diagnostic challenge not only to neurosurgeons but also to clinical microbiologists, neurologists, psychiatrists, infectologists (1).

Epidemiology

According to studies, brain abscess accounts for a disproportionate percentage of space-occupying intracranial lesions in developing countries compared to developed nations with an approximate incidence of 8% of intracranial masses compared to 1% to 2% in the Western countries with approximately four cases occurring per million. (2)

The prevalence of brain abscess in patients with acquired immunodeficiency syndrome (AIDS) is much higher. The incidence of fungal brain abscesses also has increased because of the higher usage of broad-spectrum antibiotics and immunosuppressive agents like steroids (2).

Prevalence is highest in adult men younger than 30 years while pediatric disease occurs most frequently in children ages 4 to 7 years. Neonates are third in high-risk groups. Vaccination has reduced the prevalence in young children. Data suggests that brain abscesses are more predominant in males than in females with a male-to-female ratio varying between 2:1 and 3:1. Geographical and seasonal differences have no significant impact. (2)

Etiology

The brain abscess is a pus-filled swelling surrounded by a well-vascularized capsule found in different places in the brain but most commonly exists in the frontal lobe (3). The etiology of brain abscess is usually polymicrobial, most commonly involving a variety of aerobic and obligate anaerobic bacteria (4). For example, staphylococcus and streptococcus are found to be the causative agents for cerebral abscess in patients who had surgery in their brain before, while Clostridium and Enterobacteriaceae are common in patients with penetrating head injury (5).

The immunocompromised patients that are taking chemotherapy or steroids therapy, or with HIV infections or undergo an organ transplant procedure are likely to develop brain abscess due to fungal infection (mainly Aspergillus and candida), toxoplasma, and pseudomonas. (6)

AIDS patients are more susceptible to being infected by Cryptococcus, Listeria, and Nocardia. Additionally, many cases reported that AIDS patients have developed tuberculous abscesses due to mycobacterium tuberculosis which is considered to be a rare condition. (7)

The development of brain abscess occurs in 2 manners:

1. **Contagious manner** mostly due to sinusitis, otitis media, or mastoiditis, which lead to inferior temporal and cerebellar brain abscess. While dental surgeries cause frontal lobe abscesses. (8)
2. **Hematogenous spread** is found in 9% to 43 % of cerebral abscesses cases (46).

Organs that take part in this process.

1. Primarily, hematogenous spread arises from the lungs due to various lung disorders such as bronchiectasis, cystic fibrosis, and empyema.
2. Congenital heart defect (CHD) is a leading cause that disrupts the normal blood flow through the heart and lung, most commonly in children, that results in the right-to-left shunt that affects the ability to carry the oxygen to the different sites in the body, and that will increase the risk of developing a cerebral abscess. (9)

Pathogenesis

We can classify the development of brain abscess into **four stages (6):**

1. the first stage; **early cerebritis (1-4 days)** the hallmark of this is stage is neutrophil accumulation, tissue necrosis, and edema. Also, the microglial and astrocyte will be activated.
2. The second; is **late cerebritis (4-10 days)**, predominant macrophage, and lymphocyte infiltrate.
3. The third; **Early capsule formation (11-14days)** associated with the formation of a well-vascularized abscess wall.
4. **The fourth stage is (>14 days),** approximately at 3-4 weeks, the capsule becomes thick and is amenable to excision.

Therefore, we can see in the first 1 to 2 weeks acute inflammatory characteristics like edema and vascular congestion. While, in 3 and 4weeksk we start to see necrosis and changes like the capsule, which consists of 3 layers: the inner one contains granulation tissue, the middle one is collagenous, and the outer one is an astroglial layer. (8) We can recognize these histological changes by a sing CT scan or MRI. (6) Activated microglial cells stimulate the antibacterial adaptive immune response by MHC class II and other stimulatory molecules expressions like cytokines IL-1 and TNF-alpha, these pro-inflammatory molecules initiate a response in the brain parenchyma. Thus, the usage of anti-inflammatory therapies can reduce the damage of the brain parenchyma and enhance the neurological condition of the patients. (6) (Figure 1).

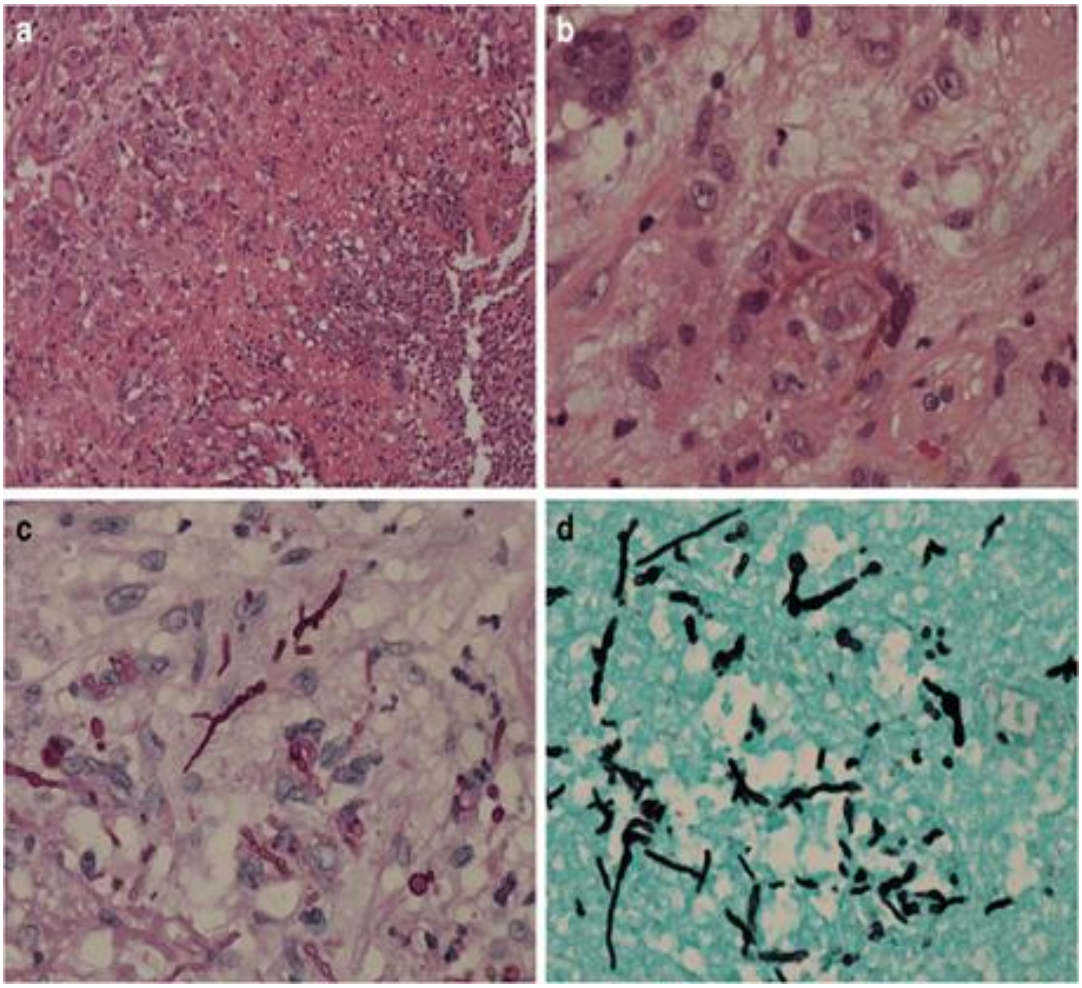


Figure 1 - available from: Acta Neurochirurgica. Histopathology of the brain abscess.

Clinical presentation and complications

The most frequent clinical manifestation of brain abscess is headache, fever while altered levels of consciousness are frequently absent (10). Neurological indications vary depending on where the abscess is located and can range from mild to severe. For days to weeks, the effect is mild. Changes in behavior may occur in patients who have abscesses in the frontal or temporal lobes. Patients with abscesses in the brain stem or cerebellum may present with cranial nerve palsy, gait disorder, or either headache or altered mental status owing to hydrocephalus (11). Clinical manifestations become more evident as the abscess grows larger and the surrounding edema increases, but these symptoms and signs may be difficult to recognize because of sedation or the nature of the underlying neurologic disease (12). Patients with hematogenous spread of bacteria may present with symptoms of the underlying infection (13).

Diagnosis

Lab tests in patients with brain abscess include the following: Complete blood count and platelet count, erythrocyte, serum C-reactive protein, serologic test (serum immunoglobulin G antibodies, RT-PCR for toxoplasma), blood cultures for microorganisms, etc., (at least 2; preferably before antibiotic therapy).

Lumbar puncture

Because of the threat of cerebrospinal fluid (CSF) leakage and death, it should only be performed after ruling out increased intracranial pressure that used a prior CT and MRI scan. Blood cultures can be done to start antibiotic therapy in acute cases presentation of patients or **suspicion** of meningitis. An elevated protein level, pleocytosis with a fluctuating neutrophil count, often a normal glucose level, and sterile cultures are the most common findings. When the white blood cell (WBC) count increases, together with elevated CSF lactic acid and numerous red blood cells (Erythrocytes) in the CSF, a lumbar puncture is performed, but this test is rarely used.

Stereotactic Computed Tomography (CT) or Surgical Aspiration

Culture, Gram stain, serology, histopathology, and PCR amplification can be done with the samples obtained.

Imaging studies

In the case of a brain abscess, CT scanning has rendered other diagnostics including angiography, ventriculography, pneumoencephalography, and radionuclide brain scanning obsolete. CT scans are less sensitive than MRI scans, but they are easier to administer. CT scanning, preferably with contrast administration, provides a rapid means of detecting the size, the number, and the location of abscesses, and it has become the mainstay of diagnosis and follow-up care. This method is used to confirm the diagnosis, localize the lesion, and monitor the progression after treatment. However, CT scan results can lag behind clinical findings. (14)(15)

CT scans usually show the brain abscess as a hypodense center with an asymmetrical enhancement ring around it after a contrast substance is injected. A well-organized abscess barrier rarely fails to provide ring augmentation. CT scans indicate nodular enhancement with areas of low attenuation without enhancement in the early stages of cerebritis. Contrast enhancement is seen as the abscess grows. After encapsulation, the contrast material is unable to distinguish the clear core, and the CT image resembles those obtained during the early stages of cerebritis. (Figure 2).

Figure (2). Ct scan of a brain abscess case courtesy of assoc prof frank gaillard, radiopaedia.org, rid: 5150

In the diagnosis of a brain abscess, many professionals consider MRI to be the first diagnostic approach. Because of its superior sensitivity and specificity, it enables accurate diagnosis and effective follow-up of lesions. MRI has a superior capacity to detect cerebritis, stronger contrast between cerebral edema and the brain, better visualization of the brainstem, and earlier detection of satellite lesions and inflammation extending into the ventricles and subarachnoid space as compared to CT scanning. (Figure 3)

Figure (3). Mri for brain abscess. Case courtesy of dr. Pat s. Kwankaew (md), radiopaedia.org, rid: 16451

Susceptibility-weighted phase imaging showed evidence of paramagnetic substances in agreement with the presence of free radicals from phagocytosis in a study of 14 patients with brain abscesses. (16) This technique could add to the characterization of pyogenic brain abscesses by providing additional information. Other tests: On occasion, an EKG will demonstrate a high voltage center with moderate activity. It is ambiguous, and it is only used to confirm a diagnosis of a brain abscess on rare occasions. This is the procedure in the diagnostic evaluation that is the least accurate.

Staging

The early stage of brain abscess (first 7-14 days) is called cerebritis and is associated with edema. Necrosis and liquefaction occur after 2-3 weeks, and the lesion becomes gradually surrounded by a fibrotic capsule. (17)

Treatment and Management

An abscess inside the brain can cause increased intracranial pressure, as well as significant morbidity and mortality. Medical and surgical approaches can also be used to manage this disease. Medical management can be considered for deep-seated, small abscesses (less than 2 cm), cases of coexisting meningitis, and a few other selected cases. Usually, a combination of both medical and surgical approaches is considered. (18)

Before abscess encapsulation and localization, antimicrobials, accompanied by measures to control increasing intracranial pressure, are essential. (19) For a single abscess, immediate intervention is required. Abscesses larger than 2.5 cm are excised or aspirated, but those smaller than 2.5 cm or at the stage of cerebritis are just aspirated for diagnostic purposes. Frequent extraction is preferred in cases of numerous abscesses or abscesses in essential tissues. In these patients, a high dose of antimicrobial(s) for an extended length of time may be an alternative.

The abscess is identified and parameters such as size and the number of abscesses is described using CT and MRI brain scanning. Large abscesses (greater than 2 cm) are usually considered for aspiration or excision, based on the surgeon's skills. Multiple abscesses are managed with a long course of high-dose antibiotics, even without aspirations, based on weekly CT scanning. The selection of an antibiotic regimen should be wisely made based on microorganisms isolated from blood or CSF. Certain antibiotics are unable to cross the blood-brain barrier and are not useful in treating brain abscess; these antibiotics include first-generation cephalosporins, Aminoglycosides, and tetracyclines. (20)

Antibiotic prescriptions aimed at specific microorganisms

- Gram-positive bacteria including streptococci: third-generation cephalosporin (e.g., cefotaxime, ceftriaxone) or penicillin G are effective. (21)
- Staph aureus, staph epidermis is usually seen in association with penetrating brain trauma and or neurosurgical procedure. It should be covered with vancomycin. It is also effective for Clostridium species. In cases of vancomycin resistance, linezolid, trimethoprim-sulfamethoxazole, or daptomycin can be considered. (20)
- Fungal infections including Candida, Cryptococcus needs to be treated with Amphotericin B. (20)
- Aspergillusand Pseudallescheria boydii. Voriconazole can be considered (20)
- Toxoplasma Gondi infection is treated with pyrimethamine and sulfadiazine, can be combined with HAART in cases of HIV. (20)

Corticosteroids, mannitol, and hyperventilation may be indicated where there is increased intracranial pressure. (21) Corticosteroids are a matter of contention. Steroids can cause encapsulation to be prolonged, necrosis to increase, antibiotic penetration into the abscess to be reduced, CT scans to be altered, and a rebound impact when they are withdrawn. If used to treat cerebral edema, the treatment should be brief. It is uncertain what dosage and when to administer it. Corticosteroids should not be used on a routine basis unless there is an increase in intracranial pressure.

In the treatment of brain abscesses, the surgical approach is extremely important. The procedure used is based on the skills and preferences of the controller. For multiple abscesses, methods include ultrasonography or CT-guided needle aspirations through the stereotactic method, bur hole, and craniotomy. Intravenous or intrathecal agents against specific microorganisms are considered with surgical therapy. (21)

Prevention

An abscess in the brain is a serious medical issue. It is important to take caution. You can reduce your risk by keeping an eye on any diseases that could lead to a brain abscess. At the first symptom of a brain abscess, contact your doctor. Based on many studies, If you have a cardiac disorder, ask your doctor before doing any dental or urological operations. Antibiotics may be given by your doctor before these procedures. This lowers your probability of gaining an infection that spreads to your brain.

Risk factor and comorbidity

Immunocompromising conditions (organ transplant, HIV, cancer): The relation between brain abscesses and HIV infection it is not clear enough to confirm if HIV by itself is responsible for the cerebral abscess. Despite that, many types of research have explained that this disease can be raised due to chronic inflammation that takes apart when there is shedding of HIV proteins that lead to disrupting the integrity of the blood-brain barrier which will lead to an increase in the entrance of bacteria to the brain via hematogenous route. (22) As well AIDS patients are susceptible to infections like Cryptococcus, Listeria, androgens, Nocardia; which leads to multiple abscesses and tuberculous abscesses. (23)

While the conjunction between brain abscess and brain tumor is rare, all the cases that conducted show it's secondary to tumor removal surgery or due to chemotherapy and steroid therapy that suppresses the immunity and affect the blood-brain barrier which eventually will lead to making the area more susceptible to bacterial infections that cause the brain abscess. (24)

Head trauma and Neurosurgery; any trauma to the brain or skull will increase the risk of nosocomial infections and the most common types of bacteria after a post-traumatic brain abscess are Gram-negative bacilli, especially staphylococcus aureus and Enterobacteriaceae. According to recent studies, the possibility of having brain abscesses after cranial trauma or neurological procedures is 2%-14%. (25)

Dental infections: the oral cavity is considered as one of the major routes for many oral commensal bacteria especially streptococci (the most common) and Porphyromonas gingivalis, which is an oral anaerobic gram-negative bacterium and was found in 14.3% of cases. (26)

They are followed by dental procedures such as the extraction of infected teeth. These microorganisms can travel to the blood and cause bacteremia and rarely abscess outside the oral cavity like it can cause brain abscess and intracranial empyema (27). Also, dental Caries, missing teeth, and oral poor hygiene are the most commonly reported causes of brain abscesses due to oral infections.

Liver and kidney disease, many studies found that patients with cirrhosis of the liver have a higher risk of different infections that leads to higher susceptibility of the occurrence of the cerebral abscess. In addition, hemodialysis patients are more prone to various infections that can proceed and cause cerebral abscesses. Also, a patient who had a kidney transplant and was receiving immunosuppressive drugs to prevent the rejection of the transplanted organ is susceptible to having brain abscess. (27) (28)

Diabetes mellitus: fungal brain abscesses that are caused by dimorphic fungi, molds, and yeast are the most common types of microorganisms that may infect immunodeficient or uncontrolled diabetes patients. Although it is a rare condition there are reported causes for patients who had uncontrolled diabetes and had a past infection like dental infections, developed a thalamic abscess. (29)

Microorganisms like bacteria, fungus, and viruses; staphylococcus aureus, and streptococcus (Streptococcus milleri and viridian group streptococci) are the main causative agents for brain abscess. Moreover, other gram-negative organisms such as Haemophilus spp, A ggregatibacter, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae. These types of bacteria can cause brain abscesses and endocarditis, but still, they are rare to cause the abscess. (30)

Congenital heart disease: the brain abscess can emerge from dental infection, mastoiditis, osteomyelitis, sinusitis, and subdural empyema via hematogenous route especially in patients with cyanotic congenital heart disease (right-to-left shunt), Such as Patent foramen ovale (PFO) is not a common cause of brain abscess in adults as opposed to children. However, it is still a cause for cerebral abscess in rare cases, especially when the cause of the disease is not clear enough so we should keep this defect in our mind when we are dealing with brain abscesses. (31)

Lung abscess and bronchiectasis; it is rare condition that is caused by a septic pulmonary embolism in which emboli-containing microorganisms migrate to the pulmonary artery which leads to the formation of pulmonary embolism and focal lung abscesses (32). This pulmonary abscess can cause the formation of a cerebral abscess. (33)

Age: Male patients that are older than 40 years are likely to develop cerebral abscess more than female patients and patients under 40 years. (45)

The prognosis (outcome)

With the advent of antimicrobials and imaging studies such as CT scanning and MRI, the mortality rate has reduced from 5% to 10%. Rupture of a brain abscess, however, is more fatal. The long-term neurological sequelae after the infection are dependent on the early diagnosis and administration of antibiotics. (34) However, many studies showed that a brain abscess is always fatal if left untreated. With treatment, the death rate declines to about 10% to 30%. The earlier you receive therapy, the better. The doctor will monitor a person during recovery, as an abscess can recur. This may involve undergoing a weekly CT scan for at least 2 weeks. Also, an abscess can return after months or years, so long-term monitoring is essential. (35)(36)(37)

Latest update on brain abscess therapy

Brain abscess is an urgent medical condition, that can progress anytime could cause pressure on the brain that leads to permanent damage and affect the blood and oxygen supply to the brain. (38) In addition, inter-ventricular rupture of brain abscess is a lethal condition, and some researchers have reported that the fatality rates after the abscess ruptured are between 39% and 80% (8). The only treatment for the interventricular rupture is urgent craniotomy with quick removal of the abscess. (6)

While we are treating the patient's abscess, we should take the clinical history of past infection and the immunity status of the patient into consideration. Also, the early detection and management of the cause of this abscess improve the neurological outcome. (8) The treatment process of the brain abscess is based on a combination of medicines and surgery, but the management processes can vary between individuals because it depends on the size and number. (5)

Antibioticgram-positive bacteria like Staph aureus, staph epidermis is found to be one of the major factors to develop abscesses, we use Cefotaxime/Ceftriaxone/Ceftazidime and metronidazole (6). Also, Vancomycin is effective for staphylococcus and Clostridium species. (9) For Nocardia, we use Sulpha drugs. (6) Fungal infections including Candida, Cryptococcus needs to be treated with Amphotericin B and 5 flucytosine. (39) (9) Toxoplasma gondii infection is treated with pyrimethamine and sulfadiazine (39) (9).

Steroids therapy

Steroids can be used in cerebral abscess management due to their function in reducing inflammation and enhancing the outcomes in some cases that are due to meningitis inducers such as S. pneumoniae, H. influenzae, N. meningitides, and M. tuberculosis. They are considered one of the essential therapies of autoimmune encephalitis. Also, steroids treatment is efficient in reducing the mass and the volume of cerebral edema. (7) (9)

Surgeries and brain abscesses

We use the operation approach when the abscesses are not responding to the medical treatment or still growing and do not shrink after 3 to 4 weeks of usage antibiotics, so here they will be treated by aspiration (41) (40) Also, the surgical application is used for abscesses that are larger than 2.5cm in combination with other treatments. (42) (39) It is known that surgeries must be done when the abscesses are located in essential and sensitive parts of the brain and causing precautions on the underlying place. (40) Now due to the development of neurosurgical techniques, the diagnosis and management of

brain abscess enhance in the last decades. Such as stereotactic surgery, when cables are able most unable to a specific part of the brain, and it has a minimally invasive form of surgical intervention that uses a three-dimensional coordinate system. (43) This process is usually used for deep-seated abscesses such as thalamic abscesses. (39) The drainage of the pus enhances the patient's condition, and the outcomes can be seen immediately, multiple abscesses that are causing a direct mass effect should be treated by aspiration. Also, the abscesses that are located peripherally may fail to be treated by aspiration procedure so, we will use craniotomy and excision for these cases. (41)

According to one of the studies that have blended the department of neurosurgery, Istanbul faculty of medicine, one of the efficient ways to treat all types of abscesses regardless of their size and number is using the stereotactic aspiration with 8 weeks of using intravenous antibiotic therapy, which ends up with positive outcomes (43) (44).

The complete resection through craniotomy is rare now, it may be done when patients have a multi-lobulated abscess and advanced cranial hypertension (43). Also, traumatic brain abscesses remove the foreign body. (41) One of the instant cases that need to be treated rapidly with craniotomy is interventricular rupture of abscess and after the surgery is done, we give the patient intravenous administration of antibiotics for 6 weeks. (39)

References

(Adams et al., Principles of Neurology, 6th ed, pp712-6)

1. The role of anaerobic bacteria in brain abscesses: a literature review Urbán E, Gajdács M. Az anaerob baktériumok szerepe az agyi tályogokban: irodalmi összefoglaló [The role of anaerobic bacteria in brain abscesses: a literature review]. Ideggyogy Sz. 2021 Jan 30;74(1-2):17-25. Hungarian. doi: 10.18071/isz.74.0017. PMID: 33497059.[PubMed]
2. **Brain Abscess** Bokhari MR, Mesfin FB. Brain Abscess. [Updated 2021 Sep 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from:https://www.ncbi.nlm.nih.gov/books/NBK441841/ [PubMed]
3. **Management of brain abscesses: where are we now?**Chen M, Low DCY, Low SYY, Muzumdar D, Seow WT. Management of brain abscesses: where are we now? Childs Nerv Syst. 2018 Oct;34(10):1871-1880. doi: 10.1007/s00381-018-3886-7. Epub 2018 Jul 3. PMID: 29968000.From: https://pubmed.ncbi.nlm.nih.gov/29968000/[PubMed]
4. **The role of anaerobic bacteria in brain abscesses: a literature review**Urbán E, Gajdács M. Az anaerob baktériumok szerepe az agyi tályogokban: irodalmi összefoglaló [The role of anaerobic bacteria in brain abscesses: a literature review]. Ideggyogy Sz. 2021 Jan 30;74(1-2):17-25. Hungarian. doi: 10.18071/isz.74.0017. PMID: 33497059.From: https://pubmed.ncbi.nlm.nih.gov/33497059/[PubMed]
5. **Brain abscess: an overview**
   Muzumdar D, Jhawar S, Goel A. Brain abscess: an overview. Int J Surg. 2011;9(2):136-44. doi: 10.1016/j.ijsu.2010.11.005. Epub 2010 Nov 16. PMID: 21087684.
   From: https://pubmed.ncbi.nlm.nih.gov/21087684/ [PubMed]
6. **Brain abscess: an overview**
   Muzumdar D, Jhawar S, Goel A. Brain abscess: an overview. Int J Surg. 2011;9(2):136-44. doi: 10.1016/j.ijsu.2010.11.005. Epub 2010 Nov 16. PMID: 21087684.
   From: https://pubmed.ncbi.nlm.nih.gov/21087684/ [PubMed]
7. Tuberculous brain abscess in AIDS patients: report of three cases and literature review
   Vidal JE, Penalva de Oliveira AC, Bonasser Filho F, Schiavon Nogueira R, Dauar RF, Leite AG, Lins DL, Coelho JF. Tuberculous brain abscess in AIDS patients: report of three cases and literature review. Int J Infect Dis. 2005 Jul;9(4):201-7. doi: 10.1016/j.ijid.2004.06.010. Epub 2005 Mar 25. PMID: 15964538.
   From: https://pubmed.ncbi.nlm.nih.gov/15964538/ [PubMed]
8. **Brain Abscess**
   Bokhari MR, Mesfin FB. Brain Abscess. 2021 Sep 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;

2022 Jan–. PMID: 28722871.
From: https://pubmed.ncbi.nlm.nih.gov/28722871/[PubMed]

9. **Antibiotics for brain abscesses in people with cyanotic congenital heart disease**
Lumbiganon P, Chaikitpinyo A. Antibiotics for brain abscesses in people with cyanotic congenital heart disease. Cochrane Database Syst Rev. 2013 Mar 28;2013(3):CD004469. doi: 10.1002/14651858.CD004469.pub3. PMID: 23543532; PMCID: PMC7197203.
From: https://pubmed.ncbi.nlm.nih.gov/23543532/ [PubMed]
10. **Clinical characteristics and outcome of brain abscess: systematic review and meta-analysis**
Brouwer MC, Coutinho JM, van de Beek D. Clinical characteristics and outcome of brain abscess: systematic review and meta-analysis. Neurology. 2014 Mar 4;82(9):806-13. doi: 10.1212/WNL.0000000000000172. Epub 2014 Jan 29. PMID: 24477107.
From: https://pubmed.ncbi.nlm.nih.gov/24477107/ [PubMed]
11. **Postneurosurgical nosocomial bacterial brain abscess in adults**
Yang KY, Chang WN, Ho JT, Wang HC, Lu CH. Postneurosurgical nosocomial bacterial brain abscess in adults. Infection. 2006 Oct;34(5):247-51. doi: 10.1007/s15010-006-5607-5. PMID: 17033747. Yang KY, Chang WN, Ho JT, Wang HC, Lu CH. Postneurosurgical nosocomial bacterial brain abscess in adults. Infection. 2006 Oct;34(5):247-51. doi: 10.1007/s15010-006-5607-5. PMID: 17033747.
From: https://pubmed.ncbi.nlm.nih.gov/17033747/ [PubMed]
12. **Cerebellar abscess. A review of 47 cases.**
Shaw MD, Russell JA. Cerebellar abscess. A review of 47 cases. J Neurol Neurosurg Psychiatry. 1975 May;38(5):429-35. doi: 10.1136/jnnp.38.5.429. PMID: 1151412; PMCID: PMC491994.
From:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC491994/[PubMed]
13. **Cerebellar abscess. A review of 47 cases.**
Shaw, M. D., & Russell, J. A. (1975). Cerebellar abscess. A review of 47 cases. Journal of neurology, neurosurgery, and psychiatry, 38(5), 429–435.
From: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC491994/[PubMed]
14. **Brain Abscess Workup**
Author: Itzhak Brook, MD, MSc; Chief Editor: Pranatharthi Haran Chandrasekar, MBBS, MD more...
From: https://reference.medscape.com/article/212946-workup[PubMed]
15. **Brain Abscess workup** Author: Itzhak Brook, MD, MSc; Chief Editor: Pranatharthi Haran Chandrasekar, MBBS, MD more...
from: https://reference.medscape.com/article/212946-workup [PubMed]
16. **Brain Abscess Workup**
Author: Itzhak Brook, MD, MSc; Chief Editor: Pranatharthi Haran Chandrasekar, MBBS, MD more...
from: https://reference.medscape.com/article/212946-workup [PubMed]
17. **Imaging of cerebritis, encephalitis, and brain abscess**
Rath TJ, Hughes M, Arabi M, Shah GV. Imaging of cerebritis, encephalitis, and brain abscess. Neuroimaging Clin N Am. 2012 Nov;22(4):585-607. doi: 10.1016/j.nic.2012.04.002. Epub 2012 Sep 28. PMID: 23122258.
From: https://pubmed.ncbi.nlm.nih.gov/23122258/ [PubMed]
18. **Pyogenic brain abscess and subdural empyema: presentation, management, and factors predicting outcome**
Widdrington JD, Bond H, Schwab U, Price DA, Schmid ML, McCarron B, Chadwick DR, Narayanan M, Williams J, Ong E. Pyogenic brain abscess and subdural empyema: presentation, management, and factors predicting outcome. Infection. 2018 Dec;46(6):785-792. doi: 10.1007/s15010-018-1182-9. Epub 2018 Jul 27. PMID: 30054798.
From: https://pubmed.ncbi.nlm.nih.gov/30054798/ [PubMed]
19. **Management of brain abscesses in children**
Yogev R, Bar-Meir M. Management of brain abscesses in children. Pediatr Infect Dis J. 2004 Feb;23(2):157-9. doi: 10.1097/01.inf.0000110272.67271.a2. PMID: 14872183.
From: https://pubmed.ncbi.nlm.nih.gov/14872183/[PubMed]
20. **Brain Abscess**
Bokhari MR, Mesfin FB. Brain Abscess. 2021 Sep 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 28722871.
From: https://pubmed.ncbi.nlm.nih.gov/28722871/ [PubMed]
21. **Brain Abscess**
Bokhari MR, Mesfin FB. Brain Abscess. 2021 Sep 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 28722871.
From: https://pubmed.ncbi.nlm.nih.gov/28722871/[PubMed]
22. **Pyogenic Brain Abscess Caused by Peptostreptococcus in a Patient with HIV-1 Infection**
Gonzales Zamora JA, Espinoza LA. Pyogenic Brain Abscess Caused by Peptostreptococcus in a Patient with HIV-1 Infection. Diseases. 2017 Nov 17;5(4):26. doi: 10.3390/diseases5040026. PMID: 29149022; PMCID: PMC5750537.
From: https://pubmed.ncbi.nlm.nih.gov/29149022/ [PubMed]
23. **Bacterial brain abscess**
Patel K, Clifford DB. Bacterial brain abscess. Neurohospitalist. 2014 Oct;4(4):196-204. doi: 10.1177/1941874414540684. PMID: 25360205; PMCID: PMC4212419.
From: https://pubmed.ncbi.nlm.nih.gov/25360205/[PubMed]

24. **Abscess formation within a cerebellar metastasis: Case report and literature review**
Goto, Y., Ebisu, T., & Mineura, K. (2015). Abscess formation within a cerebellar metastasis: Case report and literature review. International journal of surgery case reports, 10, 59–64. https://doi.org/10.1016/j.ijscr.2015.03.012
From: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4429840/[PubMed]
25. **Infectious disease of the brain**
Melike Ekizoğlu,
Chapter 16 - Infectious Diseases of the Brain,
Editor(s): Yasemin Gürsoy-Özdemir, Sibel Bozdağ-Pehlivan, Emine Sekerdag,
Nanotechnology Methods for Neurological Diseases and Brain Tumors,
Academic Press,
2017,
Pages 291-315,
ISBN 9780128037966,
https://doi.org/10.1016/B978-0-12-803796-6.00016-2.
(https://www.sciencedirect.com/science/article/pii/B9780128037966000162) [PubMed]
26. **Brain abscesses and intracranial empyema due to dental pathogens: Case series** Kichenbrand C, Marchal A, Mouraret A, Hasnaoui N, Guillet J, Rech F, Phulpin B. Brain abscesses and intracranial empyema due to dental pathogens: Case series. Int J Surg Case Rep. 2020;69:35-38. doi: 10.1016/j.ijscr.2020.03.025. Epub 2020 Mar 28. PMID: 32248015; PMCID: PMC7132046. [https://pubmed.ncbi.nlm.nih.gov/32248015/ [PubMed]
27. **Brain abscess as a rare complication in a hemodialysed patient**Barczyk MP, Łebkowski WJ, Mariak Z, Małyszko J, Myśliwiec M. Brain abscess as a rare complication in a hemodialysed patient. Med Sci Monit. 2001 Nov-Dec;7(6):1329-33. PMID: 11687752.[https://pubmed.ncbi.nlm.nih.gov/11687752/ [PubMed]
28. **Increased occurrence of brain abscesses in cirrhotic patients: A population-based 3-year follow-up study** Chen YC, Hung TH, Tseng KC, Tseng CW, Hsieh YH, Tsai CC, Tsai CC. Increased occurrence of brain abscesses in cirrhotic patients: A population-based 3-year follow-up study. Turk J Gastroenterol. 2017 Sep;28(5):342-346. doi: 10.5152/tjg.2017.6374. Epub 2017 Aug 9. PMID: 28797986. [https://pubmed.ncbi.nlm.nih.gov/28797986/ [PubMed]
29. **Rare fungal infectious agents: a lurking enemy** Skiada A, Pavleas I, Drogari-Apiranthitou M. Rare fungal infectious agents: a lurking enemy. F1000Res. 2017 Oct 31;6:1917. doi: 10.12688/f1000research.11124.1. PMID: 29152230; PMCID: PMC5664977.[https://pubmed.ncbi.nlm.nih.gov/29152230/ [PubMed]
30. **Infective endocarditis and brain abscess secondary to Aggregatibacter aphrophilus** Daoud H, Abugroun A, Olanipekun O, Garrison D. Infective endocarditis and brain abscess secondary to Aggregatibacter aphrophilus. IDCases. 2019 May 17;17:e00561. doi: 10.1016/j.idcr.2019.e00561. PMID: 31193507; PMCID: PMC6535683.[https://pubmed.ncbi.nlm.nih.gov/31193507/ [PubMed]
31. **Brain abscesses in a patient with a patent foramen ovale: a case report** Jan F, Hafiz AM, Gupta S, Meidl J, Allaqaband S. Brain abscesses in a patient with a patent foramen ovale: a case report. J Med Case Rep. 2009 Nov 25;3:9299. doi: 10.1186/1752-1947-3-9299. PMID: 20062788; PMCID: PMC2803822. [https://pubmed.ncbi.nlm.nih.gov/20062788/][PubMed]
32. **Clinical characteristics of septic pulmonary embolism in adults: a systematic review** Ye R, Zhao L, Wang C, Wu X, Yan H. Clinical characteristics of septic pulmonary embolism in adults: a systematic review. Respir Med. 2014 Jan;108(1):1-8. doi: 10.1016/j.rmed.2013.10.012. Epub 2013 Oct 17. PMID: 24183289.[https://pubmed.ncbi.nlm.nih.gov/24183289/ [PubMed]
33. **An emboligenic pulmonary abscess leading to ischemic stroke and secondary brain abscess** Albrecht P, Stettner M, Husseini L, Macht S, Jander S, Mackenzie C, Oesterlee U, Slotty P, Methner A, Hartung HP, Aktas O. An emboligenic pulmonary abscess leading to ischemic stroke and secondary brain abscess. BMC Neurol. 2012 Nov 5;12:133. doi: 10.1186/1471-2377-12-133. PMID: 23121862; PMCID: PMC3517440.[https://pubmed.ncbi.nlm.nih.gov/23121862/][PubMed]
34. **Brain Abscess** Bokhari MR, Mesfin FB. Brain Abscess. 2021 Sep 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 28722871[https://pubmed.ncbi.nlm.nih.gov/28722871/][PubMed]
35. **Brain Abscess** Bokhari MR, Mesfin FB. Brain Abscess. 2021 Sep 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 28722871.[https://pubmed.ncbi.nlm.nih.gov/28722871/ [PubMed]
36. **Brain abscess: Current management** Alvis Miranda H, Castellar-Leones SM, Elzain MA, Moscote-Salazar LR. Brain abscess: Current management. J Neurosci Rural Pract. 2013 Aug;4(Suppl 1):S67-81. doi: 10.4103/0976-3147.116472. PMID: 24174804; PMCID: PMC3808066. https://pubmed.ncbi.nlm.nih.gov/24174804/ [PubMed]
37. **Bacterial brain abscess** Patel K, Clifford DB. Bacterial brain abscess. Neurohospitalist. 2014 Oct;4(4):196-204. doi: 10.1177/1941874414540684. PMID: 25360205; PMCID: PMC4212419.[https://pubmed.ncbi.nlm.nih.gov/25360205/ [PubMed]
38. **Antibiotics for brain abscesses in people with cyanotic congenital heart disease** Lumbiganon P, Chaikitpinyo A. Antibiotics for brain abscesses in people with cyanotic congenital heart disease. Cochrane Database Syst Rev. 2013 Mar 28;2013(3):CD004469. doi: 10.1002/14651858.CD004469.pub3. PMID: 23543532; PMCID: PMC7197203. [https://pubmed.ncbi.nlm.nih.gov/23543532/ [PubMed]
39. **Brain abscess: an overview** Muzumdar D, Jhawar S, Goel A. Brain abscess: an overview. Int J Surg. 2011;9(2):136-44. doi: 10.1016/j.ijsu.2010.11.005. Epub 2010 Nov 16. PMID: 21087684.[https://pubmed.ncbi.nlm.nih.gov/21087684/][PubMed]
40. **Improved management of multiple brain abscesses: a combined surgical and medical approach** Mamelak AN, Mampalam TJ, Obana WG, Rosenblum ML. Improved management of multiple brain abscesses: a combined surgical

and medical approach. Neurosurgery. 1995 Jan;36(1):76-85; discussion 85-6. doi: 10.1227/00006123-199501000-00010. PMID: 7708172. [https://pubmed.ncbi.nlm.nih.gov/7708172/][PubMed]

41. **Brain abscess: Current management** Alvis Miranda H, Castellar-Leones SM, Elzain MA, Moscote-Salazar LR. Brain abscess: Current management. J Neurosci Rural Pract. 2013 Aug;4(Suppl 1):S67-81. doi: 10.4103/0976-3147.116472. PMID: 24174804; PMCID: PMC3808066.https://pubmed.ncbi.nlm.nih.gov/24174804/ [PubMed]
42. **Brain abscess: management and outcome analysis of a computed tomography era experience with 973 patients** Nathoo N, Nadvi SS, Narotam PK, van Dellen JR. Brain abscess: management and outcome analysis of a computed tomography era experience with 973 patients. World Neurosurg. 2011 May-Jun;75(5-6):716-26; discussion 612-7. doi: 10.1016/j.wneu.2010.11.043. PMID: 21704942. [https://pubmed.ncbi.nlm.nih.gov/21704942/ [PubMed]
43. **An update on bacterial brain abscess in immunocompetent patient** Sonneville R, Ruimy R, Benzonana N, Riffaud L, Carsin A, Tadié JM, Piau C, Revest M, Tattevin P; ESCMID Study Group for Infectious Diseases of the Brain (ESGIB). An update on bacterial brain abscess in immunocompetent patients. Clin Microbiol Infect. 2017 Sep;23(9):614-620. doi: 10.1016/j.cmi.2017.05.004. Epub 2017 May 10. PMID: 28501669.[https://pubmed.ncbi.nlm.nih.gov/28501669/][PubMed]
44. **A retrospective study on the aetiology, management, and outcome of brain abscess in an 11-year, single-centre study from China** Zhang C, Hu L, Wu X, Hu G, Ding X, Lu Y. A retrospective study on the aetiology, management, and outcome of brain abscess in an 11-year, single-centre study from China. BMC Infect Dis. 2014 Jun 6;14:311. doi: 10.1186/1471-2334-14-311. PMID: 24903315; PMCID: PMC4053580.[https://pubmed.ncbi.nlm.nih.gov/24903315/][PubMed]
45. **Management of brain abscesses: where are we now?** Chen M, Low DCY, Low SYY, Muzumdar D, Seow WT. Management of brain abscesses: where are we now? Childs Nerv Syst. 2018 Oct;34(10):1871-1880. doi: 10.1007/s00381-018-3886-7. Epub 2018 Jul 3. PMID: 29968000. [https://pubmed.ncbi.nlm.nih.gov/29968000/][PubMed]

Article topic: Pineal Gland Anatomy and Tumors.

Author: Almutazballlah Qablan.

Editor: Aseel Rabadi.

Reviewer: Omar Jbarah.

***Keywords**: Pineal gland, Pineal tumor, Pineocytoma, Pineal parenchymal tumor with intermediate differentiation, Pineoblastoma, Papillary tumor of the pineal region, Pineal germinoma, Choriocarcinoma, Teratoma.*

Introduction

The pineal gland is a tiny gland in the brain. It secretes melatonin; a hormone that affects sleep-wake cycles[1]. During the second month of gestation, the pineal gland appears as a cellular evagination of undifferentiated cells with a little amount of cytoplasm. Subsequently, it undergoes remarkable cellular differentiation, leading to the appearance of the adult gland by the end of the first year of life[2]. Histologically, human pineal gland parenchyma is composed of pinealocytes with a few neuroglial supporting cells and subdivided into lobules by a highly vascularized connective tissue stroma[1,3].

Pineal region tumors are rare, accounting for 1% of all the primary CNS tumors in adults, and up to 8% in children. Multiple pathologies are associated with this region because of the variety of cells in it, in addition to the various structures found adjacent to it [3,13].

Pineal region tumors are classified into those arising from the pineal parenchyma, germ cell neoplasms, metastasis from other organs, and lesions arising from adjacent structures [3]. Germ cell tumors make up the majority (about 35%), followed by pineal parenchymal tumors (about 28%) and neuroepithelial tumors, including astrocytomas (mostly pilocytic), ependymomas, and papillary tumors of the pineal region (about 28% combined) [4].

Pineal Gland Anatomy

The pineal gland is a small endocrine gland (10 to 14 mm) located in the midline of the brain, at the posterior wall of the third ventricle. In the coronal view, the gland is located below the splenium of the corpus callosum and above and posterior to the tectum of the midbrain [3].

The pineal gland lacks a blood-brain barrier and has a unique histopathologic appearance, with its parenchyma composed mainly of pineocytes and a few neuroglial supporting cells such as astrocytes. Pinealocytes, the principal cells in the gland, are specialized neurosecretory cells that produce the hormone melatonin and secrete it in a circadian rhythm[5]. They also exhibit some neurosensory features as they receive information from the environment about the light-dark cycle to feedback the central nervous system[6].

Anatomically, structures surrounding the pineal gland are the third ventricle (pineal recess) anteriorly, while the internal cerebral veins, the vein of Galen (posteriorly), stria medullaris, splenium of the corpus callosum, and velum interpositum makes the superior border. Habenular nuclei lie anterosuperiorly. Whereas, inferiorly, the superior colliculi of the midbrain fill the place, and the posterior commissure is found anteroinferiorly. Also, the superior cerebellar cistern makes the posteroinferior border[7], (see figure (1)).

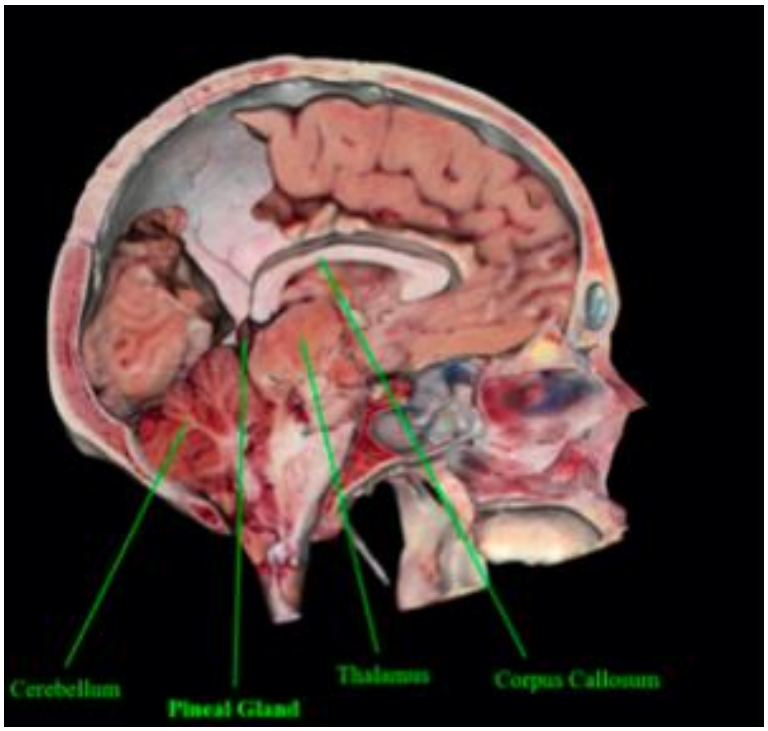


Figure (1): Human pineal gland and its anatomical boundaries. The 3D rendering of the cadaver data is from Anatomage Table.

Pathophysiology, Etiology, and Surgical approach.

Multiple pathologies are associated with this region because of the variety of cells inside it and structures located adjacent to it. Another key point is those pineal region tumors are diverse in origin because of their proximity to multiple anatomical structures[3].

Pineal region tumors are classified into those arising from the pineal parenchyma, germ cell tumors, metastasis from other organs, and lesions arising from adjacent structures[3]. Pineal parenchymal tumors in their turn are also classified into pineocytoma, pineoblastoma, pineal parenchymal tumor with intermediate differentiation, and lastly papillary tumors.[3]

Still, the pineal gland is a common locus for the sequestration of embryonic germ cells. Thus, germ cell tumors are among the most common pathologies found in this region[11]. They usually occur sporadically[12]. However, there was found to be an association with Klinefelter syndrome, Down syndrome, and Neurofibromatosis type 1 [13,14]. They're on their behalf divided into germinomatous germ cell tumors like germinoma, nongerminomatous germ cell tumors like choriocarcinoma, yolk sac tumor, and finally teratomas.

Pineal Parenchymal Tumor

Pineal parenchymal tumors are rare neuroepithelial neoplasms, accounting for less than 1% of intracranial neoplasms and constituting 15% to 30% of pineal gland tumors[15,16]. They originate from pineocytes or their precursors. The pineal parenchymal tumors have been recognized by the World Health Organization (WHO) in four distinct categories: pineocytomas, pineoblastomas, papillary pineal tumors, and pineal parenchymal tumors of intermediate differentiation [3,15,17].

Most pineal parenchymal tumors occur in the pediatric age group with no sexual predominance [17,16]. They remain localized to the pineal region where they may compress adjacent structures including the cerebral aqueduct, brain stem, and cerebellum. So, the signs and symptoms vary and are related mostly to obstructive hydrocephalus, increased intracranial pressure with consequent headaches, nausea, vomiting, upward gaze palsy (Parinaud syndrome), changes in mental status, and ataxia. Pineal parenchymal cell tumors can also produce a hypomelatoninemic or hypermelatoninemic state [13,17,18,19].

Alpha fetoprotein, beta-human chorionic gonadotropin, and placental alkaline phosphatase are three tumor markers that are found negative in pineal parenchymal tumors[19]. However, synaptophysin is expressed in pineal parenchymal tumors of intermediate differentiation, and neuronal marker positivity has no relationship to histological grade, mitosis, proliferation index, or prognosis[20].

Radiation is the standard treatment for pineal parenchymal tumors. But, another possible treatment option is surgery; however, it has a mortality rate of 5%–10% [19], and

even after complete tumor removal, recurrence presents in many patients. Therefore, adjuvant radiation or chemotherapy, or both are often suggested with the aim of improving survival[21].

Pineocytoma

Pineocytoma is a slow-growing grade I/II pineal parenchymal tumor derived from the pineal epithelium. They are characterized by the well-differentiated mature cells that are arranged in sheets. They are circumscribed, unencapsulated tumors that mostly remain locally confined [22,23].

Small pineocytomas often do not induce symptoms, but if they are large, they may induce obstructive hydrocephalus and Parinaud syndrome, defined as an upward gaze palsy, pupillary light-near dissociation, and convergence retraction nystagmus[22].

They can be seen at any age but are more frequent in adults aged from 20 to 60 years of old[16]. Pineocytomas are more frequently seen in females. They account for 14-30% of pineal parenchymal tumors. The 5-year survival was 86%–91%, and there were no reported relapses after gross total resection. Recurrences are uncommon in these tumors [3,16,24,25]. Stereotactic radiosurgery has been set as a primary treatment for these tumors [26].

As shown in figure (2), Pineocytomas appear as hyperintense, round or lobular masses on MRI [16].

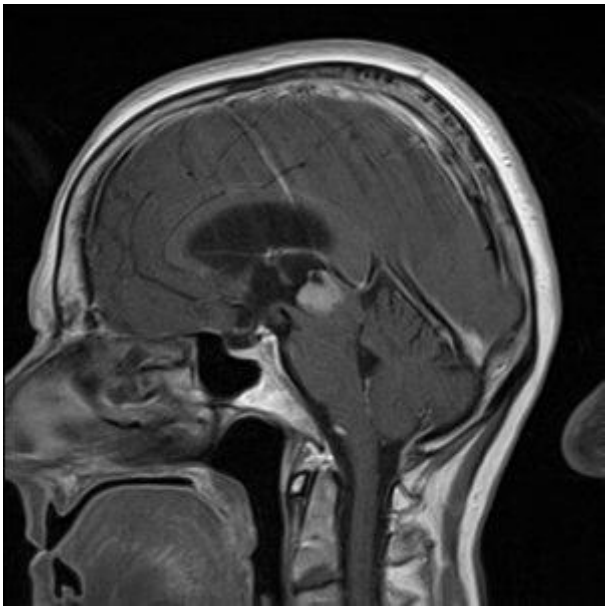


Figure (2): Pineocytomas sagittal T1 C+. Case courtesy of Dr Elshan Abdullayev.

Pineoblastoma

Pineoblastoma is a highly malignant grade IV tumor[19] that is an undifferentiated, embryonal tumor described as a primitive neuroectodermal lesion. It accounts for 24-50% of all pineal parenchymal tumors. It is more frequently seen in females[10,23].

Pineoblastomas are unencapsulated tumors that may often recur and also spread throughout the craniospinal axis, as well as metastasize to other parts of the body, such as the skull, vertebrae, lungs, peritoneum, mandible, and pelvis[27,23].

Pineoblastomas are the most aggressive pineal parenchymal tumors and have a poor prognosis because of their frequent invasion to the adjacent structures and CSF dissemination, with reported five-year survival rates of <60% [17].

The highest incidence is in childhood, particularly in children who are less than 2 years of old, where pineoblastomas can occur in combination with retinoblastomas[17]. Patients with hereditary bilateral retinoblastoma are prone to suprasellar or pineal neuroblastic tumors, a condition called trilateral retinoblastoma is seen in up to 5% of the pineoblastomas cases [28].

Synaptophysin and chromogranin are markers of primitive neuroendocrine tumors that can be expressed in pineoblastomas and can be detected in the serum or the CSF[19]. The molecular background of pineoblastoma remains unknown. However, recent studies have shown that the DICER1 and DROSHA genes, which are implicated in microRNA dysregulation, are fundamental to pineoblastoma carcinogenesis[29].

Aggressive surgical resection is the first-line therapy against pineoblastoma. It is worth mentioning that radiotherapy after resection helps to increase a patient's survival. As it has also been reported in other pineal gland tumors, combination therapy appears to be an effective approach [27].

Pineal Parenchymal Tumor of Intermediate Differentiation

Pineal parenchymal tumors of intermediate differentiation are uncommon tumors arising from the pineal parenchyma that show common features between pineocytomas and pineoblastomas[30].

They can occur at all ages and more commonly appear in women, adolescents, and middle-aged patients[30]. Pineal parenchymal tumors of intermediate differentiation are not often considered as a single disease, but rather as a spectrum of grade II and III pineal parenchymal tumors, which explains the huge variation in the behavior of these tumors[22,30].

Multiple cystic elements can also be observed. Pineal calcifications may be engulfed or peripherally displaced by the mass[22]. These tumors show positive expression for synaptophysin, neurofilament, chromogranin A, and renal S antigens[23].

Pineal parenchymal tumors of intermediate differentiation tended to present on MRI as isointense lesions on T1WI and hypointense masses on T2WI, with some cystic components, and a complete contrast enhancement[31]. Figure (3).

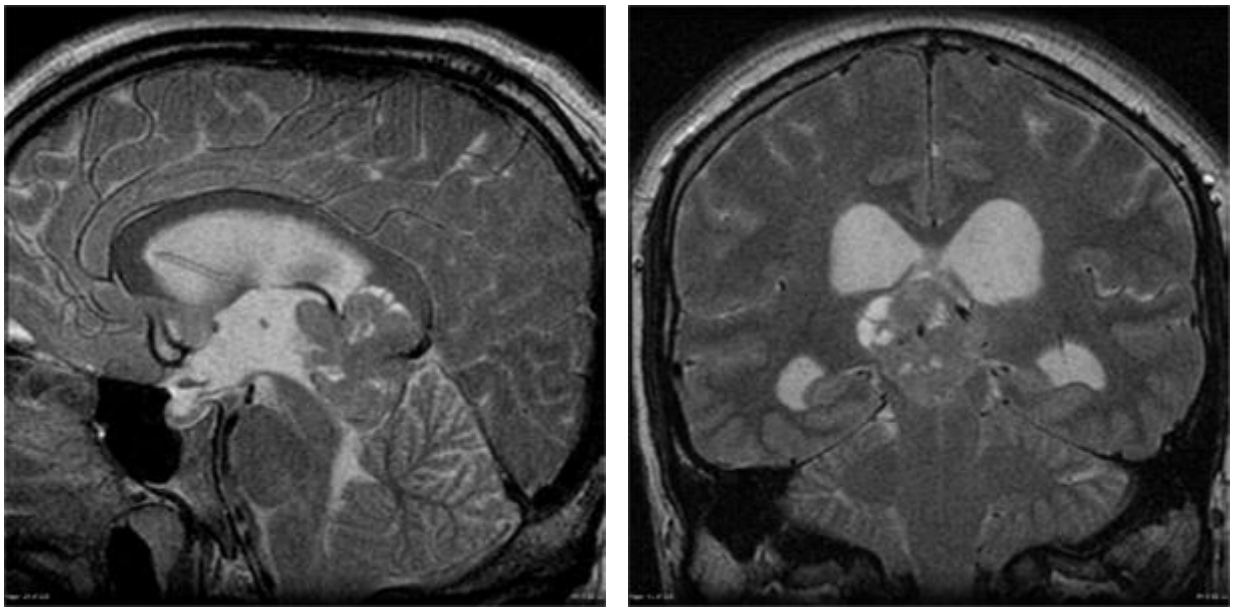


Figure (3): Pineal parenchymal tumors of intermediate differentiation (a) sagittal T1 (b) coronal T2. Case courtesy of Assoc Prof Frank Gaillard.

No best treatment has been found for pineal parenchymal tumors of intermediate differentiation, partly due to the low numbers of reported cases. The maximal surgical removal of the tumor is the treatment of choice in practice for pineal parenchymal tumors of intermediate differentiation. However, even after complete surgical removal of the tumor, many patients experience recurrence. Hence, radiotherapy or other adjuvant chemotherapy, or a combination of both, is often recommended to improve patient survival[32,33].

Papillary tumor of the pineal region

These tumors were first described in 2003 by Jouvet et al[34], as a new tumor with distinct anatomic, histologic, and immunophenotypic features. Because of its rarity, a histological grading criterion has not yet been established, but most likely according to WHO they are considered as grade II or III neuroepithelial neoplasms[16,4].

Papillary tumors have the broadest range of ages among the pineal parenchymal tumors, which are seen from 1-70 years of age, with a mild female prevalence[4].

The main symptom reported by patients with pineal papillary tumors is headache associated with obstructive hydrocephalus[35].

It is important to emphasize that pineal papillary tumors present with a wide morphological diversity. Apart from the distinct papillary structures, papillary tumors have morphological features in common with other papillary-like tumors that occur in the pineal region, including choroid plexus papillomas, papillary ependymomas, metastatic papillary carcinomas, papillary meningiomas, and germ cell tumors, which complicates the clinical diagnosis[36].

On MRI, pineal papillary tumors appear as partially cystic masses with obstructive hydrocephalus[35] as shown in figure (4).

Figure (4): Pineal papillary tumors appear in sagittal T1. Case courtesy of Dr Ali Alsmair.

Pineal papillary tumors often recur, and radiotherapy is often effective[37]. Both radiotherapy and chemotherapy are used in the initial management of the tumor and in cases of recurrence after total resection; however, the optimal adjuvant therapy is still unknown. Stereotactic radiosurgery is effective against pineal papillary tumors, but a high rate of local recurrence has also been observed after this treatment. Recurrence can be safely and successfully managed by repeating stereotactic radiosurgery[26].

Germ Cell Tumors

Germ cell tumors are derived from primitive germ cells that develop primarily in the gonads but also in the anterior mediastinum, pineal gland, and brain[38]. Germ cell tumors represent 0.5-3.2% and 11.8% of primary intracranial tumors in adults and children, respectively. They are found in male patients and account for about 50% of

intracranial germ cell tumors, appearing to be more common in the Asian population[39]. Germ cell tumors can be classified into six types: germinomas, choriocarcinomas, teratomas, embryonal carcinomas, yolk sac tumors, and mixed germ cell tumors (characterized by the features of at least two of the above-cited tumor types)[39].

Germinoma

Germinomas are the most common type of pineal tumor, accounting for up to 50% of pineal tumors in Europe, the United States, and Japan[23,40]. It is more common in males[40]. Most cases were less than 20 years of age at the time of assessment.

Only 8% of CNS germinomas' cases show the simultaneous involvement of pineal and suprasellar regions, and these are called bifocal germinomas[23,41]. Germinomas are not encapsulated tumors and therefore may invade adjacent brain structures and, through the CSF, spread along the brain surface.

Germinomas are malignant tumors characterized by a mixture of large pluripotent primordial germ cells and smaller lymphocyte-like cells. However, they often show severe inflammatory infiltrates. With that being said, corticosteroid treatment appears to be able to modulate the patient's immune defense, enabling the immune system to suppress the tumor[42,10].

On imaging, germinomas show heterogeneous features, often presenting as solid or solid-cystic masses with sunken calcifications, different from that in pineal parenchymal tumors, which show prominent calcifications[38,43]. Figure (5).

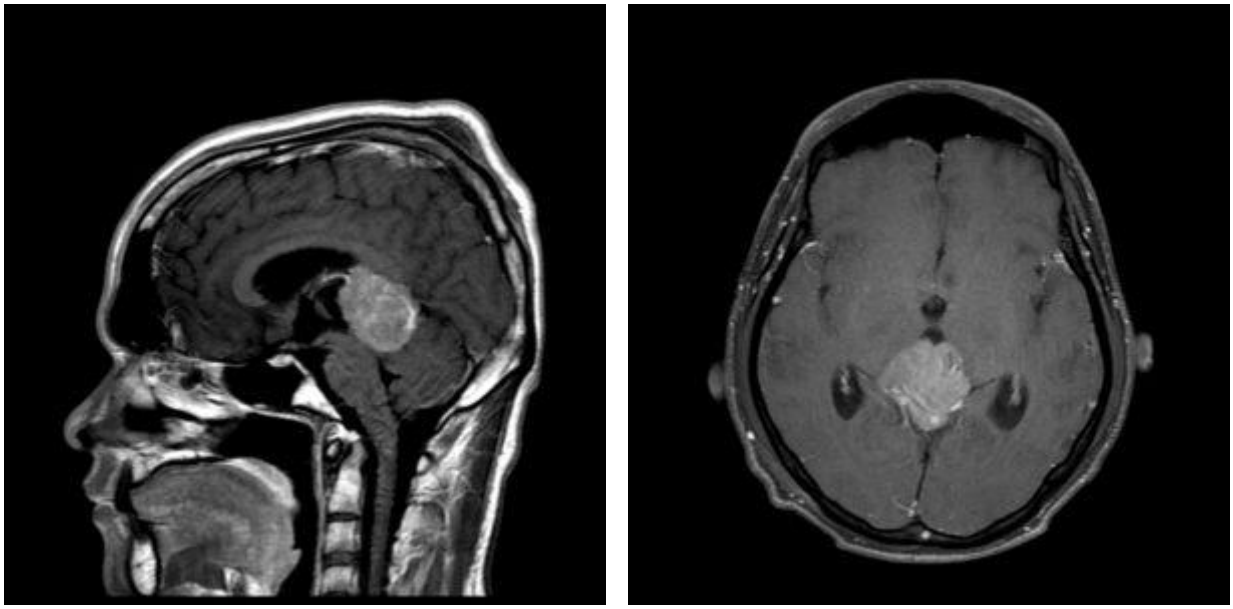


Figure (5): Pineal germinomas. (a) sagittal T1 C+ fat sat. (b) axial T1 C+ fat sat. Case courtesy of Dr Angel Donato.

Imaging alone does not allow us to distinguish germinomatous from nongerminomatous germ cell tumors and pineal parenchymal tumors. Therefore, a full evaluation is essential[38]. In fact, germinomas are diagnosed using imaging along with serum and CSF markers. These tumors present with high expression in serum and CSF oncoproteins such as alpha-fetoprotein, beta-human chorionic gonadotropin, lactate dehydrogenase, and placental alkaline phosphatase[3].

The treatment regimens used against germinomas include chemotherapy, radiotherapy, or a combination of both, resulting in a favorable prognosis and a five-year survival of at least 90% [16]. Germinomas are radiosensitive tumors that respond well to specific chemotherapies[42]. Furthermore, for germinoma, stereotactic radiosurgery appears to be effective in improving standard adjuvant treatment or in the case of recurrence[26].

Choriocarcinoma

Pineal choriocarcinomas are uncommon malignant nongerminomatous germ cell tumors (representing less than 5% of all pineal masses) [44,45] being the most aggressive form of gestational trophoblastic diseases. Choriocarcinoma shows a poor survival rate within relation to other germ cell tumors[45]. The median survival rate for primary intracranial pure choriocarcinoma was 22 months, and the three- and five-year survival rate was 45.8%. Primary intracranial choriocarcinoma mainly affects young men (3–22 years of age), with precocious puberty [4,46].

These tumors do not present with distinctive symptoms, but patients affected by choriocarcinoma mainly reported headaches, vomiting, nausea, visual impairment, polydipsia, polyuria, and endocrinologic alterations[45].

On imaging, choriocarcinomas show ovoid, heterogeneous, and slightly hyperdense masses[4].

They are associated with elevated levels of both CSF and plasma human chorionic gonadotropin[47]. Both Choriocarcinomas and germinomas are associated with elevated beta-human chorionic gonadotropin expression[19].

Unfortunately, classic treatments often fail because choriocarcinomas are extremely resistant. The first clinical choice is complete resection (even if the patient does not present with hydrocephalus). However, for their treatment, a combination of complete tumor removal, chemotherapy and radiotherapy is often used and appears to show positive results[45].

Teratoma

Intracranial teratomas constitute up to 50% of fetal brain tumors. In neonates, they make up 33% of intracranial tumors, but only 2%–4% of intracranial tumors in patients aged <15 years[46]. Intracranial teratomas usually arise from the pineal gland and involve the third ventricle[48]. Pineal teratomas have a male predominance and a survival rate of 90-100% [4,49].

Teratoma are tumors characterized by pluripotent cells of normal organogenesis, usually producing a tissue presenting a combination of two or more of the embryological layers of ectoderm, mesoderm, and endoderm [16,47]. Pineal teratomas can be partially or completely encapsulated but can be also unencapsulated and locally invasive[44].

On imaging, these pineal tumors show foci of fat, calcification, and cystic areas[16]. On MRI, teratomas appear as lobular, multiloculated, and heterogeneously wide masses[16] as in Figure (6).

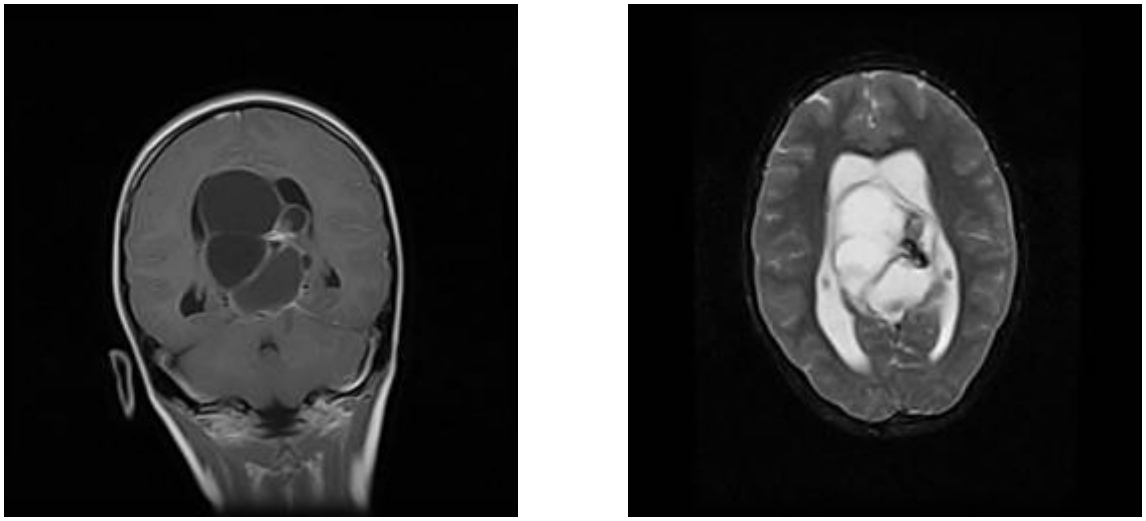


Figure (6): Pineal region teratoma. (a) coronal T1 C+. (b) axial T2. Case courtesy of Dr. Bruno Di Muzio.

Their definitive treatment is complete surgical resection. The occipital transtentorial approach is a safe, effective, and practical approach for surgical removal of these lesions without any major complications whatsoever [32,49].

Clinical Presentation [10]

Clinical presentation of all the tumors of the pineal region is secondary to obstructive hydrocephalus and compression of the tectum as mentioned before. Thus, regardless of

the pathological condition, the results of the physical examination will be similar for all of them.

Hydrocephalus causes a history of headache, nausea, blurry vision, sleepiness, drowsiness, failure to thrive, macrocephaly, or coma. On examination, we look for bilateral optic nerve swelling, bilateral sixth nerve palsy, and for Cushing's triad. Cushing's triad consists of bradycardia, irregular respirations, and hypertension.

On the other hand, compression of the tectum (Parinaud syndrome) causes a history of difficulty walking upstairs and diplopia. On examination we look for any compression of the vertical gaze center at the rostral interstitial nucleus of the medial longitudinal fasciculus which leads to paralysis of the upwards gaze and conjugate downward gaze, compression of the pretectal nucleus in the superior colliculus which leads to light-near dissociation, and for any damage to the supranuclear fibers of the third nerve at the posterior midbrain which leads to Convergence-retraction nystagmus and eyelid retraction (Collier sign).

Diagnosis

Serum tumor markers are indicated when certain tumors are suspected, including AFP, b-HCG, and placental alkaline phosphatase. While CSF analysis is indicated if there is no hydrocephalus or during endoscopy and it is useful for most tumors[10,48]. (See figure (7)).

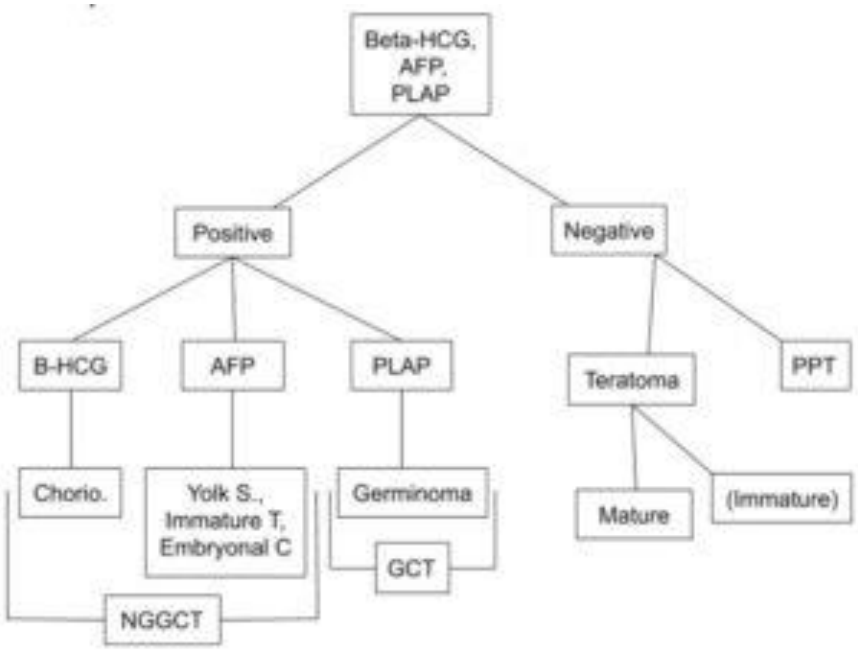


Figure (7): Cerebrospinal fluid (CSF) tumor markers. Contributed by Miguel Mayol Del Valle, MD.

Brain magnetic resonance imaging (MRI) with and without gadolinium enhancement is the gold standard for evaluating pineal region tumors. However, if MRI is not available, head-computed tomographic (CT) scan, angiography, and ultrasound (in infants) can be helpful[10].

Brain MRI will show homogenous enhancement, except those which appear with heterogeneous cellularity. Dense tumors, such as pineoblastomas and germinomas, will have limited diffusion on the diffusion-weighted images. However, pineal cysts are non-enhancing and usually have a thin wall; therefore, a thick wall excludes a cyst[51,10].

Calcifications are often present and are easily identifiable on a head CT scan and can sometimes point into the correct direction of diagnosis. Pineal parenchymal tumors (e.g., pineocytomas or pineoblastomas) tend to disperse peripheral calcification, while germ cell tumors tend to engulf the calcifications. To keep this in mind, remember that pineoblastomas tend to blast the calcifications apart[10].

Many tumors of the pineal region may seed locally or distally. Thus, a complete spinal MRI can be considered as part of the initial evaluation. Local invasion and remote seeding are important for prognosis and may alter the initial management and the adjuvant therapy[10].

Findings that could indicate a worse prognosis include local invasion (mostly seen in pineoblastomas and germ cell tumors), CSF seeding (pineoblastomas seeds distally and germinomas seeds proximally), and extensive peritumor edema[10].

Treatment [10]

Basically, the treatment depends mainly on the pathology and the age of the patient.

Radiotherapy is mostly done for germinomas and is reserved for patients who are > 3 years old.

Chemotherapy alone is given for patients who are less than 3 years of old.

Chemotherapy plus radiotherapy is combined and given for all the non-germinomatous germ cell tumors and germinomatous germ cell tumors if the patient is less than 3 years old.

Surgical resection is mainly used for pineal parenchymal tumors, mature teratomas, and residual tumors that did not recover after chemotherapy and radiotherapy. The surgical approach to the pineal region is selected based on the specific location of the pathology and the surgeon's preference. They include:

Paramedian infratentorial supracerebellar resection:[52]

The most flexible approach is to remove most of the tumor in the pineal region. It is useful for all tumors of the pineal region, except for large tumors that extend laterally

and inferiorly. A left-sided suboccipital craniotomy is performed to protect the torcula, right-side veins, and dural sinuses, including the transverse sinus.

Midline infratentorial supracerebellar resection: [53]

Performed by a bilateral midline suboccipital craniotomy. The limitations of this approach are the limited lateral or inferior visualization caused by the angle of the tentorium and the obstructive apex of the culmen, respectively. As a result, all midline bridging vermian veins are almost always sacrificed.

Occipital transtentorial resection:[54]

Performed through a unilateral occipital craniotomy and especially useful for large pineal region tumors that extend laterally and inferiorly. The limitations of this approach are anatomic orientation difficulties, the need to divide the tentorium, and the possibility of homonymous hemianopia caused by the retraction of the occipital lobe.

In the end, it is necessary to screen the full neuroaxis with all pineal region tumors. Prognosis and treatment dramatically vary depending on the spread of the tumor into the CSF. Distant CSF seeding (except for germinomas), and drop metastasis have poor prognoses. MRI of the brain, cervical, thoracic, and lumbar spine with and without contrast are required for proper neuroaxis screening. Spinal radiotherapy as a prophylactic treatment is debatable.

References

1. Aulinas A. Physiology of the Pineal Gland and Melatonin. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet].com, Inc.; South Dartmouth (MA): Dec 10, 2019. [PubMed]
2. Fèvre-Montange, Michelle, et al. "Histopathology of tumors of the pineal region." Future oncology 6.5 (2010): 791-809.
3. Smith AB, Rushing EJ, Smirniotopoulos JG. From the archives of the AFIP: lesions of the pineal region: radiologic-pathologic correlation. 2010 Nov;30(7):2001-20. [PubMed]
4. Dahiya, Sonika, and Arie Perry. "Pineal tumors." *Advances in anatomic pathology*6 (2010): 419-427.
5. Preslock, James P. "The pineal gland: basic implications and clinical correlations." *Endocrine reviews*2 (1984): 282-308.
6. Sapède, Dora, and Elise Cau. "The pineal gland from development to function." *Current topics in developmental biology*106 (2013): 171-215.
7. Yamamoto I. Pineal region tumor: surgical anatomy and approach. J Neurooncol. 2001 Sep;54(3):263-75. [PubMed]
8. Sumida M, Barkovich AJ, Newton TH. Development of the pineal gland: measurement with MR. AJNR Am J Neuroradiol. 1996 Feb;17(2):233-6. [PMC free article] [PubMed]
9. Leone, R. M., R. J. L. Hooper, and M. A. Preece. "Melatonin, the pineal gland and human puberty." *Nature*5736 (1979): 301-303.
10. Del Valle, Miguel Mayol, and Orlando De Jesus. "Pineal Gland Cancer." *StatPearls [Internet]*(2021).
11. Ueno T, Tanaka YO, Nagata M, Tsunoda H, Anno I, Ishikawa S, Kawai K, Itai Y. Spectrum of germ cell tumors: from head to toe. 2004 Mar-Apr;24(2):387-404. [PubMed]
12. Gempt J, Ringel F, Oexle K, Delbridge C, Förschler A, Schlegel J, Meyer B, Schmidt-Graf F. Familial pineocytoma. Acta Neurochir (Wien). 2012 Aug;154(8):1413-6. [PubMed]
13. Chik, Ki-wai, et al. "Intracranial germ cell tumors in children with and without Down syndrome." *Journal of pediatric hematology/oncology*2 (1999): 149-151.
14. Wong, Tai-Tong, et al. "Familial neurofibromatosis 1 with germinoma involving the basal ganglion and thalamus." *Child's Nervous System*8 (1995): 456-458.

15. Jouvet, A.; Saint-Pierre, G.; Fauchon, F.; Privat, K.; Bouffet, E.; Ruchoux, M.M.; Chauveinc, L.; FeÃÄvre-Montange, M. Pineal parenchymal tumors: A correlation of histological features with prognosis in 66 cases. Brain Pathol. 2000, 10, 49-60. [CrossRef]
16. Tamrazi, B.; Nelson, M.; Blüml, S. Pineal region masses in pediatric patients. *Neuroimaging Clin. N. Am.* **2017**, *27*, 85–97. [CrossRef] [PubMed]

17. Cuccia, F.; Mortellaro, G.; Cespuglio, D.; Valenti, V.; DE Gregorio, G.; Quartuccio, E.; Blasi, L.; Francaviglia, N.; Gallo, C.; Lo Casto, A.; et al. A case report of adult pineoblastoma occurring in a pregnant woman. Anticancer Res. 2019, 39, 2627-2631. [CrossRef]
18. Rousselle, C.; des Portes, V.; Berlier, P.; Mottolese, C. Pineal region tumors: Clinical symptoms and syndromes. *Neurochirurgie* **2015**, *61*, 106–112. [CrossRef] [PubMed]
19. Carr, C.; O'Neill, B.E.; Hochhalter, C.B.; Strong, M.J.; Ware, M.L. Biomarkers of pineal region tumors: A review. *Ochsner J.* **2019**, *19*, 26–31. [CrossRef]
20. Chatterjee, D.; Lath, K.; Singla, N.; Kumar, N.; Radotra, B.D. Pathologic prognostic factors of pineal parenchymal tumor of intermediate differentiation. *Appl. Immunohistochem. Mol. Morphol.* **2019**, *27*, 210–215. [CrossRef]

21. Mallick, Supriya, Rony Benson, and G. K. Rath. "Patterns of care and survival outcomes in patients with pineal parenchymal tumor of intermediate differentiation: An individual patient data analysis." *Radiotherapy and Oncology*2 (2016): 204-208.
22. Wang, K.Y.; Chen, M.M.; Malayil Lincoln, C.M. Adult primary brain neoplasm, including 2016 World Health Organization classification. *Radiol. Clin. N. Am.* **2019**, *57*, 1147–1162. [CrossRef] [PubMed]

23. Favero, Gaia, Francesca Bonomini, and Rita Rezzani. "Pineal Gland Tumors: A Review." *Cancers*7 (2021): 1547.
24. Fauchon F, Jouvet A, Paquis P, et al. Parenchymal pineal tumors: a clinicopathologic study of 76 cases. Int J Radiat Oncol Biol Phys. 2000;46:959–968.

25. Schild, Steven E., et al. "Histologically confirmed pineal tumors and other germ cell tumors of the brain." *Cancer: Interdisciplinary International Journal of the American Cancer Society*12 (1996): 2564-2571.
26. Iorio-Morin, C.; Kano, H.; Huang, M.; Lunsford, L.D.; Simonová, G.; Liscak, R.; Cohen-Inbar, O.; Sheehan, J.; Lee, C.C.; Wu, H.M.; et al. Histology-stratified tumor control and patient survival after stereotactic radiosurgery for pineal region tumors: A report from the International Gamma Knife Research Foundation. *World Neurosurg.* **2017**, *107*, 974–982. [CrossRef]
27. Jing, Y.; Deng, W.; Zhang, H.; Jiang, Y.; Dong, Z.; Fan, F.; Sun, P. Development and validation of a prognostic nomogram to predict cancer-specific survival in adult patients with pineoblastoma. *Front. Oncol.* **2020**, *10*, 1021, Erratum in *Front. Oncol.* **2020**, *10*, 594049. [CrossRef]

28. Rodjan F, de Graaf P, Moll AC, Imhof SM, Verbeke JI, Sanchez E, Castelijns JA. Brain abnormalities on MR imaging in patients with retinoblastoma. AJNR Am J Neuroradiol. 2010 Sep;31(8):1385-9. [PMC free article] [PubMed]
29. Blessing, M.M.; Alexandrescu, S. Embryonal tumors of the central nervous system: An update. *Surg. Pathol. Clin.* **2020**, *13*, 235–247. [CrossRef] [PubMed]
30. Bando, T.; Ueno, Y.; Shinoda, N.; Imai, Y.; Ichikawa, K.; Kuramoto, Y.; Kuroyama, T.; Shimo, D.; Mikami, K.; Hori, S.; et al. Therapeutic strategy for pineal parenchymal tumor of intermediate differentiation (PPTID): Case report of PPTID with malignant transformation to pineocytoma with leptomeningeal dissemination 6 years after surgery. *J. Neurosurg.* **2018**, 1–7. [CrossRef]
31. Choque-Velasquez,J.;Resendiz-Nieves,J.C.;Jahromi,B.R.;Colasanti,R.;Raj,R.;Tynninen,O.;Collan,J.;Hernesniemi,J.Pineal parenchymal tumors of intermediate differentiation: A long-term follow-up study in Helsinki Neurosurgery. *World Neurosurg.* **2019**, *122*, e729–e739. [CrossRef] [PubMed]

32. Tanrıkulu, Bahattin, and M. Memet Özek. "Management of mature pineal region teratomas in pediatric age group." *Child's Nervous System*1 (2020): 153-163.
33. Ostrom, Q.T.; Gittleman, H.; Xu, J.; Kromer, C.; Wolinsky, Y.; Kruchko, C.; Barnholtz-Sloan, J.S. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2009-2013. *Neuro Oncol.* **2016**, *18*, v1–v75. [CrossRef]

34. Jouvet A, Fauchon F, Liberski P, et al. Papillary tumor of the pineal region. Am J Surg Pathol. 2003;27:505–512.
35. Alkhotani, A.; Bilbao, J.M.; Mainprize, T.G. A 49 year-old woman with a pineal mass. *Brain Pathol.* **2014**, *24*, 191–192. [CrossRef]
36. Braun, M.; Tomasik, B.; Bien ´kowski, M.; Wis ´niewski, K.; Kupnicka, D.J.; Jaskólski, D.; Papierz, W.; Fijuth, J.; Kordek, R. Recurrent pineocytomalike papillary tumor of the pineal region: A case report and literature review. *World Neurosurg.* **2018**, *120*, 1–14. [CrossRef]

37. Kamamoto, D.; Sasaki, H.; Ohara, K.; Mizutani, K.; Yoshida, K. A case of papillary tumor of the pineal region with a long clinical history: Molecular characterization and therapeutic consideration with review of the literature. *Brain Tumor Pathol.* **2016**, *33*, 271–275. [CrossRef]
38. Sadiq, Q.; Khan, F.A. Germ cell seminoma. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2020.
39. Nagasawa, D.T.; Lagman, C.; Sun, M.; Yew, A.; Chung, L.K.; Lee, S.J.; Bui, T.T.; Ooi, Y.C.; Robison, R.A.; Zada, G.; et al. Pineal germ cell tumors: Two cases with review of histopathologies and biomarkers. *J. Clin. Neurosci.* **2017**, *38*, 23–31. [CrossRef] [PubMed]
40. Nomura, K. Epidemiology of germ cell tumors in Asia of pineal region tumor. *J. Neurooncol.* **2001**, *54*, 211–217. [CrossRef]
41. Kanamori, M.; Takami, H.; Yamaguchi, S.; Sasayama, T.; Yoshimoto, K.; Tominaga, T.; Inoue, A.; Ikeda, N.; Kambe, A.; Kumabe, T.; et al. So-called "bifocal tumors" with diabetes insipidus and negative tumor markers: Are they all germinoma? *Neuro Oncol.* **2020**, *20*, noaa199. [CrossRef]
42. Schipmann, S.; Keurhorst, D.; Köchling, M.; Schwake, M.; Heß, K.; Sundermann, B.; Stummer, W.; Brentrup, A. Regression of pineal lesions: Spontaneous or iatrogenic? A case report and systematic literature review. *World Neurosurg*. **2017**, *108*, 939–947. [CrossRef]

43. Kilgore, D. P., et al. "Pineal germinoma: MR imaging." *Radiology*2 (1986): 435-438.
44. Smirniotopoulos, J.G.; Rushing, E.J.; Mena, H. Pineal region masses: Differential diagnosis. *Radiographics* **1992**, *12*, 577–596. [CrossRef]
45. Causil, L.D.; Ames, R.; Puac, P.; Castillo, M. Adult brain tumors and pseudotumors: Interesting (Bizarre) cases. *Neuroimaging Clin.N. Am.* **2016**, *26*, 667–689. [CrossRef] [PubMed]
46. Jiang, T.; Raynald; Yang, H.; Zhang, W.; Li, C. Predictive factors of overall survival in primary intracranial pure choriocarcinoma. *J. Clin. Neurosci.* **2019**, *61*, 93–101. [CrossRef]
47. Qi, S.T.; Zhang, H.; Song, Y.; Zhang, J.L. Tumor cells forming sinusoids connected to vasculature are involved in hemorrhage of pineal choriocarcinoma. *J. Neurooncol.* **2014**, *119*, 159–167. [CrossRef] [PubMed]
48. Peterson, C.M.; Buckley, C.; Holley, S.; Menias, C.O. Teratomas: A multimodality review. *Curr. Probl. Diagn. Radiol.* **2012**, *41*, 210–219. [CrossRef] [PubMed]
49. Choque-Velasquez, J.; Resendiz-Nieves, J.; Jahromi, B.R.; Colasanti, R.; Raj, R.; Vehviläinen, J.; Tynninen, O.; Collan, J.; Niemelä, M.; Hernesniemi, J. Extent of resection and long-term survival of pineal region tumors in Helsinki neurosurgery. *World Neurosurg*. **2019**, *131*, e379–e391. [CrossRef]

50. Beker-Acay M, Turamanlar O, Horata E, Unlu E, Fidan N, Oruc S. Assessment of Pineal Gland Volume and Calcification in Healthy Subjects: Is it Related to Aging? J Belg Soc Radiol. 2016 Feb 01;100(1):13. [PMC free article] [PubMed]
51. Sumida M, Barkovich AJ, Newton TH. Development of the pineal gland: measurement with MR. AJNR Am J Neuroradiol. 1996 Feb;17(2):233-6. [PMC free article] [PubMed]
52. Kulwin C, Matsushima K, Malekpour M, Cohen-Gadol AA. Lateral supracerebellar infratentorial approach for microsurgical resection of large midline pineal region tumors: techniques to expand the operative corridor. J Neurosurg. 2016 Jan;124(1):269-76. [PubMed]
53. Rey-Dios R, Cohen-Gadol AA. A surgical technique to expand the operative corridor for supracerebellar infratentorial approaches: technical note. Acta Neurochir (Wien). 2013 Oct;155(10):1895-900. [PubMed]
54. Moshel YA, Parker EC, Kelly PJ. Occipital transtentorial approach to the precentral cerebellar fissure and posterior incisural space. 2009 Sep;65(3):554-64; discussion 564. [PubMed]

Figure (2): Pineocytomas sagittal T1 C+ [Internet]. Available from: https://radiopaedia.org/cases/pineocytoma-3?lang=us.

Figure (3): Radiopedia, Pineal parenchymal tumors of intermediate differentiation [Internet]. Available from: https://radiopaedia.org/cases/pineal-parenchymal-tumour-of-intermediate-differentiation?lang=us.

Figure (4): Radiopedia, Pineal papillary tumors appear sagittal T1 [Internet]. Available from: https://radiopaedia.org/cases/papillary-tumour-of-the-pineal-region?lang=us.

Figure (5): Radiopedia, Pineal germinomas [Internet]. Available from: https://radiopaedia.org/cases/pineal-germinoma-3?lang=us.

Figure (6): Radiopedia, Pineal region teratoma [Internet]. Available from: https://radiopaedia.org/cases/intracranial-mature-cystic-teratoma?lang=us.

Article topic: arachnoid cysts.

Author: Soliman Mohamed Abdelmonem Soliman.

Editor: Menna Mohamed Marwan.

Reviewer: Adam M. Abdallah.

keywords: Arachnoid cyst, Sylvian Arachnoid Cysts, Intraventricular Arachnoid Cysts, minimally invasive cyst fenestration.

Overview

Arachnoid cysts are fluid-filled duplications or detachments of the arachnoid membrane in concentrations similar to but not equal to cerebrospinal fluid. Arachnoid cysts are not a true neurodegenerative disorder, but an underlying defect in the structure of the arachnoid layer that may be congenital. They may occur sporadically or in combination with other malformations or illnesses. Arachnoid cysts can be detected during childhood. However, they can grow de novo, enlarge, or decrease in size. They can be diagnosed by screening ultrasound during fetal life or detected during childhood or adulthood. Many arachnoid cysts are asymptomatic.

Treatment strategies are controversially discussed. If they are diagnosed incidentally or if they are associated with very mild symptoms, conservative management with follow-up imaging may be preferred. If they grow larger, they can cause headaches, seizures, or other neurological symptoms and require neurosurgical treatment. This chapter discusses aspects of the pathogenesis, clinical symptoms, indications for neurosurgical treatment, and treatment options. [1,2,3]

Pathogenesis

True AC is a benign lesion and is thought to be developmental, or at least based on a congenital error in the structure of arachnids. It should be noted that arachnoid septa of varying strength are woven through the subarachnoid space, especially at the base of the skull and in the region of the Sylvian fissure. Physiologically, many inner arachnoid membranes can form the subarachnoid cistern**.** [4]

Microstructurally, the wall of AC is similar to the normal arachnoid. Miyagami and Tsubokawa analyzed the surgically resected atrioventricular wall using light and electron microscopy and found that the inner surface of the atrioventricular wall consists of one or more layers of arachnoid cells with thin cylindrical projections and large intercellular spaces. [5] Rengachary and Watanabe observed structural differences

from the normal arachnoid: (I) the splitting of the arachnoid membrane at the margin of the cyst, (2) a thicker layer of collagen in the cyst wall, (3) the absence of traversing trabecular processes within the cyst and (4) the presence of hyperplastic arachnoid cells in the cyst wall, which participate in collagen synthesis.[6]

The pathogenesis of AC is still not fully understood. Meningeal tissue is of mesectodermal origin and derives from the neural crest. AC, as well as meningiomas, may be located intraventricularly, which indicates that mesectodermal tissue may be dislocated into the neural tube during the folding of the latter, which begins around the 20th embryonic day. A network of mesenchymal cells develops between the brain and the epidermis and eventually differentiates into a dense outer layer and a reticular inner layer to form the meninges. The inner layer further differentiates to form the dura mater and the leptomeninges.[7] The frequent occurrence of these phenomena in childhood, histological features without changes after inflammation or hemorrhage, and their occurrence with genetic disorders strongly suggest the nature of development. However, this view has recently been challenged. Temporal lobe
and Sylvian localization predominate in children and adults,[8,9] whereas in prenatal analyzes the majority of AC are interhemispherically located and temporal AC is extremely rare [10] (Table 1). This observation casts some doubt on the hypothesis that AC formation is strictly congenital. As they may develop de novo in adults, may grow over time, furthermore, the cyst size on the first diagnosis is larger with increasing age.[11,12]

Table 1. Distribution of arachnoid cysts

Localization	Prenatal (n = 54)[a]	Pediatric (n = 67)[b]	Elderly (n = 23)[c]
Supratentorial	34	31	20
Middle fossa	1	13	11
Interhemispheric	16	9	
Hemispheric	1	5	9
Suprasellar	5	4	
Skull base	7		
Intraventricular	5		
Infratentorial	12	31	3
CPA	1	1	
Hemispheric	1	22	
Other	10	8	
Tentorial incisure	8	5	

Distribution of arachnoid cysts discovered by (a) routine ultrasound screening in pregnancy, (b) in children and (c) in patients older than 65 years. Arachnoid cysts rarely become symptomatic in old patients. Published cases were collected and reviewed by Caruso *et al.*[c] One of the infratentorial cysts was located within the fourth ventricle causing symptoms of normal pressure hydrocephalus. The differences in the distribution between pre- and postnatally diagnosed arachnoid cysts is apparent. Arachnoid cysts in the middle cranial fossa do practically not appear in the prenatal period but make up the majority of lesions in the pediatric and adult age. On the contrary, the predominant localization in prenatal diagnostics is interhemispheric. These lesions are less frequently found in infants and rare in adults.

Mechanisms of cyst-growth

Berle and colleagues systematically analyzed intracystic fluid and found various levels of phosphate, protein, ferritin, and lactate dehydrogenase in comparison to normal cerebrospinal fluid. A possible mechanism of cyst growth should therefore be consistent with these findings. Many mechanisms have been proposed. Mechanisms could be active secretion by the cells of the cystic wall, expansion along an osmotic pressure gradient, or a one-way valve mechanism. [13]

Active Fluid Secretion

In an ultrastructural and cytochemical study, the resected walls of AC were analyzed. They observed similarities between the neurothelial lining of arachnoid granulations. On the luminal surface, the structure's cyst wall is densely covered with microvilli, thus, suggesting active secretion. Enzyme cytochemistry demonstrated Na-K-ATPase at the Luminal plasma membrane and alkaline phosphatase at the opposite membrane. This architecture could indicate fluid transport towards the lumen. Different consistency compared to Cerebrospinal fluid may be explained by this hypothesis. [14]

Osmotic Gradient

The hypothesis that AC evolves along an osmotic gradient has been suggested due to the small difference in substance concentrations from the CSF. A thin wall with loose connective tissue may allow the permeation of water. However, the formation of an osmotic gradient must be activated. In secondary cysts, hemorrhage with hemolysis products or an inflammatory response can act as an osmotic activator. In primary AC, there is no evidence that these mechanisms exist. [15]

Valve Mechanism

Small and medium-sized cysts remain the same size and readily communicate with the normal subarachnoid space. [12,16] In larger cysts or growing cysts, a valve mechanism may develop with unidirectional fluid transport. In the case of positive intradermal/ ectodermal pressure, the cyst may enlarge. Valvular folds of the cyst wall or endometrium have been observed during laparoscopic or open procedures. [17,18]

Clinical picture

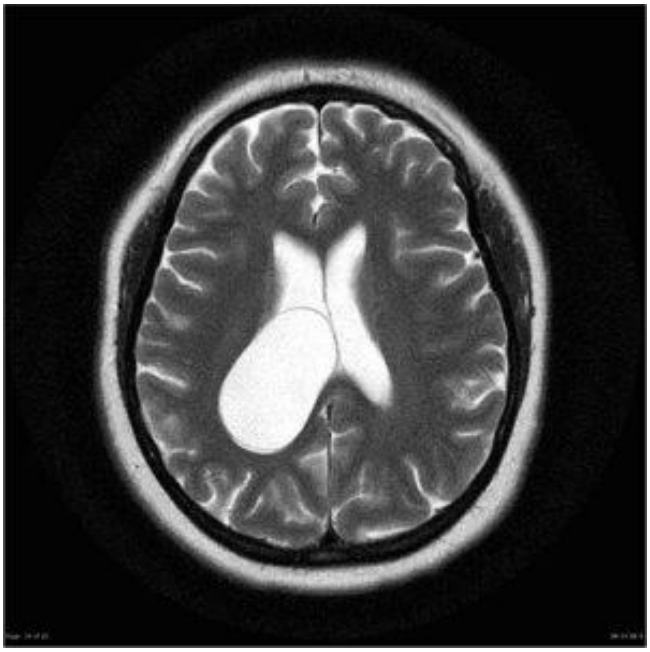
Clinical symptoms are determined by the location of the cyst. AC can occur anywhere in the skull and spine where the arachnoid is present. Typical symptoms of AC are described below.

Temporal and Sylvian Arachnoid Cysts

The middle cranial fossa is the most common location for AC. In a large series of pediatric and adult patients, about two-thirds of them suffer from AC in the middle cranial fossa or Sylvian fissure. Bilateral temporal AC is rarely seen, and these patients may suffer from glutaric aciduria. [19] Most commonly, these patients present with headaches and seizures, and contralateral movement disorders. Developmental delays and delays are more common in patients with the apex of the sphenoid bone of AC. [20,21] The link between temporary AC and psychiatric and neurobehavioral disorders is still under debate. Various cases of AC-related psychiatric disorders have been reported. These include attention deficit hyperactivity disorder, depression, hallucinations, dementia, schizophrenia, anorexia nervosa, insomnia, and other psychotic disorders. Wester published a systematic preoperative and postoperative assessment of cognitive function et al. They found that many patients with left temporal lobe AC had significant defects in various cognitive functions such as language perception, memory function, complex language tasks, visuospatial function, and visual attention. [22,23,24]

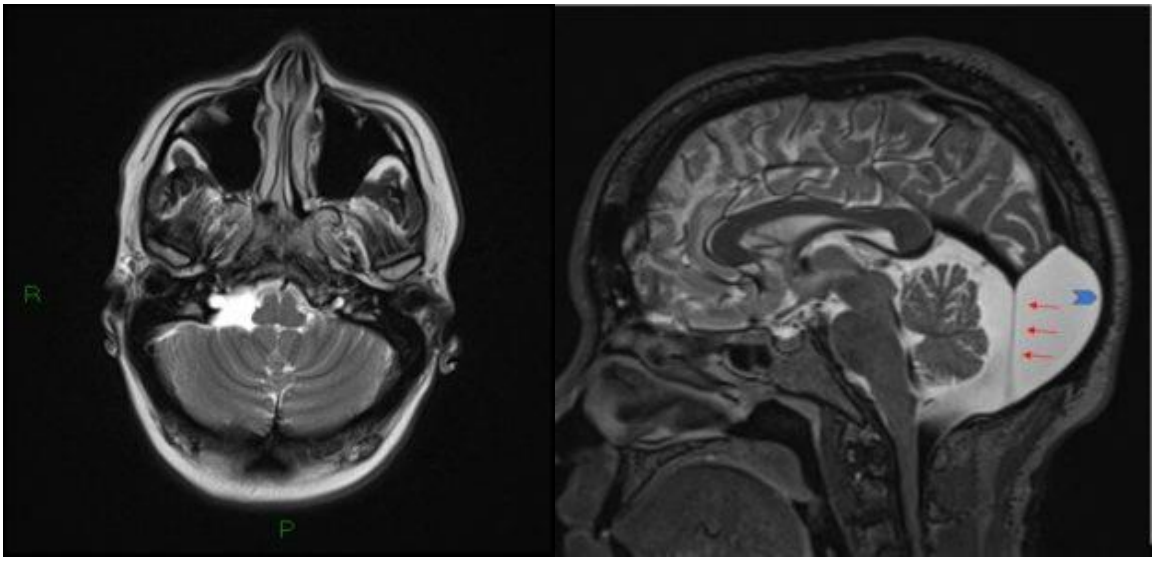
Intraventricular Arachnoid Cysts

Intraventricular AC is rare. They were found in the lateral ventricles, third ventricle, and fourth ventricle. These cysts become clinically prominent through the development of acute or chronic hydrocephalus as the size of the cyst increases. Symptoms due to compression of surrounding structures have also been reported. For example, AC in the 4th ventricle can cause symptoms such as cerebellar dysfunction or depression. [25]



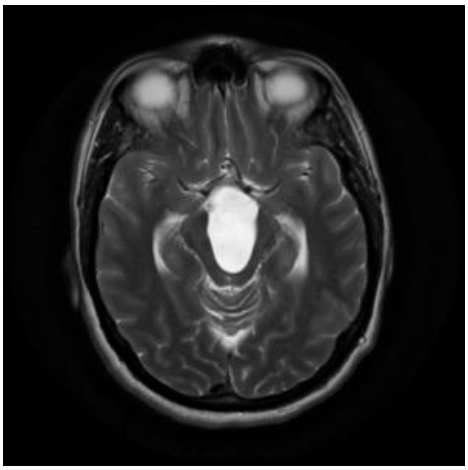
Cerebellopontine Angle and Retrocerebellar Arachnoid Cysts

Infratentorial location forms about 10% of all AC. The main site of these is located in the cerebellopontine angle or retrocerebellar. Symptoms of retrocerebellar cysts include hydrocephalus and compression of cerebellar or brainstem structures. Patients predominantly present with headaches or gait disturbances. Cerebellopontine angle AC may obstruct the CSF circulation in the posterior fossa and cause obstructive hydrocephalus. Cerebellopontine angle structures may be directly compressed or affected in terms of neurovascular compression. Cranial nerve symptoms may include hearing loss, trigeminal nerve neuralgia, hemifacial muscle spasm, diplopia, hoarseness, and dysphagia. [26-32]



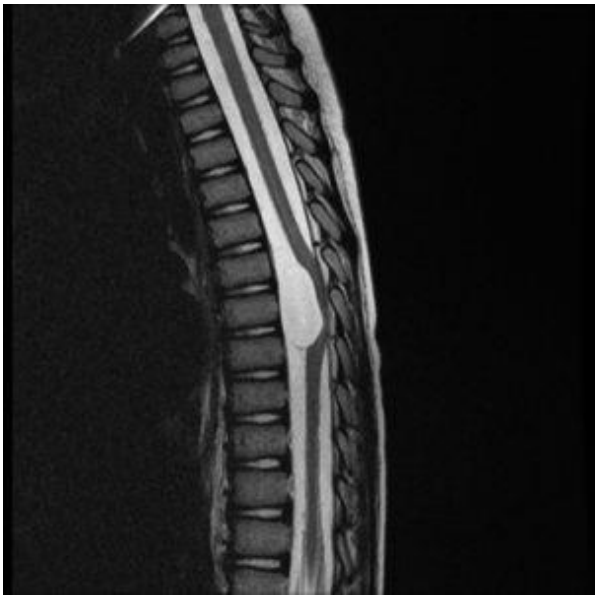
Supra- and Intrasellar Arachnoid Cysts

Intra- and suprasellar AC occur near the optic nerve, pituitary and pituitary stalks, hypothalamus, and mesencephalon. In the case of large suprasellar extension, they can interfere with the physiological outflow of cerebrospinal fluid at the level of the third ventricle or the foramen of Monroe, thus causing obstructive hydrocephalus. Visual impairment and endocrine disorders can be caused by compression of the optic nerve and compression of the pituitary gland or pituitary stalk. Compression of the hypothalamic structures can cause developmental disorders such as precocious puberty. Bobblehead puppet syndrome can be caused by compression of the third ventricle or thalamic nucleus. This is a clinical feature that strongly suggests saddle AC. However, this typical feature is found only in a small number of these patients. [33]



Spinal Arachnoid Cysts

Like cranial AC, spinal cord AC usually causes symptoms due to compression of the spinal cord and radiculopathy Myelopathy symptoms such as ataxia, recurrence of primitive reflexes, and progressive paralysis can be caused by compression of the cord. symptoms of radiculopathy due to termination of radiculopathy may include pain, sensory deficits, or weakness of the effector's muscles. [38]



Diagnostic procedures

In many patients with intracranial and spinal AC, it is difficult to assess the indication for surgical treatment. The success of the treatment strategy is based on the correlation between lesions and clinical manifestations. A detailed interview with the patient or the patient's parents and a thorough neurological examination is essential to correlate signs and symptoms with radiation findings. This probably counts random cysts. [38] Laboratory investigations for screening of glutaric aciduria must be recommended in patients with bilateral AC. In fetuses with AC detected by routine ultrasound screening, karyotype evaluation, and fetal MRI should be performed to rule out an association with other malformations. Electroencephalography is essential in patients with supratentorial AC to determine the necessity for antiepileptic medication. In spinal AC cord compression may be further evaluated by somatosensory and motor evoked potentials. Magnetic resonance imaging (MRI) is the mainstay of radiological diagnostics. Due to their worse imaging quality and because of X-ray exposure, computed tomography scan (CTS) is, especially in children, not acceptable as a diagnostic tool. Modem phase-contrast MRI and functional MRI are not only capable of proving structural abnormalities but also able to depict CSF-flow patterns and functional organization of the brain, respectively. Cisternography with contrast filling of the subarachnoid space followed by CTS, sometimes at more than one time-point to assess the time-course of contrast filling of CSF-compartments, is reserved for very few cases of diagnostic uncertainty. [38]

Treatment

There are several options for treating AC. Resection of the cyst wall requires open surgery. Cyst fenestration in the subarachnoid cistern can be done endoscopically or by open surgery microsurgical techniques. Various shunt techniques have been reported, including cystic peritoneal and subdural shunts. The optimal surgical strategy is still under debate. Which type of treatment is selected individually depends on a variety of factors. Patient symptoms, cyst location and shape, the extent of the cystic septum, proximity to relevant nerve and vascular structures, and experience of the surgeon's various techniques. Observations for patients with no associated symptoms and no associated neurological defects observation are recommended. [38] If there is an indication for treatment, endoscopic fenestration can be recommended as the treatment of the first choice for many AC, in particular, if there are no relevant intracystic septations. If suprasellar arachnoid cysts are present, promising results have been reported. Ventriculocystostomy and ventriculocystocistemostomy appear to be the most successful treatment in the long term. [38]

Temporal and temporobasal AC appear to be more difficult to be treated by endoscopic strategies. [34] If there are intracystic septations or multiple fine neural structures like in the cerebellopontine angle, the recurrence rate might be higher if treatment only consists of cyst-fenestration. Complete or near-complete excision of the cyst wall or adherences supplies the most successful treatment at these locations. [35] For small or medium-sized temporal cysts, excision or fenestration shows a good chance of complete disappearance of the cyst and complete re-expansion of the adjacent temporal lobe. For large cysts, only incomplete expansion of the adjacent brain has been demonstrated. Additional shunt placement may be needed. Shunting procedures are only a little invasive and supply good control of the cyst volumes by pressure-controlled drainage but may have a relatively high failure rate. [37] Fenestration or excision of the cyst may bear a higher operative risk but leaves the patient shunt independent. A long-term success rate of 76-90% has been reported for these ways of treatment. [34,36,37]

References

1. Bright R. Serous cysts in the arachnoid diseases of the brain and nervous system, part I: reports of medical cases selected with a view of illustrating the symptoms and cure of diseases by a reference to morbid anatomy. 1831; 2:437439.
2. Cunningham DJ. A Large sub-arachnoid cyst involving the greater part of the parietal lobe of the brain. Anat Physiol 1879; 13:508-517.
3. Robinson RG. The temporal lobe agenesis syndrome. Brain 1964; 87:87-106.
4. Inoue K, Seker A, Osawa S, et al. Micrbsurgical and endoscopic anatomy of the supratentorial arachnoidal membranes and cisterns. Neurosurgery 2009; 65:644-664.
5. Miyagami M, Tsubokawa T. Histological and ultrastructural findings of benign intracranial cysts. Noshuyo Byori 1993; 10:151-160.
6. Rengachary SS, Watanabe I. Ultrastructure and pathogenesis of intracranial arachnoid cysts. J Neuropathol Exp Neurol 1981; 40:61-83.
7. Angelov DN, Vasilev V A. Morphogenesis of rat cranial meninges. A light- and electron-microscopic study. Cell Tissue Res 1989; 257:207-216.
8. Pascual-Castroviejo I, Roche MC, Martinez BA et al. Primary intracranial arachnoidal cysts. A study of 67 childhood cases. Childs Nerv Syst 1991; 7:257-263.
9. CarusoR, Salvati M, Cervoni L. Primary intracranial arachnoidcystintheelderly. NeurosurgRev 1994; 17:195-198.

10. Pierre-Kahn A, Hanlo P, Sonigo P et al. The contribution of prenatal diagnosis to the understanding of malformative intracranial cysts: state of the art. Childs Nerv Syst 2000; 16:619-626.
11. Struck AF, Murphy MJ, Iskandar BJ. Spontaneous development of a de novo suprasellar arachnoid cyst. case report. J Neurosurg 2006; 104:426-428.
12. Becker T, Wagner M, Hofmann E et al. Do arachnoid cysts grow? A retrospective CT volumetric study. Neuroradiology 1991; 33:341-345.
13. Holmes LB, Redline RW, Brown DL, et al. Absence, "hypoplasia of tibia, polydactyly, retrocerebellar arachnoid cyst, and other anomalies: an autosomal recessive disorder. J Med Genet 1995; 32:896-900.
14. Ito J, Yamazaki Y, Honda H, et al. Angiographic appearance of a huge retrocerebellar arachnoid cyst in a Neuroradiology 1977; 13:1 15-119.
15. Cagnoni G, Fonda C, Pancani S et al. Intracranial arachnoid cyst in pediatric age. Pediatr Med Chir 1996; 18:85-90.
16. Galassi E, Tognetti F, Gaist G, et al. CT scan and metrizamide CT cisternography in arachnoid cysts of the middle cranial fossa: classification and pathophysiological aspects. Surg Neurol 1982; 17:363-369.
17. Alehan FK, Gurakan B, Agildere M. Familial arachnoid cysts in association with autosomal dominant polycystic kidney disease. Pediatrics 2002; 1 10:13.
18. Arriola G, de Castro P, Verdu A. Familial arachnoid cysts. Pediatr Neurol 2005; 33:146 148.
19. Hald JK, Nakstad PH, Skjeldal OH, et al. Bilateral arachnoid cysts of the temporal fossa in four children with glutaric aciduria type 1. AJNR Am J Neuroradiol 1991; 12:407-409.
20. Koch CA, Voth D, KraemerG et al. Arachnoid cysts: does surgery improve epileptic seizures and headaches. NeurosurgRev 1995; 18:173-181.
21. Arai H, Sato K, Wachi A, et al. Arachnoid cysts of the middle cranial fossa: experience with 77 patients who were treated with cystoperitoneal shunting. Neurosurgery 1996; 39:1108-11 12.
22. Smith RA, Smith WA. Arachnoid cysts of the middle cranial fossa. Surg Neurol 1976; 5:246-252.
23. Brugger G. Cerebral arachnoid cysts in children with local bulging of the skull. Wien Klin Wochenschr 1976; 88:764-769.
24. Wester K. Intracranial arachnoid cysts—do they Impair mental functions? J Neurol 2008; 255:1113-1120.
25. Szucs A, Varady P, Pestality P et al. Occlusive hydrocephalus caused by a fourth ventricle arachnoid cyst. Ideology Sz 2008; 61:54-58.
26. Cartwright, Ei senberg MB, Page LK. Posterior fossa arachnoid cyst presenting with an isolated twelfth nerve paresis. Case report and review of the literature. Clin Neurol Neurosurg 1991 ; 93:69-72.
27. Mastronardi L, Taniguchi R, Caroli M, et al. Cerebellommtine angle arachnoid cyst: a case of hemifacial spasm caused by an organic lesion other than neurovax-ular compression case report. Neurosurgery 2009; 65:1205.
28. Ashker L, Weinstein JM, Dias M, et al. Arachnoid cyst causing third cranial nerve palsy manifesting as isolated internal ophthalmoplegia and iris cholinergic supersensitivity. J Neuroophthalmol 2008; 28: 192-197.
29. Hayden MG, Tomabene SV, Nguyen A, et al. Cerebellopontine angle cyst compressing the vagus nerve: case report. Neurosurgery 2007; 60: 1150.
30. Chao TR. Middle cranial fossa arachnoid cysts causing sensorineural hearing loss. Eur Arch Otorhinoluyngol 2005; 262:925-927.
31. Pirotte B, Morelli D, Alessi G, et al. Facial nerve palsy in posterior fossa arachnoid cysts: report of two cases. Childs New Syst 2005; 21:587-590.
32. Achill I V, Danesi G, Cavemi L, et al. Petrous a}EX arachnoid cyst: a case report and review of the literature. Acta Otorhinolaongol Ital 2005; 25:296-300.
33. Starzyk J, Kwiatkowski S, Urbanowicz W et al. Suprasellar arachnoidal cyst as a cause of precocious puberty—report of three patients and literature overview. J Pediatr Endocrinol Metab 2003; 16:447-455.
34. Oertel JM, Wagner W, MondorfY, et al. Endoscopic treatment of arachnoid cysts: a detailed account of surgical techniques and results. Neurosurgery 2010; 67:824-836.
35. Samii M, Carvalho GA, Schuhmann MU et al. Arachnoid cysts of the posterior fossa. Surg Neurol 1999; 51:376-382.
36. Galassi E, Piazza G, Gaist G, et al. Arachnoid cysts of the middle cranial fossa: a clinical and radiological study of 25 cases treated surgically. Surg Neurol 1980; 14:211-219.
37. Raffel C, McComb JG. To shunt or to fenestrate: which is the best surgical treatment for arachnoid cysts in pediatric patients? Neurosurgery 1988; 23:338-342.
38. Westermaier T, Schweitzer T, Ernestus RI. Arachnoid cysts. Adv Exp Med Biol. 2012;724:37-50. doi: 10.1007/978-1-4614-0653-2_3. PMID: 22411232.

Article Title: Intraventricular Brain Hemorrhage

Author: Yara Alswaiti.

Editors: Yasmeen Alabdallat, Rawan AbuHammor.

Reviewer: Adam M. Abdallah.

Keywords: IVH; Hemorrhage; CSF; Hydrocephalus.

Abstract

Intraventricular brain hemorrhage (IVH) refers to blood within the brain's ventricular system (VS), a communicating network of cavities filled with cerebrospinal fluid (CSF) located within the brain parenchyma; this includes the lateral, third, and fourth ventricles. IVH is associated with severe morbidity due to the risk of obstructive hydrocephalus.[1] In this article, we aim to provide you with basic knowledge about how to assess and treat a patient with IVH.

Introduction

Blood that refluxes into the ventricles from the subarachnoid space, the interval between the arachnoid membrane and the pia mater, is commonly unclotted and settles independent portions of the VS[2]. Bleeding restricted to the brain's VS happens due to intracerebral hemorrhage rupture or subarachnoid hemorrhage that extends to the ventricles; this is most commonly a secondary symptom.

Primary intraventricular hemorrhage (PIVH) accounts for 0.31% of all stroke cases and 3.1% of all spontaneous intracranial hemorrhages. PIVH refers to nontraumatic intracranial bleeding in the VS and adjacent ependymal lining without a definite parenchymal component [3]. PIVH is more commonly seen in preterm newborns than in adults. Secondary IVH refers to IVH with subarachnoid hemorrhage or other parenchymal hemorrhages [4,5]. The underlying etiopathogenesis for adult PIVH is variable and often remains idiopathic. However, the common associations include hypertension, arteriovenous malformations (AVMs), aneurysms, moyamoya disease (MMD), coagulopathy, and arteriovenous fistula[6]. Due to the importance of this, the present review aims to provide you with basic knowledge about how to assess and treat a patient with IVH.

Epidemiology

Brain hemorrhage has the highest morbidity and mortality of any stroke subtype. Respectively, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) account for about 15% and 5% of the 750,000 strokes occurring yearly in the United States, totaling more than 45,000 patients per year.[7,8] About 45% of spontaneous ICHs and 25% of aneurysmal SAHs extend into the ventricles [9,10]. For patients with both ICH and intraventricular hemorrhage (IVH), the expected mortality is 50% to 80% [11,12]. In addition, patients with IVH are twice as likely to have poor outcomes (a modified Rankin scale [mRS] score of 4–6 at hospital discharge) and nearly three times more likely to die than the healthy controls [13].

Etiology

The quantity of blood inside the ventricles is closely associated with the severity of harm and the chance of survival. Furthermore, the quantity of bleeding into the VS is manifestly associated with the severity of the initial injury and the long-term implications of blood extending into the ventricles, keeping with the most current human clinical research [14].

A brain hemorrhage can be caused by aneurysms, arteriovenous malformations, small microaneurysms in the vessel wall, a coagulation profile, or simply increased blood pressure causing bleeding sites. As a result, a variety of disorders, such as trauma, tumors, and high blood pressure, can result in blood collections that restrict or occlude the intraventricular space [14].

Early intraventricular rupture is caused by bleeding at deep intracranial sites near the ventricles, but bleeding sites further distant from the ventricles may stockpile clotting blood before mechanical pressure, and hemorrhage cause a rupture into the ventricles. The actual rupture is typically linked with a clinically detectable loss of consciousness, frequently followed by death. The bigger the volume of blood clots injected into the ventricles in both canine and porcine IVH models, the greater the chance of animal death. Similarly, prolonged blood exposure to the ventricles causes altered consciousness as well as inflammation, fibrosis, and hydrocephalus at tissue level [14].

Although the etiology of IVH in neonates is unknown, it is believed to be caused by a shortage of oxygen to the brain, which may occur due to a traumatic birth or difficulties after delivery. Because the blood arteries in a premature baby's brain are fragile and readily ruptured, bleeding might ensue. Also, IVH is very common in babies with respiratory issues or other preterm concerns [15].

Clinical presentation and prognosis

When clots distend the ventricular system, compress the nearby brain, or restrict cerebrospinal fluid (CSF) flow, hydrocephalus and high intracranial pressure result (ICP) [2]. Common symptoms seen in IVH include apnea, bradycardia, pale or blue skin coloring, seizures, and anemia [15]. Symptoms of ICH usually emerge suddenly, such as headache, weakness, disorientation, and paralysis, often on one side of the body. Blood builds up in the brain, putting pressure on it and interfering with its oxygen supply. This can quickly harm the brain and nerves. The significance of IVH as a clinical factor is linked to its negative outcomes such as coma, death, and long-term functional disability.

To clarify, blood in the VS contributes to morbidity in various ways. First, damage to the reticular activating system and thalamus during the acute phase of hemorrhage expansion causes a decreased level of consciousness. As a result, the coma appears to be prolonged with both a larger volume of blood in the ventricles and a more prolonged exposure [16,17]. Second, ventricular blood clots blocking CSF conduits cause acute obstructive hydrocephalus, an immediately life-threatening condition limiting cerebral perfusion and potentially contributing to mass effect and resultant cerebral edema. Third, blood degradation products become embedded in the arachnoid granulations and may cause permanent occlusion and scarring, inhibiting CSF absorption and causing nonobstructive (communicating) hydrocephalus. Fourth, clotted blood may persist in the ventricles for several reasons related to coagulation and fibrinolytic pathways in the ventricular system [18].

After neonatal IVH, tissue plasminogen activator may be demonstrated, but fibrinolytic activity often is not seen for several weeks after IVH, and there appear to be insufficient concentrations of CSF plasminogen acutely [19]. The fibrinolytic state of the CSF may impair the rapid, immediate evolution of blood clot resolution in the ventricles. In the study by Naff et al. of the kinetics of intraventricular clot resolution in 17 patients with IVH, the percentage rate of clot resolution over the first ten days was 10.8% per day [20].

The inflammatory reaction caused by blood breakdown products in the ventricles also may affect long-term cognitive function independent of clot volume or mass effect, as demonstrated in experimental IVH [21,22]. In human IVH, significant cognitive deficits in SAH patients with IVH compared with those without IVH have been found on neuropsychological testing [23].

Diagnosis

Computerized tomography (CT) scanning is commonly used to diagnose intraventricular bleeding. Angiography, magnetic resonance imaging (MRI), or both are recommended if the underlying etiology of IVH is unknown, especially if thrombolytic

therapy is being explored. Any patient with main IVH and no apparent etiology and any patient younger than 45 who has an IVH should have further imaging done. Also, any patient with IVH who has no evident reason based on history and CT scans should have vascular imaging done, especially if they are 45 years old or younger than [24].

Although IVH numerical values help compare IVH volumes among patients, ventricular distention, concomitant parenchymal damage, and the underlying cause of bleeding are more closely connected to clinical status and prognosis [24].

All neonates born before 30 weeks should have a routine head ultrasound. The test is performed once between the ages of seven and fourteen days. A second standard ultrasound is recommended when the baby is supposed to arrive. When a baby's health abruptly deteriorates, especially in the first week of life, IVH should be explored. A head CT is advised if a term infant exhibits symptoms after a difficult birth, a low blood count, or other evidence of bleeding difficulties [25], as shown in **Figure 1** and **Figure 2**.

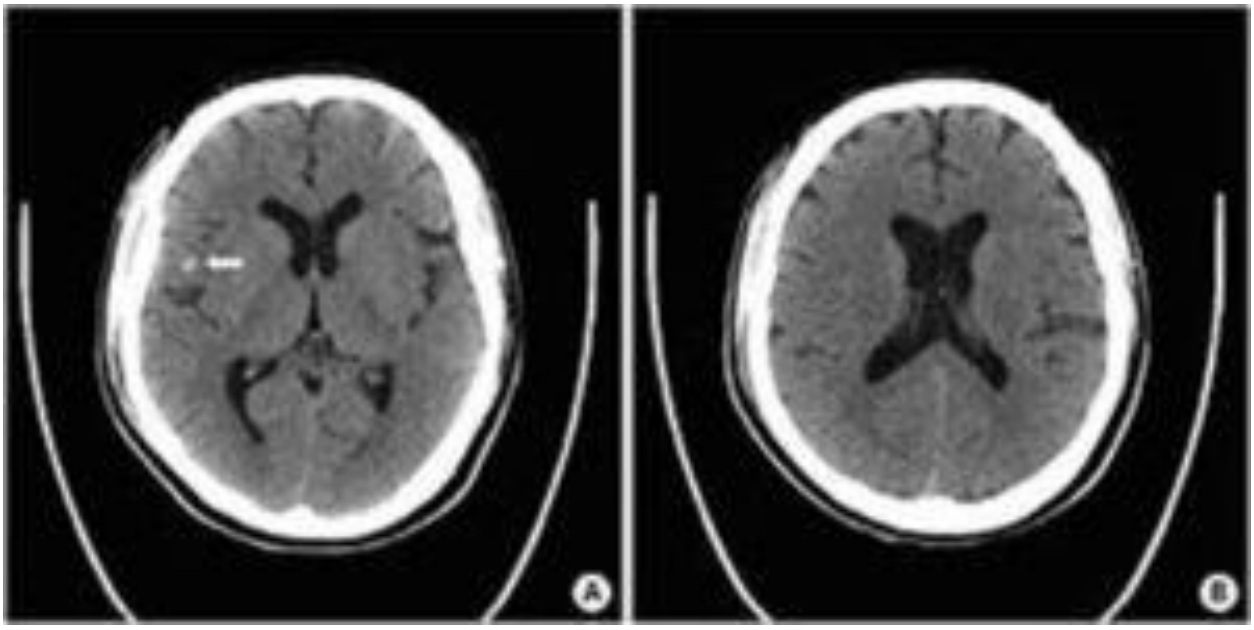


Figure 1: traumatic intraventricular hemorrhages in the frontal horn and body of bilateral lateral ventricles 40

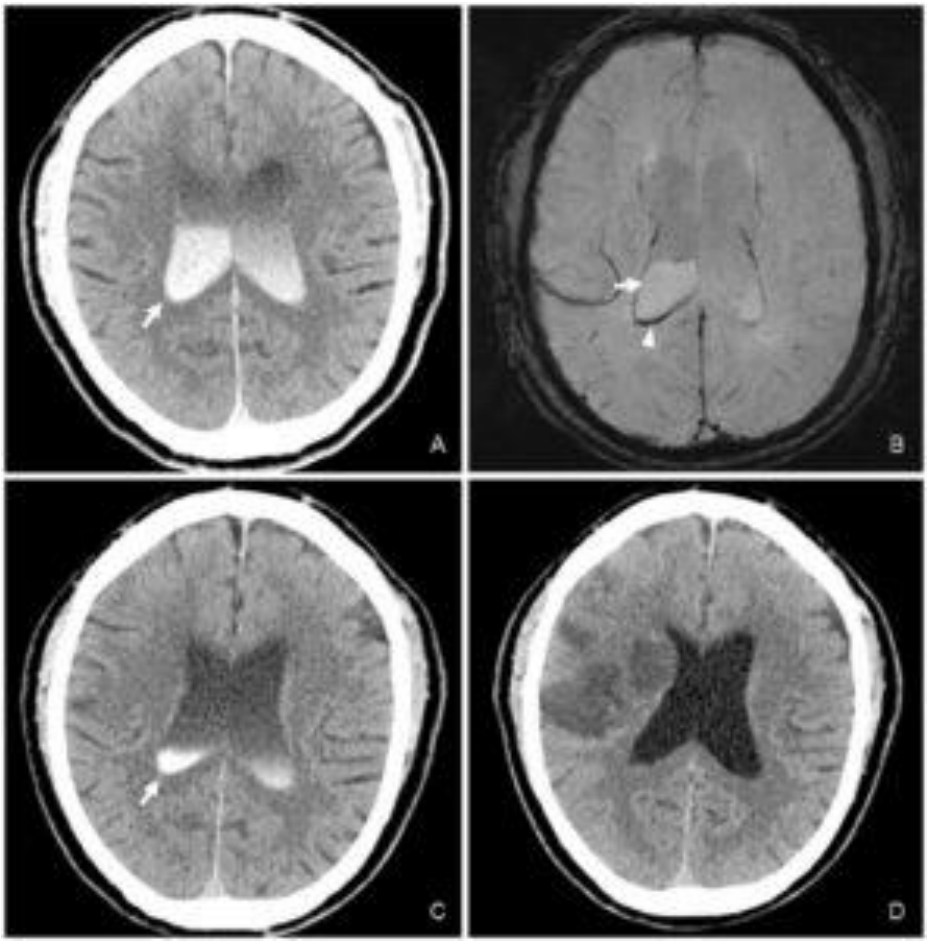


Figure 2: A Case of Contrast Leakage Mimicking Intraventricular Hemorrhage in a Patient with Intravenous Thrombolysis 39.

IVH is a Severity Factor in ICH

Tuhrim et al. initially confirmed IVH as an independent risk factor for 30-day mortality after ICH and developed a model in which IVH volume contributed significantly to outcome prediction together with GCS score [26]. Patients with IVH and ICH had a lower initial GCS score and larger ICH volume. Other contributors to the outcome included the number of ventricles containing blood and blood in the fourth ventricle. Subsequent prospective studies have continued to define the presence of IVH as an independent risk factor for mortality and poor functional outcome [27,28]. In addition, the Tuhrim algorithm continues to perform better than any other outcome prediction algorithm when compared directly with independent data sets [29].

Recently, three large randomized controlled trials reconfirmed IVH as a severity factor. The Surgical Trial in ICH (STICH) enrolled 964 subjects to test the value of early surgery versus medical management. IVH occurred in 42% of STICH subjects (n=377); IVH with hydrocephalus occurred in 23% (n=208). Both were strongly associated with poor outcomes: 31% of patients without IVH and 15% with IVH had a good outcome

(P<0.00001) [30]. When IVH and hydrocephalus were combined, the percentage of patients with a good outcome fell to 11%. Similarly, in the phase 2b proof-of-concept study of recombinant activated factor VII (rFVIIa) for ICH (n=399), IVH occurred in 49% of subjects, in whom mRS scores were consistently worse; 80% of these subjects were vegetative or dead [31]. In the multicenter Factor Seven for Acute Hemorrhagic Stroke (FAST) trial, the presence of IVH again was associated with increased mortality [32].

Hypertensive Brain Hemorrhage and IVH

In one-third to one-half of patients, spontaneous hypertensive ICHs are linked to secondary IVH. Chronic arterial hypertension is the most significant risk factor for this arteriopathy, which usually affects the lenticulostriate and thalamoperforating arterioles; other risk factors include moderate to heavy alcohol consumption and anticoagulant medication. Thalamic, putaminal, or caudate hemorrhage that spreads into the lateral or third ventricles is the most common complication of IVH. IVH has been linked to more significant parenchymal hematomas, midline shift of brain structures, and poor clinical outcomes in this situation [33].

IVH of the newborn

Intraventricular discharge of the infant is seeping into the liquid-filled regions, or ventricles, encompassed by the brain. IVH of the newborn is most commonly found in preterm babies, and the smaller and more premature the baby is, the greater the risk of IVH. This is because the blood arteries in premature infants' brains have not yet fully matured and are extremely weak. IVH is uncommon at birth, and if it does occur, it usually happens within the first few days of life [34], as in **Figure 3** which shows ultrasound images of the four grades of intraventricular hemorrhage in the newborn.

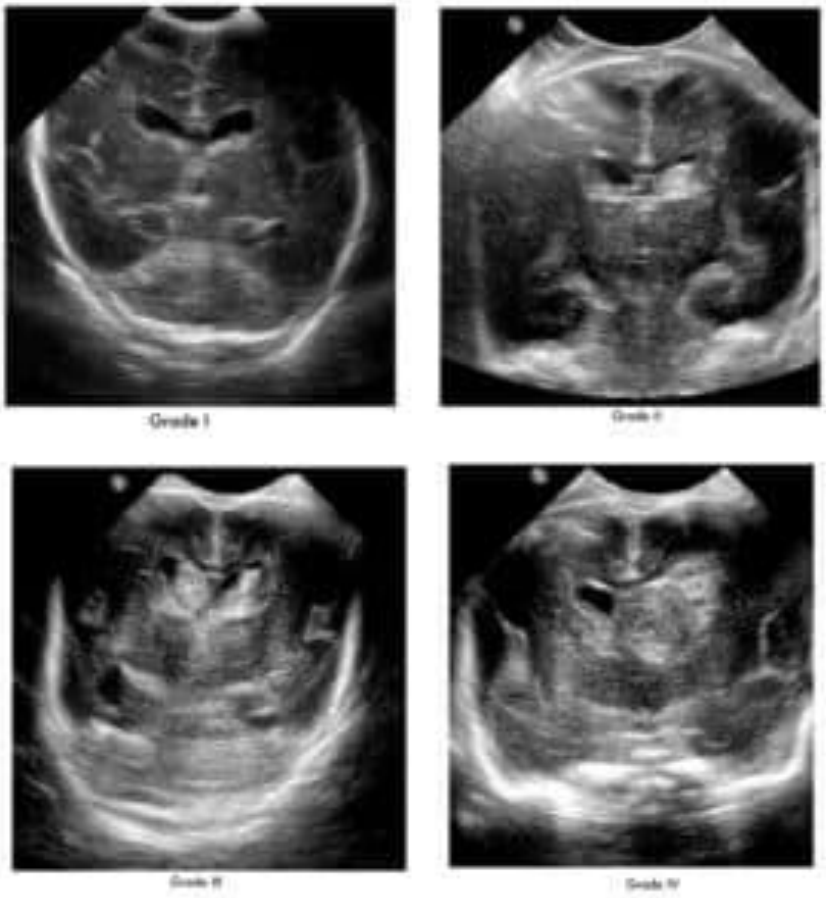


Figure 3: Germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) in the newborn

Germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) in the newborn.

Intraventricular hemorrhage (IVH) of newborns is more common in premature babies who have had physical stress, such as respiratory distress syndrome, pneumothorax, and high blood pressure [25]. IVH occurs in 45% of extremely premature neonates. 96% of IVH in neonates happens in the first four days. IVH is often described in four grades, depending on the amount of bleeding [34], as shown in **Table 1**.

	Grade 1	Grade 2	Grade 3	Grade 4
Site	bleeding occurs just in a small region of the ventricles	bleeding also occurs inside the ventricles	ventricles are expanded by blood	bleeding also occurs in the brain tissues around the ventricles.
Involvement	The germinal matrix in the subependymal Region	IVH without ventricular dilatation	IVH with ventricular dilatation	Parenchymal bleeding
Appearance	< 1 cm	blood makes a cast of the ventricle	Ventricular lining becomes echogenic, detecting ventriculitis	CSF fluid-filled cavity forms as an end result

Table 1: describes IVH severity grades depending on the amount of bleeding.

Management and Treatment

In animals, removing the clot reduces inflammation, edema, and cell death, restoring cerebrospinal fluid flow and lowering intracranial pressure [14]. Because systematic attempts to remove blood have not been done in extensive clinical studies on a broad scale, clinical knowledge about the benefits of intraventricular hemorrhage (IVH) removal in people is limited [14].

The CLEAR IVH trial treated intraventricular hemorrhage with a recombinant tissue plasminogen activator administered via a catheter. This catheter-based IVH treatment aligns with the theory that reducing intraventricular clot severity reduces disease severity by lowering mortality [35].

Lower rates of mortality have been routinely seen when a treatment strategy includes the use of an intraventricular catheter to keep ICP below normal limits and with the use of efforts to clear clots by administering low doses of thrombolytics [12].

External ventricular drainage (EVD) is the conventional treatment for substantial IVH (i.e., associated hydrocephalus). In patients with severe IVHs, intraventricular

fibrinolysis or thrombolysis (IVT) with an enzyme such as rt-PA delivered through an external drainage catheter appears to speed IVH clearance, keep catheter patency, and improve ICP management [36].

Following this were reports and case series of intraventricular fibrinolysis (IVF) in human patients, which included injections or infusions of urokinase or recombinant t-PA (rt-PA) through external ventricular drainage catheters for IVH caused by aneurysm and AVM rupture, chronic hypertension, ventricular catheter insertion, trauma, and germinal matrix hemorrhage in the newborn [21,37].

Permanent management methods currently used include VP shunt insertion, although it is associated with a high mortality rate among pediatrics. Endoscopic third ventriculostomy (ETV) is another technique used especially for patients with obstructive hydrocephalus, however, it is not considered highly successful[38].

Conclusion

Even though the kind, dose, and duration of fibrinolytic treatment varied, these exploratory investigations found that IVF increased IVH clearance and appeared to be safe. In a case series of primarily aneurysm patients, rt-PA clearance of IVH was also found to help control increased ICP, particularly in younger patients with limited intracranial compliance or those in poor neurologic condition due to extensive hemorrhage [38]. Organized, multicomponent intensive care has improved and become more widely available, including acute blood pressure control and support for impaired cardiorespiratory functions [14].

References

1. Bu, Y., Chen, M., Gao, T., Wang, X., Li, X., & Gao, F. (2016). Mechanisms of hydrocephalus after intraventricular hemorrhage in adults. *Stroke and Vascular Neurology*, *1*(1), 23. https://doi.org/10.1136/SVN-2015-000003
2. *Intraventricular Hemorrhage | Children's Hospital of Philadelphia*. (n.d.). Retrieved February 13, 2022, from https://www.chop.edu/conditions-diseases/intraventricular-hemorrhage
3. Guo, R., Ma, L., Shrestha, B. K., Yu, Z., Li, H., & You, C. (2016). A retrospective clinical study of 98 adult idiopathic primary intraventricular hemorrhage cases. *Medicine (United States)*, *95*(42). https://doi.org/10.1097/MD.0000000000005089
4. Martí-Fàbregas, J., Piles, S., Guardia, E., & Martí-Vilalta, J. L. (1999). Spontaneous primary intraventricular hemorrhage: clinical data, etiology, and outcome. *Journal of Neurology 1999 246:4*, *246*(4), 287–291. https://doi.org/10.1007/S004150050348
5. Arboix, A., García-Eroles, L., Vicens, A., Oliveres, M., & Massons, J. (2012). Spontaneous Primary Intraventricular Hemorrhage: Clinical Features and Early Outcome. *ISRN Neurology*, *2012*, 1–7. https://doi.org/10.5402/2012/498303
6. Padmanabhan, R., Stacey, R., Wimalaratna, S., & Kuker, W. (2014). Dural arteriovenous fistula causing primary intraventricular hemorrhage. *Http://Dx.Doi.Org/10.1259/Bjr/25797982*, *81*(962). https://doi.org/10.1259/BJR/25797982
7. Woo, D., Haverbusch, M., Sekar, P., Kissela, B., Khoury, J., Schneider, A., Kleindorfer, D., Szaflarski, J., Pancioli, A., Jauch, E., Moomaw, C., Sauerbeck, L., Gebel, J., & Broderick, J. (2004). Effect of untreated hypertension on hemorrhagic stroke. *Stroke*, *35*(7), 1703–1708. https://doi.org/10.1161/01.STR.0000130855.70683.c8
8. Brott, T., Thalinger, K., & Hertzberg, V. (1986). Hypertension as a risk factor for spontaneous intracerebral hemorrhage. *Stroke*, *17*(6), 1078–1083. https://doi.org/10.1161/01.STR.17.6.1078

9. Daverat, P., Castel, J. P., Dartigues, J. F., & Orgogozo, J. M. (1991). Death and functional outcome after spontaneous intracerebral hemorrhage. A prospective study of 166 cases using multivariate analysis. *Stroke*, *22*(1), 1–6. https://doi.org/10.1161/01.STR.22.1.1
10. Mohr, G., Ferguson, G., Khan, M., Malloy, D., Watts, R., Benoit, B., & Weir, B. (1983). Intraventricular hemorrhage from a ruptured aneurysm. Retrospective analysis of 91 cases. *Journal of Neurosurgery*, *58*(4), 482–487. https://doi.org/10.3171/JNS.1983.58.4.0482
11. Steiner, T., Diringer, M. N., Schneider, D., Mayer, S. A., Begtrup, K., Broderick, J., Skolnick, B. E., & Davis, S. M. (2006). Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage: risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor VII. *Neurosurgery*, *59*(4), 767–773. https://doi.org/10.1227/01.NEU.0000232837.34992.32
12. Coplin, W. M., Vinas, F. C., Agris, J. M., Buciuc, R., Michael, D. B., Diaz, F. G., & Muizelaar, J. P. (1998). A cohort study of the safety and feasibility of intraventricular urokinase for nonaneurysmal spontaneous intraventricular hemorrhage. *Stroke*, *29*(8), 1573–1579. https://doi.org/10.1161/01.STR.29.8.1573
13. Hallevi, H., Albright, K. C., Aronowski, J., Barreto, A. D., Martin-Schild, S., Khaja, A. M., Gonzales, N. R., Illoh, K., Noser, E. A., & Grotta, J. C. (2008). Intraventricular hemorrhage: Anatomic relationships and clinical implications. *Neurology*, *70*(11), 848–852. https://doi.org/10.1212/01.WNL.0000304930.47751.75
14. Hanley, D. F., Fisher, M., & Lees, K. (2009). Intraventricular hemorrhage severity factor and treatment target in spontaneous intracerebral hemorrhage. *Stroke*, *40*(4), 1533–1538. https://doi.org/10.1161/STROKEAHA.108.535419
15. *Intraventricular Hemorrhage Symptoms & Causes | Boston Children's Hospital*. (n.d.). Retrieved February 13, 2022, from https://www.childrenshospital.org/conditions-and-treatments/conditions/i/intraventricular-hemorrhage/symptoms-and-causes
16. W, S., RL, S., JP, M., MA, F., TK, T., PA, W., TR, P., & DB, H. (1992). Thalamic stroke. Presentation and prognosis of infarcts and hemorrhages. *Archives of Neurology*, *49*(7), 65–81. https://doi.org/10.1001/ARCHNEUR.1992.00530310045011
17. Pang, D., Sclabassi, R. J., & Horton, J. A. (1986). Lysis of intraventricular blood clot with urokinase in a canine model: Part 1. Canine intraventricular blood cast model. *Neurosurgery*, *19*(4), 540–546. https://doi.org/10.1227/00006123-198610000-00008
18. Whitelaw, A., Mowinckel, M. C., Fellman, V., & Abildgaard, U. (1996). Endogenous tissue plasminogen activator in neonatal cerebrospinal fluid. *European Journal of Pediatrics*, *155*(2), 117–119. https://doi.org/10.1007/BF02075763
19. Whitelaw, A. (1993). Endogenous fibrinolysis in neonatal cerebrospinal fluid. *European Journal of Pediatrics*, *152*(11), 928–930. https://doi.org/10.1007/BF01957533
20. Naff, N. J., Williams, M. A., Rigamonti, D., Keyl, P. M., & Hanley, D. F. (2001). Blood clot resolution in human cerebrospinal fluid: evidence of first-order kinetics. *Neurosurgery*, *49*(3), 614–621. https://doi.org/10.1097/00006123-200109000-00015
21. Pang, D., Sclabassi, R. J., & Horton, J. A. (1986). Lysis of intraventricular blood clot with urokinase in a canine model: Part 1. Canine intraventricular blood cast model. *Neurosurgery*, *19*(4), 540–546. https://doi.org/10.1227/00006123-198610000-00008
22. Pang, D., Sclabassi, R. J., & Horton, J. A. (1986). Lysis of intraventricular blood clot with urokinase in a canine model: Part 2. In vivo safety study of intraventricular urokinase. *Neurosurgery*, *19*(4), 547–552. https://doi.org/10.1227/00006123-198610000-00009
23. Hütter, B. O., Kreitschmann-Andermahr, I., & Gilsbach, J. M. (1998). Cognitive deficits in the acute stage after subarachnoid hemorrhage. *Neurosurgery*, *43*(5), 1054–1064. https://doi.org/10.1097/00006123-199811000-00030
24. Daou, B., Hasan, D., & Jabbour, P. (2017). Clinical Aspects of Intraventricular Hemorrhage. *Primer on Cerebrovascular Diseases: Second Edition*, 457–467. https://doi.org/10.1016/B978-0-12-803058-5.00093-X
25. *Intraventricular Hemorrhage | Johns Hopkins Medicine*. (n.d.). Retrieved February 13, 2022, from https://www.hopkinsmedicine.org/health/conditions-and-diseases/intraventricular-hemorrhage
26. Tuhrim, S., Dambrosia, J. M., Price, T. R., Mohr, J. P., Wolf, P. A., Hier, D. B., & Kase, C. S. (1991). Intracerebral hemorrhage: external validation and extension of a model for prediction of 30-day survival. *Annals of Neurology*, *29*(6), 658–663. https://doi.org/10.1002/ANA.410290614
27. Hemphill, J. C., Bonovich, D. C., Besmertis, L., Manley, G. T., & Johnston, S. C. (2001). The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*, *32*(4), 891–896. https://doi.org/10.1161/01.STR.32.4.891
28. Mayfrank, L., Hütter, B., Kohorst, Y., Kreitschmann-Andermahr, I., Rohde, V., Thron, A., & Gilsbach, J. (2001). Influence of intraventricular hemorrhage on outcome after rupture of intracranial aneurysm. *Neurosurgical Review*, *24*(4), 185–191. https://doi.org/10.1007/S101430100160
29. Ariesen, M. J., Algra, A., van der Worp, H. B., & Rinkel, G. J. E. (2005). Applicability and relevance of models that predict short-term outcome after intracerebral hemorrhage. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*(6), 839–844. https://doi.org/10.1136/JNNP.2004.048223
30. Mendelow, A. D., Gregson, B. A., Fernandes, H. M., Murray, G. D., Teasdale, G. M., Hope, D. T., Karimi, A., Shaw, M. D. M., & Barer, D. H. (2005). Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral hematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomized trial. *Lancet (London, England)*, *365*(9457), 387–397. https://doi.org/10.1016/S0140-6736(05)17826-X
31. SA, M., NC, B., K, B., J, B., S, D., MN, D., BE, S., & T, S. (2005). Recombinant activated factor VII for acute intracerebral hemorrhage. *The New England Journal of Medicine*, *352*(8), 280. https://doi.org/10.1056/NEJMOA042991

32. Mayer, S. A., Brun, N. C., Begtrup, K., Broderick, J., Davis, S., Diringer, M. N., Skolnick, B. E., & Steiner, T. (2008). Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *The New England Journal of Medicine*, *358*(20), 2127–2137. https://doi.org/10.1056/NEJMOA0707534
33. *ivf-pdf*. (n.d.).
34. *Intraventricular Hemorrhage | Children's Hospital of Philadelphia*. (n.d.). Retrieved February 13, 2022, from https://www.chop.edu/conditions-diseases/intraventricular-hemorrhage
35. Ziai, W. C., Tuhrim, S., Lane, K., Mcbee, N., Lees, K., Dawson, J., Butcher, K., Vespa, P., Wright, D. W., Keyl, P. M., Mendelow, A. D., Kase, C., Wijman, C., Lapointe, M., John, S., Thompson, R., Thompson, C., Mayo, S., Reilly, P., … Hanley, D. F. (2014). A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III). *International Journal of Stroke : Official Journal of the International Stroke Society*, *9*(4), 536–542. https://doi.org/10.1111/IJS.12097
36. Findlay, J. M. (n.d.). *71 Intraventricular Hemorrhage*.
37. Staykov, D., Kuramatsu, J. B., Bardutzky, J., Volbers, B., Gerner, S. T., Kloska, S. P., Doerfler, A., Schwab, S., & Huttner, H. B. (2017). Efficacy and safety of combined intraventricular fibrinolysis with lumbar drainage for prevention of permanent shunt dependency after intracerebral hemorrhage with severe ventricular involvement: A randomized trial and individual patient data meta-analysis. *Annals of Neurology*, *81*(1), 93–103. https://doi.org/10.1002/ANA.24834
38. *70 - Intraventricular Hemorrhage*. (n.d.).

Article Topic: Normal Pressure Hydrocephalus (NPH).

Author: Tasneem Khallad.

Editor: Philip Sweidan

Reviewer: Ethar Hazaimeh.

Keywords: iNPH, sNPH, Hakim's triad, CSF shunt.

Overview

Normal-pressure hydrocephalus (NPH) is a neurological disorder first described in 1965 and considered to be the first treatable type of dementia ever known. (1) It is a potentially reversible syndrome that presents with dilated cerebral ventricles in combination with a triad of symptoms, urinary incontinence, gait impairment, and dementia. Diagnosis is based on medical history, neurological examination, and brain imaging. CSF ventriculoperitoneal shunting is the most used treatment modality for NPH. (2)

Introduction

Hydrocephalus refers to the distension of the cerebral ventricles due to abnormal accumulation of cerebrospinal fluid (CSF) and is said to be of two types: communicating or obstructive. If the accumulation is because of the increase in intracranial CSF content, this is a communicating or non-obstructive hydrocephalus, where the flow of CSF from the ventricular system to the lumbar subarachnoid space is not blocked and communication between the ventricles is still maintained. On the other hand, it is considered noncommunicating or obstructive when the accumulation of CSF is due to a blockage in the pathway of CSF flow. (1) The subject of this article will be the communicating type of hydrocephalus.

More than 50 years ago, Raymond Adams and Salomón Hakim described 3 cases of adults who had chronic symptomatic hydrocephalus with normal CSF pressure and a triad of symptoms, commonly known as the Hakim triad, including urinary incontinence, dementia, and gait disturbances. (3) They also reported remarkable restoration of neurologic function after CSF shunting. (1)

Pathophysiology

NPH is divided into two different entities: idiopathic (iNPH) and secondary (sNPH). iNPH accounts for 50% of total cases, occurring most commonly in older adults due to unknown causes. In contrast, sNPH occurs in any age group because of an underlying disease, such as meningitis, subarachnoid hemorrhage, or cranial trauma. (4,5) A

common feature of both is that men and women are equally affected. (5) Also, the two carry a similar prognosis. (6–9) Whereas weeks to months are required for sNPH to develop after the onset of the initial incident, the preclinical stage for iNPH is gradual over years. (10) Although it is called “normal pressure” hydrocephalus, the CSF pressure is initially elevated, and once that raised pressure had caused ventricular distension, it drops again to normal levels while ventriculomegaly is maintained. (1)

Idiopathic NPH

It is not yet understood what mechanisms can lead to the increase in CSF volume in iNPH. The earliest theories referred to the increase in CSF volume to be a result of a decrease in CSF absorption and therefore, increased ventricular volume as a compensatory mechanism to maintain normal CSF flow. (11)

Many studies have shown an association between vascular risk factors and iNPH pathophysiology, where patients with iNPH had a history of hypertension, diabetes mellitus (DM), or white matter lesions (WML). (12–15)

WML is thought to cause iNPH through microvascular disturbances in the white matter. Remarkably, patients with iNPH who were found to be having reduced blood flow in the periventricular white matter have shown improved blood flow after CSF removal. (16–19) Also, postoperative reduction of WML has improved clinical symptoms in iNPH. (20,21)

However, DM and hypertension increase the risk of iNPH through different mechanisms than that of WML as they increase the risk of iNPH independent of WML. One of the assumptions said that hypertension could cause iNPH through a direct mechanical effect on ventricular size. (1)

Secondary NPH

In order to consider NPH as secondary, a well-established event should precede the onset of symptoms of NPH. (22) Subarachnoid hemorrhage (SAH) is considered the leading cause of sNPH, accounting for 45.6% of the total cases. 7-37% of those patients develop chronic hydrocephalus. (23) The mechanism by which SAH causes sNPH is through fibrosis and adhesion in the subarachnoid space and arachnoid granulations. (22) 6.2% of sNPH cases occur secondary to intracranial malignancies as tumors release proteinaceous products as well as cellular components into the CSF, increasing its viscosity and resulting in impaired reabsorption at the level of the arachnoid granulations. (24) NPH can also occur post-traumatically when there is an impairment in CSF dynamics (i.e., absorption, or flow). Post-traumatic NPH has a wide variation in incidence, ranging from 1% to 29%. (10) However, patients with sNPH may show other atypical symptoms like seizures, motor, and sensory deficits, and altered consciousness.

This is explained by severe neurological deficits caused by the primary disease masking the classical NPH manifestations. (25)

Clinical Features

NPH patients present with three cardinal symptoms that are not always seen in all patients and differ between presenting cases depending on their onset, severity, and progression. (26) These include:

Impairments of Gait and Balance

They are typically the earliest clinical manifestations to be noticed and considered the most responsive to CSF shunting. (27) Initially, patients will have difficulty walking on stairs and slopes and will struggle with transitional movements (standing to sitting or sitting to standing). (26) As the disease progresses, the gait becomes short-stepped and broad-based with reduced speed and step heights, therefore described as “magnetic” or “glued to the floor.” (28) Slow movement of upper extremities is also common. (29)

Urinary Incontinence

Bladder function will be disturbed because of detrusor overactivity. This disturbance presents in a gradual course, starting with increased urinary frequency, later, urge continence, and finally, permanent incontinence. (4,30) And it improves with CSF shunting in about 80% of patients if performed early. If performed in advanced stages, urinary incontinence improves in only 50-60% of cases. (31–33)

Cognitive Impairment and Dementia

The earliest cognitive symptoms in NPH patients are impaired attention and concentration, psychomotor slowing, executive and visuospatial dysfunction, and short-term memory impairment occurring mainly due to subcortical frontal dysfunction. (34) Later, bradyphrenia, reduced speech production, apathy, reduced drive, and indifference can occur. (8,9,35,36) Of note, patients with NPH do not show psychiatric abnormalities, therefore, signs of mood, personality, and behavior changes may exclude NPH from diagnosis. (37) CSF shunting improves cognitive decline, but this is less likely to happen if the patient has Alzheimer's or vascular dementia concomitantly. (37)

Differential Diagnosis

When Hakim’s triad is incomplete or its manifestations are atypical, the differential diagnosis may be steered toward another disease making the process of diagnosis more

difficult. Moreover, the complete triad can be caused by other diseases than NPH. As a result, complementary tests, including neuroimaging and CSF tap test should be done to aid in NPH diagnosis and management.

Table 1: Differential diagnosis of NPH (26,38).

Vascular Dementia
Stroke
Multi-infarct state
Cerebrovascular disease
Binswanger's disease
Leukoencephalopathy
Vertebrobasilar insufficiency
Cerebral autosomal dominant arteriopathy
Subcortical infarct
Neurodegenerative Disorder
Alzheimer's disease
Parkinson's disease
Huntington's disease
Lewy body disease
Frontotemporal dementia
Multisystem atrophy
Amyotrophic lateral sclerosis
Spongiform encephalopathy
Progressive supranuclear palsy
Corticobasal degeneration
Infectious Disease
Lyme
Syphilis
Human immunodeficiency virus
Progressive multifocal leukoencephalopathy

Other hydrocephalus disorders

Arrested hydrocephalus
Aqueductal stenosis
Long-standing overt ventriculomegaly syndrome
Noncommunicating - obstructive - hydrocephalus

Urological diseases

Urinary tract infection
Benign prostatic hyperplasia
Prostate or bladder cancer

Others

Depression
Epilepsy
Collagen vascular disorder
Traumatic brain injury
Spinal stenosis
Spinal cord tumor
Brain tumor
Organ failures
Hypothyroidism
Peripheral neuropathy
B_{12} deficiency
Chiari malformation
Carcinomatous meningitis
Wernicke's encephalopathy
Chronic subdural hematoma

Diagnosis

Diagnosis is done by the evaluation of clinical manifestations, neuroimaging, and CSF dynamics parameters combined. In the past, the presence of the complete triad was obligatory for the diagnosis and treatment of NPH, but nowadays the presence of two out of the three symptoms is enough to diagnose and start the treatment of NPH. (1,3,39) or even one symptom is enough. (9,35) This is explained by the fact that the

presence of the full triad represents an advanced stage and thus worsened prognosis if remained untreated. (9)

Ventriculomegaly is considered the only definitive diagnostic finding for NPH, (40) which is measured by Evans' index (the ratio between the maximal width of the frontal horns and the widest brain diameter). (Figure 1) Some findings tend to decrease the probability of NPH including cortical deficits, asymmetrical manifestations, progressive dementia in the absence of gait disturbances, and lack of progression of symptoms. (37)

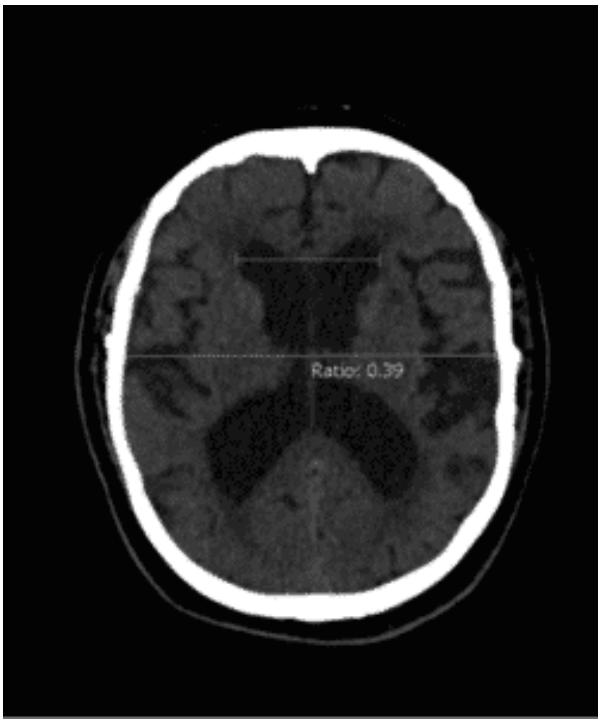


Figure 1: Evan's index. Case courtesy of Dr Yuranga Weerakkody (41).

International and Japanese guidelines were published on NPH for its diagnosis.

The International Guidelines include the following key imaging features (42):

1. Ventricular enlargement with Evans index that is more than 0.3.
2. No obstruction to CSF flows microscopically.
3. At least one of these supportive features:
   - Enlarged temporal horns of the lateral ventricles, are not entirely attributable to hippocampus atrophy.
   - Callosal angle of 40º or greater (Figure 2).
   - Periventricular signal changes on CT and MRI, not due to microvascular ischemic changes or demyelination, indicating altered brain water content.
   - Flow void on MRI in the Sylvian aqueduct or 4th

According to The Japanese Guidelines, periventricular changes are not necessary, and the following key imaging features are required for NPH diagnosis (43):

1. Enlarged Sylvian fissures and basal cistern.
2. Narrowing of the sulci and subarachnoid spaces over the high convexity and midline surface of the brain.

In NPH, the volume of CSF could also increase in the subarachnoid space along with the ventricular spaces, accumulating in the major fissures of the brain, and thus displacing the surrounding brain tissue. This leads to compressed adjacent sulci resulting in what is known as disproportionately enlarged subarachnoid space hydrocephalus (DESH), which is included in the Japanese guideline for NPH diagnosis. (Figure 3) Tight high convexity and dilated Sylvian fissures with ventriculomegaly are characteristics of DESH. (40) However, DESH is proven to be associated with a good response to CSF shunt. (39)

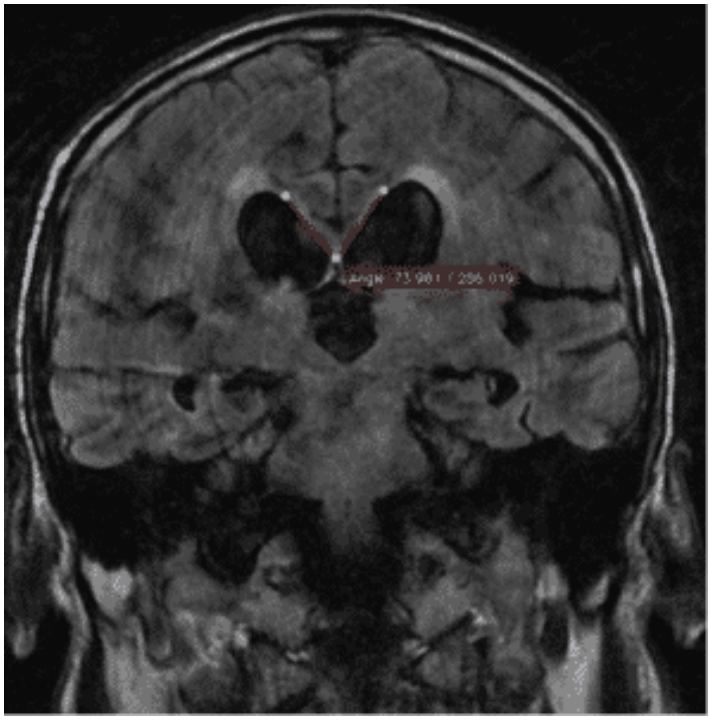


Figure 2: Callosal angle. Case courtesy of Dr. Andrei Tsoriev (45).

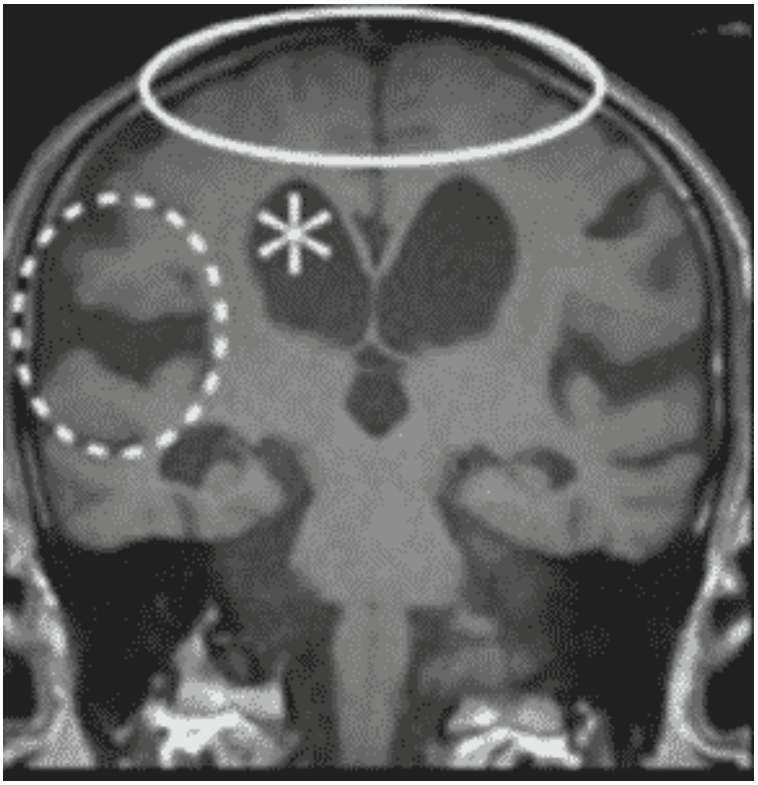


Figure 3: Disproportionately enlarged subarachnoid space hydrocephalus (DESH) showing ventriculomegaly (*), enlarged Sylvian fissure (dotted circle), and high convexity tightness (solid circle) (46).

Diagnostic Techniques

Complementary tests should be used along with clinical findings assessment to reach a better diagnosis and management. Diagnostic techniques include gait and urinary symptoms assessment, neurological examination, CSF dynamics assessment, laboratory tests, and imaging modalities.

Imaging Modalities

Neuroimaging is routinely used as the first diagnostic tool whenever NPH is suspected, looking for ventricular enlargement that is not due to atrophy, CSF collection outside the ventricles, and documenting the absence of macroscopic CSF flow obstruction, thus ruling out other pathologies. (9) Magnetic resonance imaging (MRI) is the method of choice, but computed tomography (CT) could be an acceptable alternative. (9)

Other neuroimaging methods can be used but are not considered as part of the routine diagnostic procedures, including positron emission tomography (PET) and single-photon emission computed tomography (SPECT) which show reduced cerebral blood flow and metabolism. (47) Also, diffusion tensor imaging (DTI) and resting-state

functional MRI, which are newer MRI techniques, allow the detection of NPH biomarkers. (48,49)

Shunt Effectiveness Evaluation

The international guidelines recommend testing CSF dynamics to evaluate whether improvement after shunting is possible. (50,51) The idea of these tests is to temporarily simulate the effect of shunting by draining a certain amount of CSF and examining the patient's gait and cognition before and after. If the patient has NPH, a significant response to CSF drainage happens and shunting is predicted to be helpful. CSF tap test (CSF-TT) is done by draining 40-50 ml of lumbar CSF. False-negative results are suspected due to its low sensitivity, which is about 26-61%. In these cases, surgery is not excluded, but a repeated CSF-TT (RTT) is performed by removing 30-40 ml CSF for three consecutive days.

Another alternative procedure is called external lumbar drainage (ELD) in which a minimum of 150 ml of CSF is drained daily for 3 to 5 days. ELD is superior to the others and is considered the most effective test for identifying shunt-responsive cases due to its high sensitivity (50-100%) and high positive predictive value (80-100%). However, ELD requires hospitalization, and complications are liable to develop such as nerve root inflammation, subdural hematoma, and meningitis. The third one is the most important and is seen in about 2-3% of patients. (15,42)

Shunt Patency Evaluation

Lumbar infusion test and radionuclide cisternography are done to evaluate CSF shunt malfunction. (52,53) Radionuclide cisternography is considered a simple, effective, and low-radiation dose method in which a small volume radioisotope is injected into the shunt reservoir, then images are obtained every minute for 20 minutes to create a time-activity curve. (54) Lumbar infusion test depends on measuring the CSF outflow resistance (R_{out}), a measure of the resistance to CSF resorption, as an indicator for shunt function. This is done by infusing ringer lactate through one spinal needle and recording CSF pressure through a second spinal needle at the same time. (55) If the shunt is obstructed, R_{out} value will be the same as before the surgery but if it is patent, the values after will be lower than before. (56)

Treatment

The first-line treatment for NPH is CSF shunting. It can be done by implanting a ventriculoperitoneal, ventriculopleural, or ventriculoatrial shunt where CSF is drained from the lateral ventricles to different body areas. (2) The standard procedure is done using a ventriculoperitoneal shunt. This intervention leads to improvement in

symptoms, being more significant in sNPH patients; up to 70% compared to 50% seen in iNPH individuals. (57) The best shunting results are achieved when the CSF tap test is positive along with MRI and CT showing the key features of NPH.

Conclusion

NPH faces a serious problem of underdiagnoses; up to 80% of patients remain unrecognized and thus, inappropriately treated. (37) Hence, it should always be taken into consideration as a differential diagnosis whenever its characteristics are present and treated as early as possible when diagnosed.

References

1. ADAMS RD, FISHER CM, HAKIM S, OJEMANN RG, SWEET WH. SYMPTOMATIC OCCULT HYDROCEPHALUS WITH "NORMAL" CEREBROSPINAL-FLUID PRESSURE.ATREATABLE SYNDROME. N Engl J Med. 1965 Jul;273:117–26.
2. Reddy GK, Bollam P, Caldito G. Long-Term Outcomes of Ventriculoperitoneal Shunt Surgery in Patients with Hydrocephalus. World Neurosurg [Internet]. 2014;81(2):404–10. Available from: https://www.sciencedirect.com/science/article/pii/S1878875013001952
3. Hakim S, Adams RD. The special clinical problem of symptomatic hydrocephalus with normal cerebrospinalfluid pressure. Observations on cerebrospinal fluid hydrodynamics. J Neurol Sci. 1965;2(4):307–27.
4. Hebb AO, Cusimano MD. Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis andoutcome. Neurosurgery. 2001 Nov;49(5):1166.
5. Williams MA, Malm J. Diagnosis and Treatment of Idiopathic Normal Pressure Hydrocephalus. Continuum (Minneap Minn). 2016 Apr;22(2 Dementia):579–99.
6. Meier U, Lemcke J, Neumann U. Predictors of outcome in patients with normal-pressure hydrocephalus. Acta Neurochir Suppl. 2006;96:352–7.
7. Kiefer M, Meier U, Eymann R. Does idiopathic normal pressure hydrocephalus always mean a poor prognosis? Acta Neurochir Suppl. 2010;106:101–6.
8. Tisell M, Hellström P, Ahl-Börjesson G, Barrows G, Blomsterwall E, Tullberg M, et al. Long-term outcome in 109 adult patients operated on for hydrocephalus. Br J Neurosurg. 2006 Aug;20(4):214–21.
9. Tsakanikas D, Relkin N. Normal pressure hydrocephalus. Semin Neurol. 2007 Feb;27(1):58–65.
10. Marmarou A, Foda MA, Bandoh K, Yoshihara M, Yamamoto T, Tsuji O, et al. Posttraumatic ventriculomegaly: hydrocephalus or atrophy? A new approach fordiagnosis using CSF dynamics. J Neurosurg. 1996 Dec;85(6):1026–35.
11. Graff-Radford NR, Jones DT. Normal Pressure Hydrocephalus. Continuum (Minneap Minn). 2019 Feb;25(1):165–86.
12. Eide PK, Pripp AH. Increased prevalence of cardiovascular disease in idiopathic normal pressurehydrocephalus patients compared to a population-based cohort from the HUNT3 survey. Fluids Barriers CNS. 2014;11:19.
13. Graff-Radford NR, Godersky JC. Idiopathic normal pressure hydrocephalus and systemic hypertension. Neurology. 1987 May;37(5):868–71.
14. Bradley WGJ, Whittemore AR, Watanabe AS, Davis SJ, Teresi LM, Homyak M. Association of deep white matter infarction with chronic communicatinghydrocephalus: implications regarding the possible origin of normal-pressure hydrocephalus. AJNR Am J Neuroradiol. 1991;12(1):31–9.
15. Jaraj D, Agerskov S, Rabiei K, Marlow T, Jensen C, Guo X, et al. Vascular factors in suspected normal pressure hydrocephalus: A population-basedstudy. Neurology. 2016 Feb;86(7):592–9.
16. Momjian S, Owler BK, Czosnyka Z, Czosnyka M, Pena A, Pickard JD. Pattern of white matter regional cerebral blood flow and autoregulation in normalpressure hydrocephalus. Brain. 2004 May;127(Pt 5):965–72.
17. Hertel F, Walter C, Schmitt M, Mörsdorf M, Jammers W, Busch HP, et al. Is a combination of Tc-SPECT or perfusion weighted magnetic resonance imagingwith spinal tap test helpful in the diagnosis of normal pressure hydrocephalus? J Neurol Neurosurg Psychiatry. 2003 Apr;74(4):479–84.
18. Kimura M, Tanaka A, Yoshinaga S. Significance of periventricular hemodynamics in normal pressure hydrocephalus. Neurosurgery. 1992 May;30(5):701–5.
19. Ziegelitz D, Starck G, Kristiansen D, Jakobsson M, Hultenmo M, Mikkelsen IK, et al. Cerebral perfusion measured by dynamic susceptibility contrast MRI is reduced inpatients with idiopathic normal pressure hydrocephalus. J Magn Reson Imaging. 2014 Jun;39(6):1533–42.
20. Tullberg M, Hultin L, Ekholm S, Månsson J-E, Fredman P, Wikkelsø C. White matter changes in normal pressure hydrocephalus and Binswanger disease:specificity, predictive value and correlations to axonal degeneration and demyelination. Acta Neurol Scand. 2002 Jun;105(6):417–26.

21. Tullberg M, Jensen C, Ekholm S, Wikkelsø C. Normal pressure hydrocephalus: vascular white matter changes on MR images mustnot exclude patients from shunt surgery. AJNR Am J Neuroradiol. 2001 Oct;22(9):1665–73.
22. Daou B, Klinge P, Tjoumakaris S, Rosenwasser RH, Jabbour P. Revisiting secondary normal pressure hydrocephalus: does it exist? A review. Neurosurg Focus. 2016 Sep;41(3):E6.
23. Chen Z, Song W, Du J, Li G, Yang Y, Ling F. Rehabilitation of Patients with Chronic Normal-Pressure Hydrocephalus After Aneurysmal Subarachnoid Hemorrhage Benefits from Ventriculoperitoneal Shunt. Top Stroke Rehabil [Internet]. 2009 Sep 1;16(5):330–8. Available from: https://doi.org/10.1310/tsr1605-330
24. Pirouzmand F, Tator CH, Rutka J. Management of hydrocephalus associated with vestibular schwannoma and othercerebellopontine angle tumors. Neurosurgery. 2001 Jun;48(6):1244–6.
25. Wang C, Du H, Yin L, He M, Zhang G, Tian Y, et al. Analysis of related factors affecting prognosis of shunt surgery in patients withsecondary normal pressure hydrocephalus. Chinese J Traumatol = Zhonghua chuang shang za zhi. 2013;16(4):221–4.
26. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic normal-pressure hydrocephalus. Neurosurgery. 2005 Sep;57(3 Suppl):S4-16; discussion ii-v.
27. Pujari S, Kharkar S, Metellus P, Shuck J, Williams MA, Rigamonti D. Normal pressure hydrocephalus: long-term outcome after shunt surgery. J Neurol Neurosurg Psychiatry. 2008 Nov;79(11):1282–6.
28. Ghosh S, Lippa C. Diagnosis and prognosis in idiopathic normal pressure hydrocephalus. Am J Alzheimers Dis Other Demen. 2014 Nov;29(7):583–9.
29. Nowak DA, Topka HR. Broadening a classic clinical triad: The hypokinetic motor disorder of normalpressure hydrocephalus also affects the hand. Exp Neurol. 2006 Mar;198(1):81–7.
30. Sakakibara R, Kanda T, Sekido T, Uchiyama T, Awa Y, Ito T, et al. Mechanism of bladder dysfunction in idiopathic normal pressure hydrocephalus. Neurourol Urodyn. 2008;27(6):507–10.
31. Eide PK, Sorteberg W. Changes in intracranial pulse pressure amplitudes after shunt implantation andadjustment of shunt valve opening pressure in normal pressure hydrocephalus. Acta Neurochir (Wien). 2008 Nov;150(11):1141–7; discussion 1147.
32. Siraj S. An overview of normal pressure hydrocephalus and its importance: how much do wereally know? J Am Med Dir Assoc. 2011 Jan;12(1):19–21.
33. Gallia GL, Rigamonti D, Williams MA. The diagnosis and treatment of idiopathic normal pressure hydrocephalus. Nat Clin Pract Neurol. 2006 Jul;2(7):375–81.
34. Iddon JL, Pickard JD, Cross JJ, Griffiths PD, Czosnyka M, Sahakian BJ. Specific patterns of cognitive impairment in patients with idiopathic normalpressure hydrocephalus and Alzheimer's disease: a pilot study. J Neurol Neurosurg Psychiatry. 1999 Dec;67(6):723–32.
35. Shprecher D, Schwalb J, Kurlan R. Normal pressure hydrocephalus: diagnosis and treatment. Curr Neurol Neurosci Rep. 2008 Sep;8(5):371–6.
36. Petrella G, Czosnyka M, Keong N, Pickard JD, Czosnyka Z. How does CSF dynamics change after shunting? Acta Neurol Scand. 2008 Sep;118(3):182–8.
37. Kiefer M, Unterberg A. The differential diagnosis and treatment of normal-pressure hydrocephalus. Dtsch Arztebl Int. 2012 Jan;109(1–2):15–25; quiz 26.
38. Adult Hydrocephalus [Internet]. Cambridge: Cambridge University Press; 2014. Available from: https://www.cambridge.org/core/books/adult-hydrocephalus/D58D0902A3CC3DA86ED17157BBC9F9AA
39. Wallenstein MB, McKhann GM 2nd. Salomón Hakim and the discovery of normal-pressure hydrocephalus. Neurosurgery. 2010 Jul;67(1):155–9; discussion 159.
40. Oliveira LM, Nitrini R, Román GC. Normal-pressure hydrocephalus: A critical review. Dement Neuropsychol. 2019;13(2):133–43.
41. Radiopedia. Evans' index.
42. Damasceno BP. Neuroimaging in normal pressure hydrocephalus. Dement Neuropsychol. 2015;9(4):350–5.
43. Mori E, Ishikawa M, Kato T, Kazui H, Miyake H, Miyajima M, et al. Guidelines for management of idiopathic normal pressure hydrocephalus: secondedition. Neurol Med Chir (Tokyo). 2012;52(11):775–809.
44. Hashimoto M, Ishikawa M, Mori E, Kuwana N, (SINPHONI) T study of I on neurological improvement. Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res [Internet]. 2010;7(1):18. Available from: https://doi.org/10.1186/1743-8454-7-18
45. Radiopaedia. Callosal Angle [Internet]. Available from: https://radiopaedia.org/cases/34294?lang=us
46. Ishikawa M, Oowaki H, Takezawa M, Takenaka T, Yamada S, Yamamoto K, et al. Disproportionately Enlarged Subarachnoid Space Hydrocephalus in IdiopathicNormal-Pressure Hydrocephalus and Its Implication in Pathogenesis. Acta Neurochir Suppl. 2016;122:287–90.
47. Calcagni ML, Taralli S, Mangiola A, Indovina L, Lavalle M, De Bonis P, et al. Regional cerebral metabolic rate of glucose evaluation and clinical assessment inpatients with idiopathic normal-pressure hydrocephalus before and after ventricular shunt placement: a prospective analysis. Clin Nucl Med. 2013 Jun;38(6):426–31.
48. Hoza D, Vlasák A, Hořínek D, Sameš M, Alfieri A. DTI-MRI biomarkers in the search for normal pressure hydrocephalus aetiology: areview. Neurosurg Rev. 2015 Apr;38(2):239–44; discussion 244.
49. Khoo HM, Kishima H, Tani N, Oshino S, Maruo T, Hosomi K, et al. Default mode network connectivity in patients with idiopathic normal pressurehydrocephalus. J Neurosurg. 2016 Feb;124(2):350–8.
50. Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G, Gloss D. Practice guideline: Idiopathic normal pressure hydrocephalus: Response toshunting and predictors of response: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2015 Dec;85(23):2063–71.

51. Bergsneider M, Black PM, Klinge P, Marmarou A, Relkin N. Surgical management of idiopathic normal-pressure hydrocephalus. Neurosurgery. 2005 Sep;57(3 Suppl):S29-39; discussion ii-v.
52. Kharkar S, Shuck J, Kapoor S, Batra S, Williams MA, Rigamonti D. Radionuclide shunt patency study for evaluation of suspected ventriculoperitonealshunt malfunction in adults with normal pressure hydrocephalus. Neurosurgery. 2009 May;64(5):908–9.
53. Eklund A, Lundkvist B, Koskinen L-OD, Malm J. Infusion technique can be used to distinguish between dysfunction of ahydrocephalus shunt system and a progressive dementia. Med Biol Eng Comput. 2004 Sep;42(5):644–9.
54. Chiewvit S, Nuntaaree S, Kanchaanapiboon P, Chiewvit P. Assessment lumboperitoneal or ventriculoperitoneal shunt patency by radionuclidetechnique: a review experience cases. World J Nucl Med. 2014 May;13(2):75–84.
55. Eklund A, Smielewski P, Chambers I, Alperin N, Malm J, Czosnyka M, et al. Assessment of cerebrospinal fluid outflow resistance. Med Biol Eng Comput. 2007 Aug;45(8):719–35.
56. Malm J, Lundkvist B, Eklund A, Koskinen L-OD, Kristensen B. CSF outflow resistance as predictor of shunt function. A long-term study. Acta Neurol Scand. 2004 Sep;110(3):154–60.
57. Vanneste JA. Diagnosis and management of normal-pressure hydrocephalus. J Neurol. 2000 Jan;247(1):5–14.

Title of article: Spondylodiscitis.

Authors: Rand Al-Qaseer, Qusay Fadel.

Editor: Menna Mohamed Marwan.

Reviewer: Adam M. Abdallah.

Keywords: vertebral osteomyelitis, spondylitis, Pyogenic infections, discitis, Spondylodiscitis

Overview

Spondylodiscitis is an infectious inflammation of the vertebrae, discs, and surrounding structures. Bacteria or non-bacterial pathogens can cause it; in the former case, a wide range of pathogens are thought to cause spondylodiscitis. The largest spondylodiscitis cases are caused by Staphylococcus aureus, Escherichia coli, brucellosis, and mycobacterium tuberculosis. [43,13,4].

Spondylodiscitis affects seven out of every million people, with men three times more likely than women to be affected. Due to vascular architecture, the pure discitis described previously does not occur in children. Because the intervertebral disc has a network of vascular anastomoses, the infection begins in the disc and subsequently travels to the vertebral endplates.

Even though spondylodiscitis is a rare disease, the widespread use of immune-suppressing medicines and an aging population have increased infection cases [4,44]. However, the disease is most common in those in the sixth decade of life, it can affect anyone at any age. Diabetes mellitus, malnutrition, conditions that cause weight loss, steroid administration, rheumatic diseases, and spinal surgery are also risk factors in addition to age. Often, the actual source of infection is no longer detectable at diagnosis [45,46,47]. Also, secondary spinal infections and soft-tissue consequences should be considered in managing COVID-19 patients with neuromuscular symptoms, and a thorough neurological and neurosurgical evaluation is required to rule out spinal involvement [48]. Finally, the best therapeutic approach is not precisely defined—contrary to adult SD, for which treatment guidelines have been issued, no guidelines exist for pediatric patients. Optimal antimicrobial treatment is still under debate in terms of molecule and duration. Several data suggest that a long-term therapeutic course is usually required to control symptoms and normalize laboratory tests [50].

In radiology, vertebral involvement is not visualized; however, MRI shows changes in intensity in sequences T1 and T2 at vertebral discs, L3-L4 with involvement of the respective vertebral disc.

Etiology and pathogenesis:

Spondylodiscitis can be caused by various bacteria and fungi, which must be considered when diagnosing and treating patients. The main causative organisms are staphylococci [4] [19] [21]. Also, as mycobacterium tuberculosis [19] [9]. Staphylococcus causes pyogenic spondylodiscitis, which has become more common in recent years due to the increased life expectancy of older individuals with chronic physical disabilities. This type of spondylodiscitis represents 2-5% of all cases of osteomyelitis and is more prevalent in patients older than 50 years [21]. Tuberculous spondylodiscitis is another common type of spondylodiscitis. In this situation, the causal bacteria is Mycobacterium tuberculosis. Patients between the ages of 30 and 40 are most likely to develop this type of spondylodiscitis [19].

The classic route of infection is hematogenous bacterial colonization [22]. Pathogen-associated spondylodiscitis usually starts in the vertebral endplates and extends to the adjacent intervertebral disc in adults. On the other hand, the infection frequently affects the intervertebral disc first in adolescents because of the blood flow. Irrespective of age, the infection can spread paravertebrally, subdurally, and epidurally [25]. Subdural abscesses and spread to the central nervous system, such as meningitis, myelitis, or encephalitis, are added problems in addition to paravertebral or epidural abscesses.

Spondylodiscitis is primarily caused by bacterial pathogens, mostly in the context of urogenital, dermal, or respiratory infections. The most common pathogens are *Staphylococcus aureus* (up to 60%), followed by enterobacteria (up to 30%), and more rarely e.g., B. *Staphylococcus epidermidis, Haemophilus influenza*, or streptococci species [22]. Mycobacteria, fungi, and parasitoses play a much lower influence, with Mycobacterium tuberculosis being the most common. Candidiasis, aspergillosis, coccidioidomycosis, blastomycosis, cryptococcosis, and atrichosporosissis are all fungal infections [26].

Cervical signs are usually linked to intravenous drug misuse, while thoracic manifestations are more commonly linked to tuberculosis. Tuberculous spondylodiscitis or spondylitis often affects more than two segments and, like a fungal infection, can affect the dorsal parts of the vertebrae, such as the posterior parts of the arch or vertebral processes [25].

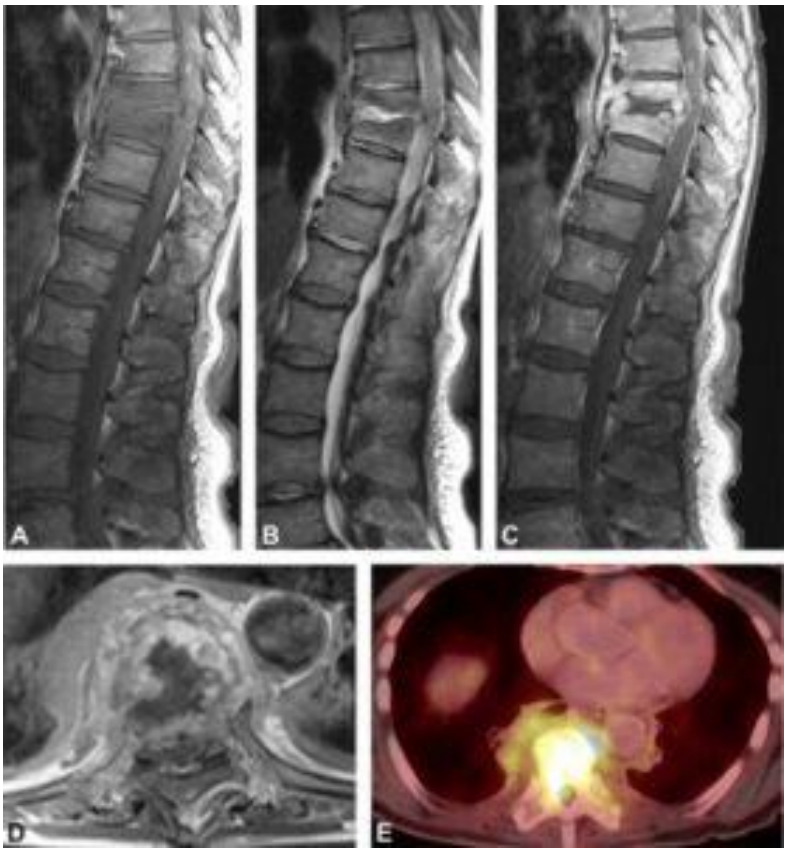


Figure. Spondylodiscitis. From: Handbook of Clinical Neurology, 2021

Clinical presentation and complications:

Back pain is the most common presenting symptom (86%). Fever can be present in up to 60% of patients; in a systematic review of 14 studies, however, fever was often absent

at presentation. The lack of fever in the setting of back pain can mask the possibility of infection, delaying the diagnosis from 11 to 59 days [26]. Manifestations of neurologic deficits at presentation, such as radiculopathy, limb weakness, or paralysis, can aid in the prompt and accurate diagnosis of spondylodiscitis but are present in only about 34% of cases [27]. The symptoms of spondylodiscitis are very non-specific. Back or neck pain is common but may be absent in up to 15% of cases. Also typical are constant pains that worsen at night and differential diagnosis of osteoid osteoma. Radicular radiating pain is not uncommon and can lead to misdiagnosis and unnecessary interventions. Fever occurs in only about half of patients. Neurological deficits are present in about one-third of the cases and are more likely to be associated with a delayed diagnosis, epidural abscesses, manifestations in the area of the cervical spine, or tuberculous spondylodiscitis or spondylitis [28].

- Back or neck pain [4] [21].
- Constant pain, worse at night [13] [19] [21].
- Radicular pain radiating to the chest or abdomen.
- Fever (less common in patients with tuberculous spondylodiscitis, 1/2 of the cases). [4] [21] [21]
- Spinal deformities, predominantly kyphosis and gibbus formation (commoner in tuberculous spondylodiscitis). [29]
- Epidural abscess formation (**cervical:** severe cervical rigidity, dysphagia, or torticollis; **thoracic**: symptoms are localized at the legs; **lumbar:** spread through the ischiatic foramen and involve gluteus muscles; **lumbosacral:** cauda equine syndrome)
- Weight loss (when the delay in diagnosis is long) [21].
- Compared with adults, children are less likely to have comorbidities, and neurological deficits are uncommon [4].

The intensity of the infection does not necessarily fit the degree of the discomfort symptoms. According to N. Bettini et al., when digital pressure was given to the spinal area, the pain radiated to the homolateral periumbilical area, causing an increase in pain symptoms. Also, patients suffered radicular irradiation in the sciatica or crural fascia area. Untreated chronic infections can progress to sinus formation. Also, secondary instability can occur towards kyphosis deformity with paraplegia or tetraplegia. Cervical spondylodiscitis may manifest with dysphagia or torticollis [21]. Spontaneous pyogenic spondylodiscitis usually spreads hematogenously from infections of the skin, subcutaneous tissues, and urinary tract [30].

Diagnosis:

Infectious spondylodiscitis is one of the diseases that is hard to be diagnosed in its early phases because it has general symptoms like fever, weakness, and weight loss. [13] but the quick diagnosis and treatment enhance patient health status and management

outcomes. [2] The diagnosis of discitis is based on a combination of clinical presentation, laboratory tests, and imaging. [17]

Laboratory and microbiological tests

Leukocytosis which is an elevation of white blood cell (WBC) count, can be one of the laboratory parameters but only exists in 36–61% of patients with Vertebral osteomyelitis. [14]

Erythrocyte Sedimentation Rate (ESR) is another parameter for this disease and it indicates that there is an inflammation in the body. High ESR is present in 76-80% of patients with spondylodiscitis. Also, is one of the most important diagnostic tests because ESR is mainly used while we are following the state of the patients after the administration of antibiotics and their response to the treatment. [14] The previous two parameters both commonly exist with epidural abscess formation which is one of the common side effects of this disease and usually these abscesses involve the thoracic region. [14] [5]

C-reactive protein (CRP) is seen to be elevated in 90%–98% of cases; this test is very beneficial because it reduces the time required for diagnosis. [2] CPR count has a sensitivity of 84% and a specificity of 71%. [13]

Moreover, it is important to know the causative agent of spondylodiscitis disease to use the proper antibiotic treatment. We can reach this essential information by using the culturing technique. [14] Firstly, we prepare at least two sets of blood cultures (aerobic/anaerobic) [13] then we analyze 3–5 tissue specimens, collected either during open surgery or by transpedicular biopsy with a 10-gauge Jamshidi needle. [15]

Spondylodiscitis tuberculosis is more commonly diagnosed by using the polymerase chain reaction (PCR) technique. [9]

Blood cultures are a significant step while treating the patients because spinal infection's main route is through the bloodstream. [14] Thus, culture is considered one of the simplest, most affordable, and most effective methods for confirming the presence of a causative microorganism. Scientifically, we can detect the pathogens of infectious discitis in 40-70% of patients who still do not receive any antibiotic therapy. [2] [13] In addition, in patients who have epidural abscesses their blood cultures have a greater pathogen detectability which is up to 82% [13]

One of the most common pathogens because of spinal infection is *Staphylococcus aureus, which can be detected using Species-specific PCR, which is* the best technique to target this microorganism. [9]

Imaging: X-Ray, CT scan, Radionuclide Imaging, MRI.

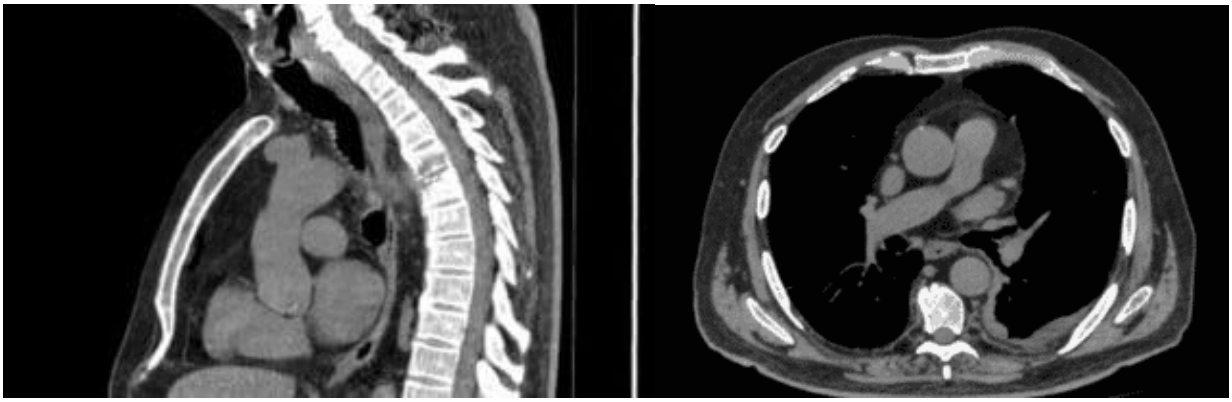
X-Ray

Radiographs are present in only one-third of patients [14]; it's useful as the first imaging modality for patients with low back pain. [18] but X-rays have limited benefit in examining this disease because of the delay in appearance of characteristic findings. [14] when the characteristics appear it will look like a severe lesion, including two adjacent vertebrae with the collapse of the vertebral bodies and the intervening disc is highly suggestive of spondylodiscitis.

Other characteristics include endplate irregularity, defects of the subchondral portion of the end plate, and hypertrophic/sclerotic bone formation. [14]

CT scan

CT-scan is commonly used to guide biopsy taking and this feature gives the CT-scan little benefit over other imaging modalities. [14] [9] CT-scan and MRI are effective and sensitive in patients with chronic diseases. Although, they are less sensitive when the patients have an acute disease. [14] This type of imaging is well known for its role in detecting, soft tissue abnormalities and destruction of vertebral bodies. [14] [18] CT-scan, compared to MRI has very little sensitivity in detecting epidural abscess formation. [14]



case courtesy of Dr. Mostafa El-Feky ◉ rID: 56584

Radionuclide Imaging

Bone scan is used when MRI cannot be addressed, especially in patients with artificial devices or pacemakers. [9] [14] In addition, radionuclide can be used when it's difficult to distinguish the infection from the deterioration changes in the MRI images, in this scenario we can use fluorine-18 fluorodeoxyglucose positron emission tomography

(FDG-PET). [9] Many researchers confirm that the sensitivity of this scan is 90–95%. unfortunately, it has poor specificity and cannot identify the abscesses. [14]

MRI

This technique is considered one of the best imaging we are diagnosing due to its high sensitivity and specificity in detecting spondylodiscitis in its early phases. [18] T1 image features include a lack of signal intensity and changes in the shape of vertebral bodies and intervertebral discs like a decrease in height. [14] Enhancement inT1 images are typical for an acute inflammatory process while in T2 images its main feature compared to T1 is the high signal intensity of the disk. In pyogenic and tuberculous spondylodiscitis was a low signal of the subcortical bone marrow on T1-weighted sagittal images, which had improved after Gd-DTPA administration and became intermediate or high on T2-weighted images. [14] [18] Recent studies approved that MRI is essential in showing the details of soft tissue and in revealing epidural abscesses. [14]

A comparative study was done on thirty-seven patients who were clinically suspected of having vertebral osteomyelitis had found that MRI with gadolinium enhancement is the optimal choice for image diagnosis of spondylodiscitis because of its high sensitivity and specificity, mainly because of its anatomical information. [9] [38]

Case courtesy of Dr. Mostafa El-Feky ◉ rID: 56584

http://img.medscapestatic.com/pi/meds/ckb/50/15350tn.jpg

Diskitis/osteomyelitis is seen on this T2-weighted MRI of the lumbar spine, demonstrating the destruction of the L3-4 disk space with the adjacent endplate and/or vertebral body. L3 and L4 vertebral bodies show increased T2 signals, indicating edema and/or infarction. Also shown is a retropulsion of debris, which compresses the thecal sac. The MRI will reveal air changes in the disc and possibly external involvement involving the bone or epidural regions.

Treatment and management

Spondylodiscitis is a life-threatening condition and is considered an emergency, which varies in its severity according to patients' health status and the pathogen that causes the disease [2].

The standard therapy for spondylodiscitis consists of antibiotics, fixing the affected intervertebral disc to protect and stabilize the spinal structure; spinal decompression surgery is performed to ensure that there is no pressure on the nerve to maintain the function and flexibility of the spine [3] [4].

Antibiotics approach

In most cases, intravenous antibiotics are given only if we detect the causative agent using blood culture techniques, except for patients who come to the emergency room suffering from neutropenia and sepsis, they should be given antibiotics for the most common pathogens such as Staphylococcus aureus and Escherichia coli for at least two to four weeks via parenteral route [2] [6] [7]. If the patient's condition improves and inflammation parameters start to return to normal values, we can start prescribing oral

antibiotics with high bioavailability such as fluoroquinolones, clindamycin, and linezolid [4].

In high-risk patients like if the spondylodiscitis was due to tuberculous infection, we use antibiotic therapy for at least 18-24 months [8] It should be noted that for tuberculous infection cases, we use a six-month combination of isoniazid and rifampicin with pyrazinamide and ethambutol for the first two months. [9]

Until now, the efficiency and role of the combined antibiotics are still unclear. However, according to the latest studies, the best treatment approach after surgeries is using a combination of quinolones and rifampicin, which has shown good outcomes. [9]

Surgery approach

The surgical treatment whether it is by using an endoscope or open surgery; is applied when we want to:

1) Eliminate the infected tissue.

2) Relieve pressure on the root, spinal cord, or dura mater.

3) Recover the infected column segment and restore spinal alignment.

4) Improving the spinal instability due to bone destruction. [8][9]

5) spinal canal abscesses

6) paravertebral abscess >2.5 cm [16]

Endoscopy is very popular now in treating spondylodiscitis and in taking a biopsy because it is more suitable due to its ability to discectomy and drainage, and its outcome for bacterial recovery is greater than CT-guided spinal biopsy.

The biopsies should be studied in different cultures like aerobic, anaerobic, fungal, brucellosis, and mycobacterial cultures. [9]

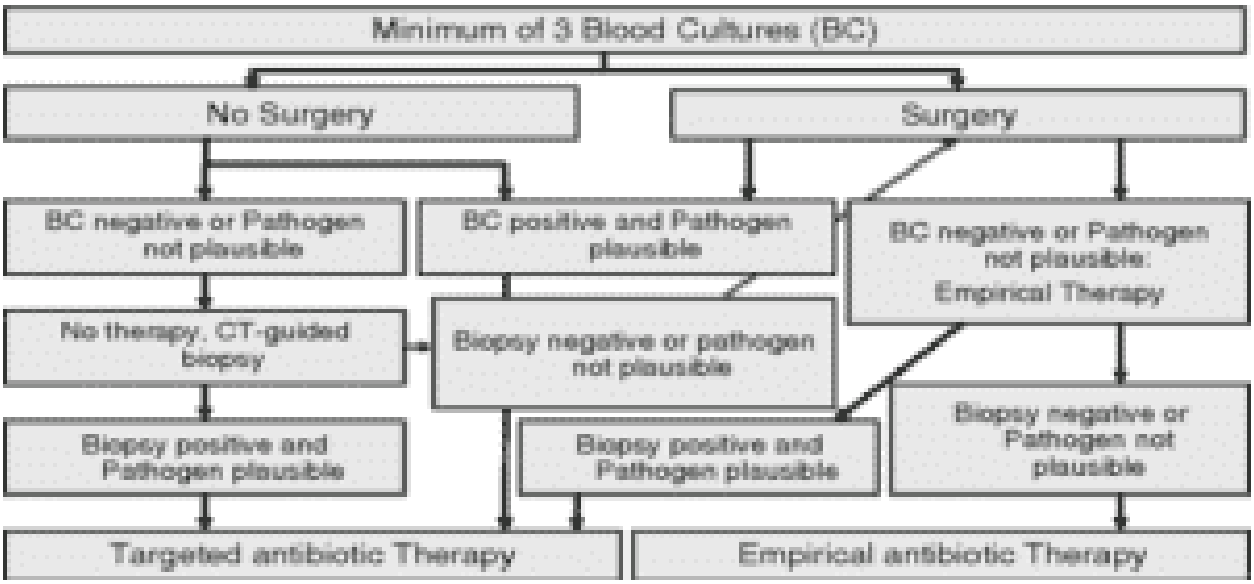
Generally, the surgical approach is usually chosen when the conventional treatment fails to treat the symptoms and relieve the pain. Despite this, the majority of Vertebral osteomyelitis patients don't undergo surgery. Only 50% of cases have an operation. [16]

One of the strange things in the neurosurgery world is that when spondylodiscitis is due to tuberculosis and the abscess and sequestered bone, or disk is so extensive the surgeon feels more comfortable and works confidently in both surgery approaches and

chemotherapy. The weird thing is that patients with active infection of tuberculosis show better outcomes after surgery than patients who were already healed. [9]

Prevention

Prevention for spondylodiscitis aims to eliminate infection, preserve or restore the spinal structure, stability, and neurological impairments, as well as provide pain relief. Conservative treatment constitutes the standard of care, and most patients are successfully treated with non-operative means [37]. Most cases, antibiotics combined with non-pharmacological treatments like immobilization and physical therapy are effective. Immobilization with bed rest or bracing decreases pain stabilizes the spine and prevents deformity [37].



Zarghooni, Kourosh, et al. “Treatment of spondylodiscitis.” International Orthopaedics 36 (2011): 405-411.

Risk factors

The infection of the vertebral bodies and the intervertebral disk space is relatively rare with an incidence between 1:100,000 and 1: 250,000 per year [5] [10]. Its rapidly increasing each year due to using intravenous drugs, spinal devices, and surgeries that all may lead to vertebral body infection as a side effect [17].

Discitis can be divided into two categories; the first one is granulomatous (tuberculosis and other mycobacterial pathogens), and the second one is pyogenic (most commonly *Staphylococcus aureus*). [17]

Even though the injuries that are induced by spondylodiscitis are very harmful, specifically when the motor segment is injured, leading to instability, and increasing the pressure on the neural elements. [5]

According to recent studies, spondylodiscitis incidence is higher with age and is diagnosed more often in males. [11] One of the retrospective studies identifies some risk factors that cause an elevation of the mortality rate due to spondylodiscitis, like cirrhosis, diabetes mellitus, hemodialysis use, malignancy, and concomitant infective endocarditis. [11]

One of the studies that were published on 13, Dec 2008, reported that this infectious disease should be in physicians' minds when they are dealing with any patient complaining about localized pain at any level of the spine, particularly patients who suffer from uncontrolled diabetes mellitus and they had fever and indicators of acute phase response. [12]

Septic discitis can be associated with intravenous drug abuse, catheter-associated infections, surgical procedures, heavy drinkers, and immunosuppressed patients. [12]

Prognosis

Spondylodiscitis had a poor prognosis before antibiotics became available. Even still, it also has the potential to be fatal. Current studies report that the meantime in hospital is from 30 to 57 days and that hospital mortality is from 2% to 17% [31, 32-34,35,36]. After spondylodiscitis treatment, either conservative or surgical, persistent symptoms are common.

Recent update

The incidence of spinal infection has increased over the years. Although the improvement in imaging techniques, spondylodiscitis is still challenging due to the insidious onset and misleading clinical aspects. [5]

A recent retrospective observational study found that endoscopic surgery is an effective and safe treatment for discitis in the thoracic and lumbar regions, as well as for cases with epidural or paraspinal abscesses. Open surgery is recommended as a secondary approach if endoscopic surgery is unsuccessful for a certain reason. [40]

A study that was done in 2020, explains the relationship between obesity and spondylodiscitis. It was found that obese people were more susceptible to postoperative side effects like liver failure and sepsis. Moreover, they had a severe course of this disease and show a special bacterial spectrum compared to normal-weight patients.

Despite this, the length of hospital stay, and mortality rate were similar between both groups (overweight people and normal weight). [41]

Another study published in 2021 showed that neonatal spondylodiscitis could lead to vertebral body deterioration with resulting angular kyphosis and the surgery must be done in early phases to avoid surgical risks and severe deformities. [42]

Furthermore, it has been found that spinal epidural abscesses (SEA) cases have increased during the covid-19 outbreak and they hypothesized that it may be related to asymptomatic bacterial colonization and associated with the injury in the vascular endothelium prompted by COVID-19. [49]

References

[1]Sur A, Tsang K, Brown M, Tzerakis N. Management of adult spontaneous spondylodiscitis and its rising incidence.[https://pubmed.ncbi.nlm.nih.gov/26274746/]
[2]Herren C, Jung N, Pishnamaz M, Breuninger M, Siewe J, Sobottke R. Spondylodiscitis: Diagnosis and Treatment Options [https://pubmed.ncbi.nlm.nih.gov/29321098/]
[3]Duarte RM, Vaccaro AR. Spinal infection: state of the art and management algorithm.[https://pubmed.ncbi.nlm.nih.gov/23756630/]
[4]Sobottke R, Seifert H, Fätkenheuer G, Schmidt M, Gossmann A, Eysel P. Current diagnosis and treatment of spondylodiscitis. [https://pubmed.ncbi.nlm.nih.gov/19629222/]
[5]Gentile L, Benazzo F, De Rosa F, Boriani S, Dallagiacoma G, Franceschetti G, Gaeta M, Cuzzocrea F. A systematic review: characteristics, complications and treatment of spondylodiscitis [https://pubmed.ncbi.nlm.nih.gov/30977878/]
[6]Sato K, Yamada K, Yokosuka K, Yoshida T, Goto M, Matsubara T, Iwahashi S, Shimazaki T, Nagata K, Shiba N; RESEARCH GROUP FOR SPINE AND SPINAL CORD DISORDERS (HONNEKAI). Pyogenic Spondylitis: Clinical Features, Diagnosis, and Treatment.[https://pubmed.ncbi.nlm.nih.gov/31406038/]
[7]Skaf GS, Domloj NT, Fehlings MG, Bouclaous CH, Sabbagh AS, Kanafani ZA, Kanj SS. Pyogenic spondylodiscitis: an overview.[https://pubmed.ncbi.nlm.nih.gov/20701886/]
[8]Palumbo P, Bruno F, Arrigoni F, Zappia M, Ierardi AM, Guglielmi G, Zugaro L, Carotti M, Di Cesare E, Splendiani A, Brunese L, Masciocchi C, Barile A. Diagnostic and interventional management of infective spine diseases. [https://pubmed.ncbi.nlm.nih.gov/32945287/]
[9]Guerado E, Cerván AM. Surgical treatment of spondylodiscitis. An update.[https://pubmed.ncbi.nlm.nih.gov/22215365/]
[10]Zarghooni K, Röllinghoff M, Sobottke R, Eysel P. Treatment of spondylodiscitis.[https://pubmed.ncbi.nlm.nih.gov/22143315/]
[11]Widdrington JD, Emmerson I, Cullinan M, Narayanan M, Klejnow E, Watson A, Ong ELC, Schmid ML, Price DA, Schwab U, Duncan CJA. Pyogenic Spondylodiscitis: Risk Factors for Adverse Clinical Outcome in Routine Clinical Practice.[https://pubmed.ncbi.nlm.nih.gov/30380776/]
[12]Kapsalaki E, Gatselis N, Stefos A, Makaritsis K, Vassiou A, Fezoulidis I, Dalekos GN. Spontaneous spondylodiscitis: presentation, risk factors, diagnosis, management, and outcome.[https://pubmed.ncbi.nlm.nih.gov/19071050/]
[13]Homagk L, Marmelstein D, Homagk N, Hofmann GO. SponDT (Spondylodiscitis Diagnosis and Treatment): spondylodiscitis scoring system.[https://pubmed.ncbi.nlm.nih.gov/30971277/]
[14]Amini MH, Salzman GA. Infectious spondylodiscitis: diagnosis and treatment.[https://pubmed.ncbi.nlm.nih.gov/23457758/]
[15]Stangenberg, M., Mende, K.C., Mohme, M. *et al.* Influence of microbiological diagnosis on the clinical course of spondylodiscitis. [https://link.springer.com/article/10.1007/s15010-021-01642-5]
[16] Tsantes AG, Papadopoulos DV, Vrioni G, Sioutis S, Sapkas G, Benzakour A, Benzakour T, Angelini A, Ruggieri P, Mavrogenis AF, World Association Against Infection In Orthopedics And Trauma W A I O T Study Group On Bone And Joint Infection Definitions. Spinal Infections: An Update.[https://pubmed.ncbi.nlm.nih.gov/32230730/]
[17]McNamara AL, Dickerson EC, Gomez-Hassan DM, Cinti SK, Srinivasan A. Yield of Image-Guided Needle Biopsy for Infectious Discitis: A Systematic Review and Meta-Analysis.[https://pubmed.ncbi.nlm.nih.gov/28882866/]
[18]Ramadani N, Dedushi K, Kabashi S, Mucaj S. Radiologic Diagnosis of Spondylodiscitis, Role of Magnetic Resonance.[https://pubmed.ncbi.nlm.nih.gov/28484299/]
[19]Coates JR. Intervertebral disk disease.[https://pubmed.ncbi.nlm.nih.gov/10680210/]
[20]Erhard R, Relative Effectiveness of an Extension Program and a Combined Program of Manipulation and Flexion and Extension Exercises in Patients With Acute Low Back Syndrome, Journal of The American Physical Therapy Association 1994. (level of evidence 1A)[https://pubmed.ncbi.nlm.nih.gov/7991650/]
[21]Titlic M, Josipovic-Jelic Z. Spondylodiscitis. Bratisl Lek Listy. 2008;109(8):345-7. PMID: 18837241.[https://pubmed.ncbi.nlm.nih.gov/18837241/]

[22]Ahlhelm FJ, Lieb JM, Ulmer S, Sprenger T, Stippich C, Kelm J. Entzündliche Erkrankungen der Wirbelsäule und des Myelons [Inflammatory diseases of the spinal column and the myelon].[https://pubmed.ncbi.nlm.nih.gov/21826567/]
[23]Völker A, Schubert S, Heyde CE. Spondylodiszitis im Kindes- und Jugendalter [Spondylodiscitis in children and adolescents].[https://pubmed.ncbi.nlm.nih.gov/27221307/]
[24]Caldera G, Lemus MAC, Cobar A, Gómez G, Rodríguez O. Fungal spondylodiscitis: review[Google Scholar].
[25]Gouliouris T, Aliyu SH, Brown NM. Spondylodiscitis: update on diagnosis and management.[https://pubmed.ncbi.nlm.nih.gov/20876624/]
[26]Völker A, Schubert S, Heyde CE. Spondylodiszitis im Kindes- und Jugendalter [Spondylodiscitis in children and adolescents].[https://pubmed.ncbi.nlm.nih.gov/27221307/]
[27]Zimmerli W. Clinical practice. Vertebral osteomyelitis.[https://pubmed.ncbi.nlm.nih.gov/20237348/]
[28]Rotzinger, R., Omidi, R., Gebhard, H. et al. Spondylodiszitis und epiduraler Abszess. Radiologe 61, 275–282 (2021).[https://doi.org/10.1007/s00117-021-00814-6]
[29]Amin RM, Andrade NS, Neuman BJ. Lumbar Disc Herniation.[https://pubmed.ncbi.nlm.nih.gov/28980275/]
[30]Sans N, Faruch M, Lapègue F, Ponsot A, Chiavassa H, Railhac JJ. Infections of the spinal column--spondylodiscitis. Diagn Interv Imaging.[https://pubmed.ncbi.nlm.nih.gov/22677300/]
[31]Frangen TM, Kälicke T, Gottwald M, Andereya S, Andress HJ, Russe OJ, Müller EJ, Muhr G, Schinkel C. Die operative Therapie der Spondylodiszitis. Eine Analyse von 78 Patienten [Surgical management of spondylodiscitis. An analysis of 78 cases].[https://pubmed.ncbi.nlm.nih.gov/16897028/]
[32]Schinkel C, Gottwald M, Andress HJ. Surgical treatment of spondylodiscitis. Surg Infect (Larchmt).[https://pubmed.ncbi.nlm.nih.gov/15012865/]
[33]Butler JS, Shelly MJ, Timlin M, Powderly WG, O'Byrne JM. Nontuberculous pyogenic spinal infection in adults: a 12-year experience from a tertiary referral center.[https://pubmed.ncbi.nlm.nih.gov/17077738/]
[34]Nolla JM, Ariza J, Gómez-Vaquero C, Fiter J, Bermejo J, Valverde J, Escofet DR, Gudiol F. Spontaneous pyogenic vertebral osteomyelitis in nondrug users.[https://pubmed.ncbi.nlm.nih.gov/11836660/]
[35]Linhardt O, Matussek J, Refior HJ, Krödel A. Long-term results of ventro-dorsal versus ventral instrumentation fusion in the treatment of spondylitis.[https://pubmed.ncbi.nlm.nih.gov/16708233/]
[36]Woertgen C, Rothoerl RD, Englert C, Neumann C. Pyogenic spinal infections and outcome according to the 36-item short-form health survey.[https://pubmed.ncbi.nlm.nih.gov/16776354/]
[37]Mavrogenis AF, Megaloikonomos PD, Igoumenou VG, Panagopoulos GN, Giannitsioti E, Papadopoulos A, Papagelopoulos PJ. Spondylodiscitis revisited.[https://pubmed.ncbi.nlm.nih.gov/29218230/]
[38]Modic MT, Feiglin DH, Piraino DW, Boumphrey F, Weinstein MA, Duchesneau PM, Rehm S. Vertebral osteomyelitis: assessment using MR. Radiology.[https://pubmed.ncbi.nlm.nih.gov/3875878/]
[39] Kucuk A, Karademir M, Tumturk A, Ulutabanca H, Ercal BD, Senol S, Menku A. Surgical Strategies for Spondylodiscitis due to Lumbar Disc Surgery.[https://pubmed.ncbi.nlm.nih.gov/27560533/]
[40]Lin CY, Chang CC, Chen YJ, Tsai CH, Tsou HK, Lin CS, Ho MW, Chen HT, Hsu HC. New Strategy for Minimally Invasive Endoscopic Surgery to Treat Infectious Spondylodiscitis in the Thoracolumbar Spine.[https://pubmed.ncbi.nlm.nih.gov/31151336/]
[41]Schoof B, Stangenberg M, Mende KC, Thiesen DM, Ntalos D, Dreimann M. Obesity in spontaneous spondylodiscitis: a relevant risk factor for severe disease courses.[https://pubmed.ncbi.nlm.nih.gov/33318604/]
[42]Romano S, Vittoria F, Cattaruzzi E, Barbi E, Carbone M. Infectious spondylodiscitis and kyphosis correction in an infant: a case report.[https://pubmed.ncbi.nlm.nih.gov/34225775/]
[43]Lehner B, Akbar M, Rehnitz C, Omlor GW, Dapunt U, Burckhardt I. Standards der mikrobiologische Diagnostik der Spondylodiszitis [Standards of microbiological diagnostics of spondylodiscitis].[https://pubmed.ncbi.nlm.nih.gov/22945398/]
[44]D'Agostino C, Scorzolini L, Massetti AP, Carnevalini M, d'Ettorre G, Venditti M, Vullo V, Orsi GB. A seven-year prospective study on spondylodiscitis: epidemiological and microbiological features.[https://pubmed.ncbi.nlm.nih.gov/20191397/]
[45]Akbar M, Lehner B, Doustdar S, Fürstenberg CH, Hemmer S, Bruckner T, Carstens C, Wiedenhöfer B. Pyogene Spondylodiszitis der Brust- und Lendenwirbelsäule : Eine neue Klassifikation zur Entscheidungsfindung bei der Wahl der operativen Therapie [Pyogenic spondylodiscitis of the thoracic and lumbar spine : a new classification and guide for surgical decision-making].[https://pubmed.ncbi.nlm.nih.gov/21451996/]
[46]Bettini N, Girardo M, Dema E, Cervellati S. Evaluation of conservative treatment of nonspecific spondylodiscitis.[https://pubmed.ncbi.nlm.nih.gov/19415345/]
[47]Vos FJ, Kullberg BJ, Sturm PD, Krabbe PF, van Dijk AP, Wanten GJ, Oyen WJ, Bleeker-Rovers CP. Metastatic infectious disease and clinical outcome in Staphylococcus aureus and Streptococcus species bacteremia.[https://pubmed.ncbi.nlm.nih.gov/22391470/]
[48]Erok, B., & Kıbıcı, K. (2021). COVID-19 Infection Manifesting with Lumbar Spondylodiscitis Complicating With Psoas Abscess without Pneumonia. *Indian Journal of Neurosurgery*.[https://doi.org/10.1055/s-0041-1741405]
[49]Talamonti G, Colistra D, Crisà F, Cenzato M, Giorgi P, D'Aliberti G. Spinal epidural abscess in COVID-19 patients.[https://pubmed.ncbi.nlm.nih.gov/32910251/]
[50]Ferri I, Ristori G, Lisi C, Galli L, Chiappini E. Characteristics, Management and Outcomes of Spondylodiscitis in Children: A Systematic Review. From: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7824456/

Article Topic: Skull fractures.

Author: Zaid Sayegh.

Editor: Philip Sweidan.

Reviewer: Ethar Hazaimeh.

Keywords: Skull fractures; Cranial fractures; head trauma; CSF leaks.

Overview

Over the past two decades, there has been a considerable increase in the number of head injuries which led to a spike in the number of skull fractures.[1] So in this article, we will discuss skull fractures which fall into four main categories: linear, depressed, diastatic, and basilar.[2] Cranial fractures are generally more common in children than in adults because children are more prone and vulnerable to head trauma due to their thinner and more pliable skulls which provide less protection to the brain.[3] Skull fractures can affect the brain either directly by inducing neurological or vascular damage or indirectly by the commonly associated intracranial hemorrhages that can compress the underlying brain tissue. [1,4]

Epidemiology

Skull fractures occur mostly between the ages of 1 and 20 years.[5] Basilar skull fractures are rare and occur in about 4% of all patients with severe head injuries. They are also approximately 20% of all skull fractures.[6] Meanwhile, depressed skull fractures are present in around 10% of patients with severe head injury and are more frequent in males than females (7:1 ratio). [1,7]

On the contrary, Linear and diastatic fractures have a higher rate of occurrence in females which could be explained by the difference in the skull architecture between both sexes where males have thicker and stronger skulls that can absorb impact force.[1,5] When it comes to linear fractures, they happen more often in children because of their thinner skulls and happen to account for three-fourths of all pediatric skull fractures.[3,8]

Etiology

Skull fractures are caused by trauma to the head which can be categorized by etiology into accidental and non-accidental injuries. Some of the most common accidental causes

of head injuries include a fall, motor vehicle accidents, sports-related injuries, pedestrian injuries, penetrating injuries like gunshot wounds, and direct blows to the head. [3,6] An example of a non-accidental head injury would be abuse which is more commonly seen in children and assault. [3,6] Depressed "ping-pong" fractures can sometimes occur in neonates due to injury at birth. [3]

Pathophysiology

The skull can be divided into two parts: the calvarium and the skull base. The former is composed of the frontal, parietal, occipital, and temporal bones while the latter is made up of the sphenoid, palatine, and maxillary bones as well as some parts of the temporal and occipital bones. [3] Now we will discuss each type of skull fracture:

Linear skull fractures usually occur in the temporal or parietal areas and involve no bone displacement. [3] While diastatic skull fractures occur when the fracture happens along one of the suture lines in the skull. [3]

Depressed skull fractures occur when part of the bony skull is displaced into the brain which increases the risk of underlying cerebral contusion or laceration. The most common sites of depression are the frontal area (53%) followed by the parietal region (28%). [9] These usually require surgical intervention. The damage caused by depressed skull fractures depends on the region of the brain affected by the displaced bone. [8,10]

Basilar fractures typically involve the temporal bones, the external auditory canal, and the tympanic membrane but may involve the occipital, sphenoid, ethmoid, and orbital plate of the frontal bone as well. Therefore, the location of the fracture can be utilized to predict the associated injuries. For instance, the most common kind of fractures, temporal fractures, are linked to carotid injury, injury to cranial nerves VII (Facial nerve) or VIII (vestibulocochlear nerve), and mastoid cerebrospinal fluid leak. Furthermore, Anterior skull base fractures are correlated with, nasal cerebrospinal fluid leak, orbital injury, and injury to cranial nerve I (olfactory nerve). Moreover, Central skull base fractures are linked to an injury to cranial nerves III, IV, V, or VI (oculomotor, trochlear, trigeminal, and abducens respectively) and carotid injury. Finally, Posterior skull-based fractures are related to a vertebral artery injury, cervical spine injury, and injury to the lower cranial nerves. The said kind of injuries tends to be critical and dreadful thus leaving the patients with hemiplegia or paraplegia.

Basilar skull fractures are usually seen with other central nervous systems (CNS) pathologies such as epidural hematoma due to the fragility of the temporal bone (which is the bone most involved in basilar skull fractures) and its close proximity to the middle meningeal artery.[6]

Clinical presentation

The clinical presentation of basilar skull fractures is determined by the degree of cranial nerve and brain injury. Patients may experience nausea, and vomiting, or show signs of mental status alterations. These clinical features can be used to predict a basilar skull fracture. For instance, one of the earliest features of a basilar skull fracture is the tympanic membrane appearing purple which happens due to the accumulation of blood behind it from a fracture that involves the petrous ridge of the temporal bone. This is clinically known as Hemotympanum. [6]

A clinical manifestation typically occurs immediately after injury where the cerebrospinal fluid (CSF) seeps out of the ears or nose (CSF rhinorrhea or otorrhea) and mixes with blood to form a “Halo” sign which looks like a double ring pattern consisting of the two mentioned fluids. However, the “Halo” sign is not specific to CSF leaks as it can appear when blood mixes with water, saline, or mucous. CSF leaks can also occur within days to weeks after the initial trauma. [3,6] Distinguishing between CSF and mucous discharge presents difficulty due to the presence of glucose in both of these fluids which makes it hard to discern between them but the high level of chloride compared to serum can indicate that the fluid is the CSF.[11].

Furthermore, about 1 to 3 days after the initial trauma in fractures of the anterior cranial fossa, blood pools around the eyes causing periorbital ecchymosis (raccoon eyes). [6] Another clinical feature that appears 1 to 3 days after the incident is retroauricular or mastoid ecchymosis (Battle sign), where blood pools around the ears. This finding is associated with fractures to the middle cranial fossa. [6] Other clinical manifestations include tinnitus, nystagmus, hearing loss, vertigo, or cranial nerve palsies. [6,11]

Complications

The most common complications of cranial fractures include:

- CSF leak. [6]
- Pneumocephalus. [7]
- Cranial nerve palsies. [6]
- Hearing loss. [6]
- Cavernous sinus thrombosis. [6]
- Vertigo. [6]
- Carotid dissection, pseudoaneurysm or thrombosis. [6]
- Carotid-cavernous fistula. [6]
- Injury to cranial nerves III, IV, VI, VII and VIII. [6]
- Intracranial hemorrhage. [6]

- Seizures. [9]
- Meningitis. [3]
- Hydrocephalus. [12]
- Death. [6]

Diagnosis

The diagnosis of skull fractures starts with a physical exam, Fractures like open compound depressed skull fractures can be palpitated through the laceration as depressions.[7] Usually, plain x-rays are not sensitive enough for a diagnosis especially for basilar skull fractures therefore computed tomography (CT) scans are used. Initially, evaluation is done using a non-contrast CT scan which cannot easily detect linear or non-displaced skull fractures.

If there is any suspicion that a basilar skull fracture is present, then a multidetector CT (MDCT) thin-slice scanning through the face and skull base is used to detect subtle fractures. Unfortunately, small neural and vascular channels seen on MDCT can be misinterpreted as fractures so further imaging with CT angiography and venography (CTA, CTV) is done to look for any vascular injuries. [6] MRI can also be utilized to assess nerve injury and look for CSF leak. [6] It is difficult to diagnose a CSF leak therefore the fluid should be sent for analysis of beta transferrin. [6] CT scanning should be done in all patients with suspected skull fractures to rule out any underlying intracranial pathologies. [8]

Figure 1: Long linear branching left parietal fracture, case courtesy of Dr Dalia Ibrahim [13].

Figure 2 shows a biparietal diastatic skull fracture, case courtesy of Dr Ian Bickle [14].

Figure 3 shows a depressed skull fracture, case courtesy of Dr Ian Bickle [15].

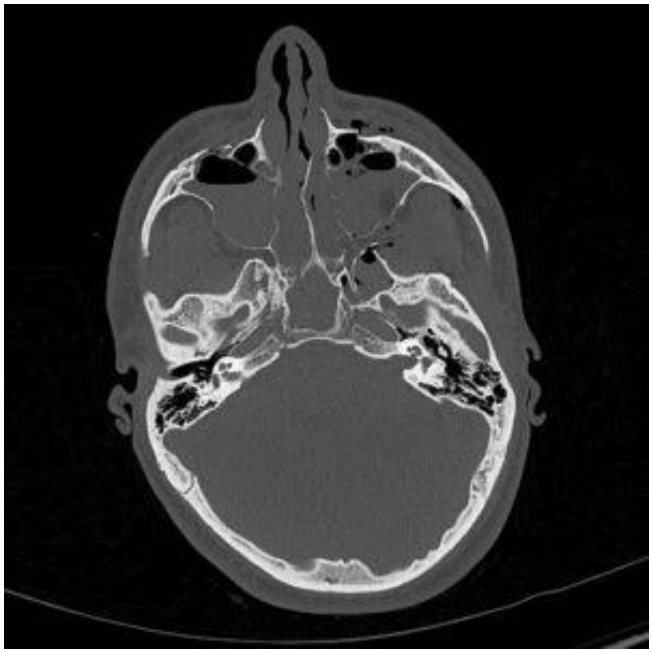


Figure 4 shows Heavily comminuted facial bone and base of skull fractures with bilateral Le Fort fractures. The right side demonstrates a Le Fort II while the left is a Le Fort III fracture. The base of the skull fracture extends through the body of the sphenoid consistent with a lateral frontal diagonal fracture pattern (see transsphenoidal basilar skull fractures). Case courtesy of Dr Amit Chacko [16].

Management

The approach to dealing with cranial fractures depends on the location and type of the fracture along with the presence of any other intracranial pathologies. For instance, most simple linear fractures heal without intervention. [3]

Compound depressed skull fractures typically require neurosurgical intervention specifically in patients with radiological evidence of dural penetration, intracranial hemorrhage, frontal sinus involvement, or even pneumocephalus. In any of these cases, the advocated course of action is early operation and antibiotics. Delaying the treatment results in an elevated risk of meningitis, cerebritis, epilepsy, and death. However, open depressed skull fractures with no dural laceration are treated with local wound washout, closure, and antibiotics alone. [7]

Because basilar skull fractures are caused by significant trauma, the first step when treating them is a thorough trauma evaluation with interventions to stabilize the airway, ventilation, and circulatory issues. Nasogastric tubes, and nasotracheal intubation should be avoided due to the risk of inadvertent intracranial tube placement while nasal intermittent positive pressure ventilation (NIPPV) should be avoided since it can cause pneumocephalus. Patients with basilar skull fractures should be admitted for observation especially those who are taking anticoagulants. Some cases might be

complicated by vascular injury, significant cranial nerve injury, persistent cerebrospinal fluid leak or intracranial bleeding which requires decompression, and these cases are considered in dire need of surgical management. In basilar skull fractures, there is an elevated risk of meningitis due to the increased possibility of bacteria from paranasal sinuses, nasopharynx, and the ear canal directly contacting the central nervous system. Therefore, patients with this kind of fracture are often treated with prophylactic antibiotics to prevent meningitis. However, there is no evidence to support the use of prophylactic antibiotics in preventing meningitis even in the presence of a CSF leak. Conversely, the use of antibiotics for prophylaxis is still considered appropriate in procedures like intracranial pressure (ICP) monitor placement.[6]

Surgery

Compound depressed skull fractures tend to be considered surgical emergencies and if they are not treated immediately certain serious complications could arise like meningitis, cerebral abscess, osteomyelitis, or post-traumatic seizure. [18] Therefore, patients with cranial fractures that are depressed to a degree that is greater than the thickness of the skull should be surgically treated by elevation, debridement, and antibiotics. [19] If the dura is injured, lacerated brain matter could be present in the wound which should be drained out and after proper hemostasis, the dural tear should be repaired in a watertight fashion where the pericranial graft or fascia lata could be used. [18] However, if there is no clinical or radiographic proof of dural penetration, significant intracranial hematoma, depression greater than 1 cm, frontal sinus involvement, gross cosmetic deformity, wound infection, pneumocephalus, or gross wound contamination, in all these situations a non-surgical approach can be taken. [19]

Prognosis

The prognosis of cranial fractures depends on:

- The associated dural tear and CSF leak. [6]
- The time the patient takes to get to the hospital. [17]
- Instability. [6]
- Associated injuries. [6]
- Initial severity of neurologic and vascular injuries. [6]

Usually, CSF leaks spontaneously resolve within 5-10 days while hearing loss typically resolves within 7-21 days. [6]

Acknowledgment

Thanks to IFMSA-JO.

References

[1] A. Prakash, V. Harsh, U. Gupta, J. Kumar, A. Kumar, Depressed fractures of skull: An institutional series of 453 patients and brief review of literature, Asian Journal of Neurosurgery. 13 (2018) 222. https://doi.org/10.4103/ajns.ajns_168_16.

[2] A. Meyyappan, E. Jagdish, J. Jeevitha, Bone cements in depressed frontal bone fractures, Annals of Maxillofacial Surgery. 9 (2019) 407–410. https://doi.org/10.4103/ams.ams_155_19.

[3] A. McGrath, R.S. Taylor, Pediatric Skull Fractures, 2022.

[4] I.F. Dunn, A.H. Kim, W.B. Gormley, Brain Trauma, Encyclopedia of Neuroscience. (2009) 407–416. https://doi.org/10.1016/B978-008045046-9.00564-7.

[5] M. Asirdizer, E. Kartal, A. Ekiz, I. Oymak, İ. Tilki, G.D. Sever Tilki, The effect of the presence or absence of skull fractures on intracranial lesion development in road traffic accidents, Journal of Forensic and Legal Medicine. 84 (2021). https://doi.org/10.1016/j.jflm.2021.102269.

[6] L. v. Simon, E.J. Newton, Basilar Skull Fractures, 2022.

[7] A.J. Gamble, G. Kapinos, N. Bastidas, R.K. Narayan, Depressed Skull and Facial Fractures, Neurocritical Care Management of the Neurosurgical Patient. (2018) 283–292. https://doi.org/10.1016/B978-0-323-32106-8.00028-5.

[8] J.T. Lerner, C.C. Giza, Traumatic Brain Injury in Children, Swaiman's Pediatric Neurology: Principles and Practice: Sixth Edition. (2017) 781–793. https://doi.org/10.1016/B978-0-323-37101-8.00102-8.

[9] B.H.G.D.J.W.Y.I.G.B.B.J. Lee Kyeong Seok Back Seung Ho, Prognosis and Complications of Depressed Skull Fracture., J Korean Neurosurg Soc. 23 (1994) 1143–1149. http://www.jkns.or.kr/journal/view.php?number=4640.

[10] A.J. Gardner, R. Zafonte, Neuroepidemiology of traumatic brain injury, Handbook of Clinical Neurology. 138 (2016) 207–223. https://doi.org/10.1016/B978-0-12-802973-2.00012-4.

[11] C.C. Stewart, Chapter 143 - Neurosurgical Issues, in: L.B. Zaoutis, V.W. Chiang (Eds.), Comprehensive Pediatric Hospital Medicine, Mosby, Philadelphia, 2007: pp. 908–914. https://doi.org/https://doi.org/10.1016/B978-032303004-5.50147-2.

[12] D.W. Marion, Complications of head injury and their therapy., Neurosurg Clin N Am. 2 (1991) 411–24.

[13] D. Ibrahim, Skull fracture (linear), in: Radiopaedia.Org, Radiopaedia.org, 2014. https://doi.org/10.53347/rID-28686.

[14] I. Bickle, Diastatic skull fracture, in: Radiopaedia.Org, Radiopaedia.org, 2020. https://doi.org/10.53347/rID-81578.

[15] H. Knipe, I. Bickle, Depressed skull fracture, in: Radiopaedia.Org, Radiopaedia.org, 2014. https://doi.org/10.53347/rID-29473.

[16] F. Gaillard, A. Chacko, Base of skull fracture with bilateral Le Fort fractures, in: Radiopaedia.Org, Radiopaedia.org, 2016. https://doi.org/10.53347/rID-47094.

[17] R.S. Satardey, S. Balasubramaniam, J.S. Pandya, R.C. Mahey, Analysis of Factors Influencing Outcome of Depressed Fracture of Skull., Asian J Neurosurg. 13 (n.d.) 341–347. https://doi.org/10.4103/ajns.AJNS_117_16.

[18] M.Z. Hossain, M.S. Mondle, M.M. Hoque, Depressed Skull Fracture : Outcome of Surgical Treatment, The Journal of Teachers Association RMC, Rajshahi. 21 (2008).

[19] M.R. Bullock, R. Chesnut, J. Ghajar, D. Gordon, R. Hartl, D.W. Newell, F. Servadei, B.C. Walters, J. Wilberger, Surgical Management of Traumatic Brain Injury Author Group, Surgical management of depressed cranial fractures., Neurosurgery. 58 (2006) S56-60; discussion Si-iv. https://doi.org/10.1227/01.NEU.0000210367.14043.0E.

Article topic: Choroid Plexus Tumors.

Author: Haneen Diab.

Editor: Rahmeh Adel.

Reviewer: Ethar Hazaimeh.

Keywords*: *choroid plexus tumors, choroid plexus papilloma, choroid plexus carcinoma

Overview

The choroid plexus is a capillary network lined with specialized cells called ependyma. Ependymal cells, which are ciliated simple columnar glial cells that line the ventricles and central canal of the spinal cord, are necessary for CSF production. So, the choroid plexus can secrete up to 500 ml of CSF per day in the adult human brain.[1] The choroid plexus, in collaboration with the arachnoid matter, forms a pair of membranes that separate the blood from the CSF. This barrier is made up of ependymal (choroid epithelial) cells with tight junctions on their apical surface (the side facing the ventricles), as well as a core of fenestrated capillaries surrounded by connective tissue. The blood-CSF barrier, like the blood-brain barrier (BBB), eases the exchange and removal of metabolites while preventing the passage of blood-borne substances into the brain. Microglia, white blood cells, macrophages, dendritic cells, and lymphocytes are all found in the choroid plexus and work together to keep harmful pathogens out.[2]

Choroid plexus tumors (CPTs) are rare and highly vascularized central nervous system neoplasms that account for 1% of all brain tumors,[3] but 12-20% of brain tumors in the first year of life, male to female ratio is 1.2:1, The age at diagnosis range from 0 years (fetus) to 72 years, but the majority of the patients are children, resulting in median age at diagnosis of 3.5 years.[4]

According to the World Health Organization's 2007 classification of Tumors of the Central Nervous System, choroid plexus tumors include choroid plexus papilloma (CPPs), atypical choroid plexus papilloma (aCPPs), and choroid plexus carcinomas (CPCs) [5]

Most cases occur in the ventricles (the lateral ventricles being the most common). CPPs prefer the third and fourth ventricles compared to CPCs and are more likely to be found in older patients. Extra-ventricular cases have also been reported. [6] CPPs accounted for 74% of all CPTs according to a study from 2004 to 2009.[7]

Etiology and Pathophysiology

Some choroid plexus tumors have been linked to SV40 infections[8], but they could also be influenced by other factors like X-chromosome-linked syndromes. Based on the findings of the study, it was hypothesized that SV40 is more common in infant tumors and that adult choroid plexus tumors have a distinct etiology.[4] Aicardi syndrome, an X-linked genetic disorder characterized by agenesis of the corpus callosum, chorio-retinal lacunae, infantile spasms, and an increased risk of developing (sometimes multifocal) CPTs, is another rare genetic disease associated with CPTs.[9]

CPCs are strongly linked to Li-Fraumeni syndrome (LFS), a classic cancer predisposition disorder caused by TP53 tumor suppressor gene germline mutations.[10]

Histopathological feature

Choroid plexus tumors are classified as papilloma (grade I), atypical tumors (grade II), and carcinomas (grade III). by the World Health Organization (2016). CPPs have less than two mitotic figures per ten high power fields, atypical ones have two to five per ten high power fields, and carcinomas have more than five mitotic figures per ten high power fields.[11]

CPPs have a similar histological architecture to normal choroid plexus, but the cells are generally more crowded, elongated, or stratified. They have a fibrovascular stalk that is surrounded by a single layer of cuboidal to columnar epithelium that is arranged in a papillary pattern. [5] As shown in figure 1. CPPs are described macroscopically as pink-grey, pedunculated, cauliflower-like masses that are well circumscribed from the normal brain.[12]

CPCs, which are rarely confused with CPPs, are invasive lesions with overt signs of malignancy that include at least four of the following: increased cellularity, papillary architecture blurring, high mitotic activity (0.5 per 10 HPFs), nuclear pleomorphism, and necrosis.[15]

CPT shows an immunohistochemical expression of cytokeratin, vimentin, podoplanin, and S-100.[13] Markers such as glial fibrillary acidic protein, transthyretin (prealbumin), and synaptophysin show variable expressivity, although CPPs are more common than CPCs. Kir7.1 and stanniocalcin-1 are both considered sensitive as well as specific CPP markers.[14]

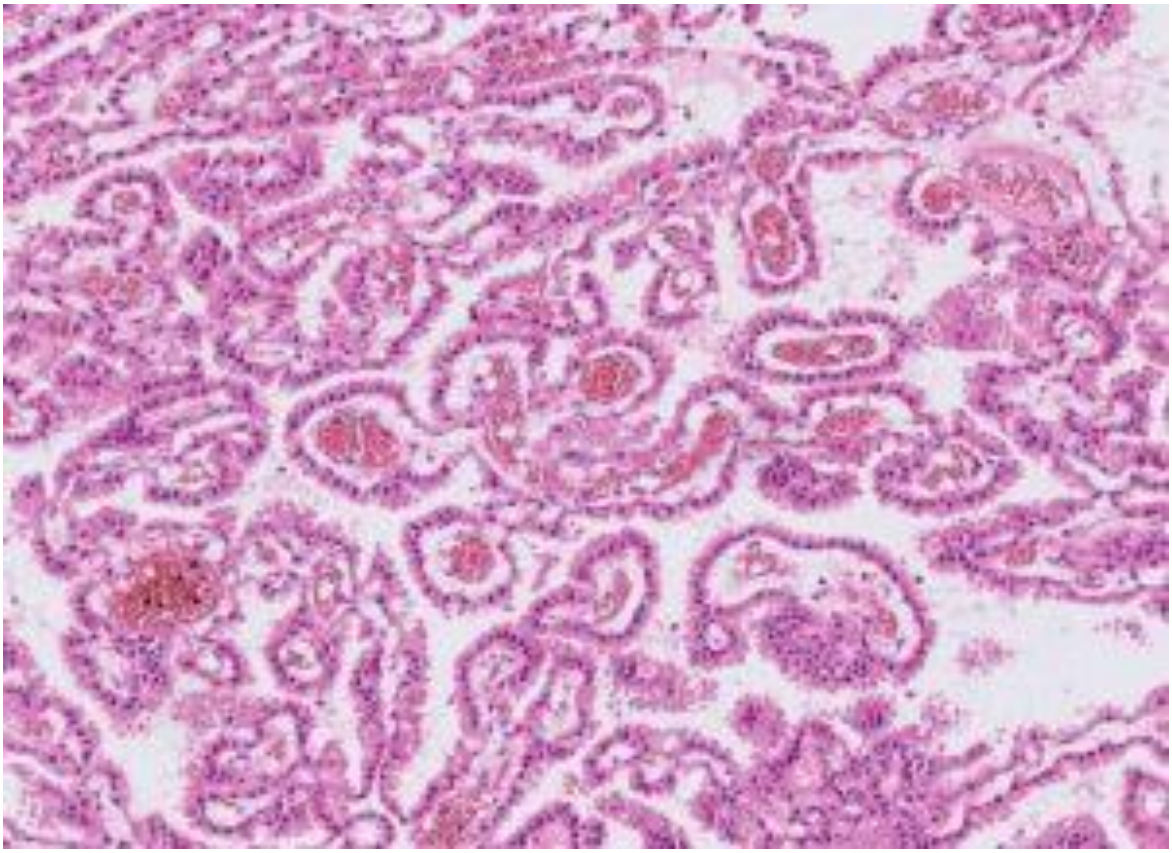


Figure1: choroid plexus papilloma
CPPs are benign tumors with preserved papillary or finger-like architecture, with fibrovascular cores, lined by a single layer of cuboidal to the columnar epithelium, almost resembling nonneoplastic choroid plexus but with mild cellular atypia and without significant mitosis

Epigenetic dysregulation, including changes in DNA methylation, has long been recognized as a factor in tumorigenesis and tumor maintenance. Specific changes in DNA methylation in small genomic regions have been shown to be promising targets for the development of powerful prognostic and predictive biomarkers.[16]

CPTs have three distinct and molecular subgroups, according to DNA methylation profiling [17].

- Supratentorial pediatric choroid plexus tumors of low risk (CPP and aCPP)
- Adults with infratentorial low-risk choroid plexus tumors (CPP and aCPP) and
- Supratentorial pediatric choroid plexus tumors of high risk (CPP and aCPP and CPC)

Epigenetic profiling will hopefully help us understand choroid plexus tumor biology, can be used to identify patients at risk of recurrence, and is expected to play a key role in treatment stratification and patient management in future clinical trials.[18]

Clinical presentations

The most common primary presenting symptom was a headache with nausea or vomiting caused by increased intracranial pressure, followed by ataxia and lower extremity weakness.[19]

Children's symptoms include macrocephaly, splayed sutures, and tense fontanelles. The majority of these are caused by a combination of obstructive hydrocephalus, increased CSF production, and impaired CSF reabsorption at the arachnoid granulations due to scarring from hemorrhage or tumor debris.

Clinical characteristics and signs at the time of diagnosis were hydrocephalus, papilledema, gait impairment, and other conditions. Seizures, cerebellar signs, and psychomotor retardation are all symptoms of cranial nerve palsy.[20] CSF rhinorrhea or hemifacial spasm may be the only clinical manifestations in some cases, particularly in fourth ventricle CPP.[21, 22]

Diagnosis and radiographic features

CPPs appear iso- or hyperdense on CT imaging, with calcifications in 25% of cases. Hydrocephalus is a common radiographic feature of these tumors and can be caused by increased CSF secretion or obstruction by tumor, hemorrhage, or debris. These lesions are well vascularized, brighten with contrast, and may have cystic features.[23, 24] MRI revealed an enhancing mass in the ventricle that was isointense on T1-weighted images *as shown in figure 2* but hyperintense on T2-weighted images.[24]

Recent research has shown that arterial spin labeling can help distinguish choroid plexus papilloma from choroid plexus carcinoma, ASL measured a higher rCBF in carcinomas, allowing differentiation between choroid plexus papilloma and carcinoma. *As shown in figure 3.*[25]

Prenatal ultrasound and fetal MRI were used in rare cases of prenatal CPP that revealed bilateral enlarged, echogenic choroid plexus with increased Doppler flow suggestive of vascularized choroid tissue.[26]

Angiograms are helpful to neurosurgeons in preoperative planning. Because these tumors are highly vascularized, intraoperative hemorrhage is a serious risk, particularly in pediatric patients who have a low threshold for intraoperative blood loss.[27]

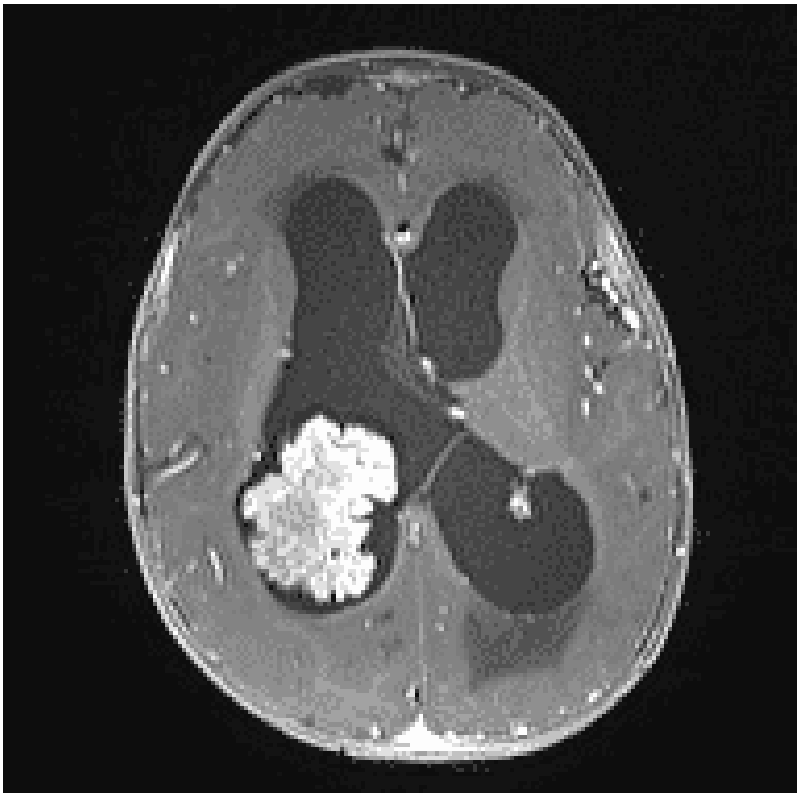


Figure 2: choroid plexus papilloma, MRI (T1 with Contrast + fat sat) 28.

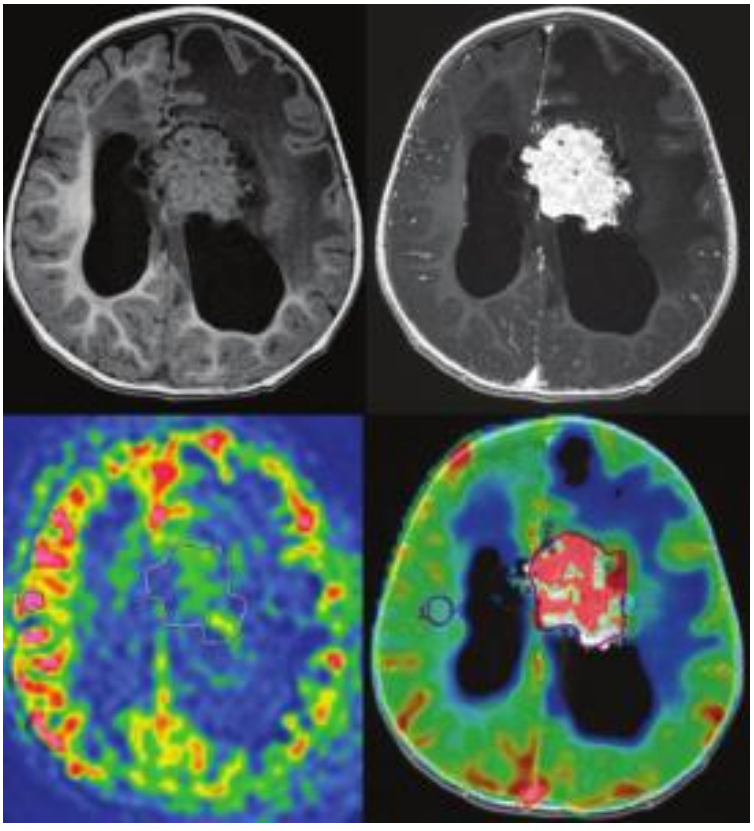


Figure 3: Measurement of ASL and DSC-PWI of a choroid plexus papilloma.
Top left: T1-weighted MR imaging. Top right: T1-weighted MR imaging with gadolinium injection. Bottom left: arterial spin-labeling. ROIs are drawn around the whole tumor and in the contralateral gray matter. Bottom right: DSC-PWI dynamic susceptibility contrast perfusion-weighted imaging. ROIs are drawn around the whole tumor and in the contralateral white matter. ROIs: regions of interest. 25

Treatment

Surgical resection

Surgery is still the most important and effective treatment for CPP patients. Survival has increased from 50% in early studies to nearly 100% in more recent reports, owing primarily to advances in imaging, surgical approaches, and intensive care quality.[29]

Several factors influence the overall outcome, including surgical complications, histological grading, age, lesion size, and location.[30]

The extent of resection is an important predictor of outcome, but the extent of resection depends on factors such as vascularity of the lesion, invasive nature of the lesion[31], achieving gross total resection (GTR) is difficult, complications during surgery may occur due to the tumor's hypervascularity, particularly intraoperative hemorrhage, which is a serious risk, particularly in pediatric patients with a low threshold for intraoperative blood loss [32]

Preoperative embolization is an adjunct that is used in specific settings to reduce the vascularity of the lesions [31]. Many studies have been published on the role of preoperative neoadjuvant therapy in reducing vascularity and aiding in gross total resection.[33]

Chemotherapy and radiotherapy

The CPT-SIOP-2000 study by the International Society of Pediatric Oncology reported on the use of etoposide, vincristine, and either carboplatin or cyclophosphamide for the treatment of various choroid plexus tumors.[34]

The role of radiosurgery in CPP management is unclear. it is not recommended for patients under the age of three, but it may be beneficial in treating recurrent or disseminated lesions or patients who are poor surgical candidates [35, 32]

Prognosis

According to a study conducted at The Johns Hopkins Hospital, Patients with CPPs had 100% 5- and 10-year survival, while patients with CPCs had 71% 5-year survival.[3]

Long-term survival of patients with CPPs is expected because they are benign tumors though we suspected that tumor size might be related to patients' prognosis [19]

Complications

Postoperative vision changes, new onset seizures, unilateral weakness, and wound infection necessitating surgical debridement and wound revision were the most common complications in patients with CPPs.[3]

Recent clinical trials

A study provided one of the most detailed assessments of first and second cancer risks in Li-Fraumeni syndrome (LFS) patients published to date, the study found a high cumulative cancer risk, with females being more at risk than males, owing to early-onset breast cancer.

We also confirmed a recent finding that among children, brain cancer, osteosarcoma, Soft-tissue sarcomas (STS), and Adenoid cystic carcinoma (ACC) were the most common diagnoses, while breast cancer and STS were the most common diagnoses among adults.

Following the first cancer diagnosis, the risk of subsequent malignancies was approximately 50%, and it occurred from birth to 49 years later.[36]

References

1. Wolburg H, Paulus W. Choroid plexus: Biology and pathology. *Acta Neuropathol*. 2010;119(1):75-88. doi:10.1007/s00401-009-0627-8
2. Strazielle N, Ghersi-Egea JF. *Choroid Plexus in the Central Nervous System: Biology and Physiopathology*. Vol 59.; 2000. https://academic.oup.com/jnen/article/59/7/561/2609852
3. Bettegowda C, Adogwa O, Mehta V, et al. Treatment of choroid plexus tumors: A 20-year single institutional experience. *J Neurosurg Pediatr*. 2012;10(5):398-405. doi:10.3171/2012.8.PEDS12132
4. Wolff J, Sajedi M, Brant R, Coppes MJ, Egeler RM. Choroid plexus tumours. *Br J Cancer*. 2002;87:1086-1091. doi:10.1038/sj.bjc.6600609
5. Louis DN, Ohgaki H, Otmar ·, et al. The 2007 WHO ClassiWcation of Tumours of the Central Nervous System. *Acta Neuropathol*. 2007;114:97-109. doi:10.1007/s00401-007-0243-4
6. Lozier AP, Arbaje YM, Scheithauer BW. Supratentorial, extraventricular choroid plexus carcinoma in an adult: Case report. *Neurosurgery*. 2009;65(4). doi:10.1227/01.NEU.0000348291.48810.C2
7. Cannon DM, Mohindra P, Gondi V, Kruser TJ, Kozak KR. Choroid plexus tumor epidemiology and outcomes: implications for surgical and radiotherapeutic management. *J Neurooncol*. 2015;121(1):151-157. doi:10.1007/s11060-014-1616-x
8. Zhen HN, Zhang X, Bu XY, et al. Expression of the simian virus 40 large tumor antigen (Tag) and formation of Tag-p53 and Tag-pRb complexes in human brain tumors. Accessed November 15, 1999. PMID: 10570441
9. Aicardi J. Aicardi syndrome. In: *Brain and Development*. Vol 27. Elsevier; 2005:164-171. doi:10.1016/j.braindev.2003.11.011
10. Malkin D. Li-fraumeni syndrome. *Genes Cancer*. 2011;2(4):475-484. doi:10.1177/1947601911413466
11. Ruggeri L, Alberio N, Alessandrello R, et al. Rapid malignant progression of an intraparenchymal choroid plexus papillomas. *Surg Neurol Int*. 2018;9(1). doi:10.4103/sni.sni_434_17
12. Gaudio RM, Tacconi L, Rossi MLM. Pathology of choroid plexus papillomas: A review. *Clin Neurol Neurosurg*. 1998;100(3):165-186. doi:10.1016/S0303-8467(98)00033-X

13. Ikota H, Tanaka Y, Yokoo H, Nakazato Y. Clinicopathological and immunohistochemical study of 20 choroid plexus tumors: Their histological diversity and the expression of markers useful for differentiation from metastatic cancer. In: *Brain Tumor Pathology*. Vol 28. ; 2011:215-221. doi:10.1007/s10014-011-0024-6
14. Hasselblatt M, Böhm C, Tatenhorst L, et al. *Identification of Novel Diagnostic Markers for Choroid Plexus Tumors A Microarray-Based Approach*. www.affymetrix.
15. Merve A. Choroid plexus tumors (papilloma, atypical papilloma, carcinoma). PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/cnstumorchoroidplexuspapillomas.html. Accessed October 22nd, 2022.
16. Dunn J, Baborie A, Alam F, et al. Extent of MGMT promoter methylation correlates with outcome in glioblastomas given temozolomide and radiotherapy. *Br J Cancer*. 2009;101:124-131. doi:10.1038/sj.bjc.6605127
17. Capper D, Stichel D, Sahm · Felix, et al. Practical implementation of DNA methylation and copy-number-based CNS tumor diagnostics: the Heidelberg experience. 2018;136(2):181-210. doi:10.1007/s00401-018-1879-y
18. Thomas C, Metrock K, Kordes U, Hasselblatt M, Dhall G. Epigenetics impacts upon prognosis and clinical management of choroid plexus tumors. *J Neurooncol*. 2020;148(1):39-45. doi:10.1007/s11060-020-03509-5
19. Zhou WJL, Wang X, Peng JY, et al. Clinical features and prognostic risk factors of choroid plexus tumors in children. *Chin Med J (Engl)*. 2018;131(24):2938-2946. doi:10.4103/0366-6999.247195
20. Safaee M, Oh MC, Bloch O, et al. Choroid plexus papillomas: Advances in molecular biology and understanding of tumorigenesis. *Neuro Oncol*. 2013;15(3):255-267. doi:10.1093/neuonc/nos289
21. Mula-Hussain L, Malone J, dos Santos MP, Sinclair J, Malone S. CSF Rhinorrhea: A Rare Clinical Presentation of Choroid Plexus Papilloma. doi:10.3390/curroncol28010073
22. Navarro-Olvera JL, Covaleda-Rodriguez JC, Diaz-Martinez JA, Aguado-Carrillo G, Carrillo-Ruiz JD, Velasco-Campos F. Hemifacial Spasm Associated with Compression of the Facial Colliculus by a Choroid Plexus Papilloma of the Fourth Ventricle. *Stereotact Funct Neurosurg*. 2020;98(3):145-149. doi:10.1159/000507060
23. Cao LR, Chen J, Zhang RP, Hu XL, Fang YL, Cai CQ. Choroid plexus papilloma of bilateral lateral ventricle in an infant conceived by in vitro fertilization. *Pediatr Neurosurg*. 2018;53(6):401-406. doi:10.1159/000491639
24. Jaiswal AK JSSRDKJVBS. Choroid plexus papilloma in children: Diagnostic and surgical considerations. . *J Pediatr Neurosci* . Published online January 4, 2009. Accessed October 16, 2022. doi: 10.4103/1817-1745.49100. PMID: 21887168; PMCID: PMC3162829.
25. Dangouloff-Ros X v, Grevent D, Pagè M, et al. Choroid Plexus Neoplasms: Toward a Distinction between Carcinoma and Papilloma Using Arterial Spin-Labeling. doi:10.3174/ajnr.A4332
26. Li Y, Chetty S, Feldstein VA, Glenn OA. Bilateral Choroid Plexus Papillomas Diagnosed by Prenatal Ultrasound and MRI. Published online 2021. doi:10.7759/cureus.13737
27. García-Valtuille R AFGVAPJCLSFTFMF. Adult choroid plexus papilloma of the posterior fossa mimicking a hemangioblastoma. Case report. *J Neurosurg*. Published online May 2000. Accessed October 16, 2022. doi: 10.3171/jns.2000.92.5.0870. PMID: 10794304.
28. Case courtesy of Dr Utkarsh Kabra. choroid plexus papilloma. Radiopaedia.org. Accessed October 16, 2022. Radiopaedia.org. From the case rID: 84612
29. Tacconi L, Delfini R, Cantore G. *Choroid Plexus Papillomas: Consideration of a Surgical Series of 33 Cases*. Springer-Verlag; 1996.
30. Turkoglu E, Kertmen H, Sanli AM, et al. Clinical outcome of adult choroid plexus tumors: Retrospective analysis of a single institute. *Acta Neurochir (Wien)*. 2014;156(8):1461-1468. doi:10.1007/s00701-014-2138-1
31. Kamaly-Asl I, Ramaswamy V, Lafay-Cousin L, et al. Neoadjuvant chemotherapy reduces blood loss during the resection of pediatric choroid plexus carcinomas. *PEDIATRICS cliNical article J Neurosurg Pediatr*. 2015;16:126-133. doi:10.3171/2014.12.PEDS14372
32. Ahmed SI, Javed G, Laghari AA, et al. Third Ventricular Tumors: A Comprehensive Literature Review. *Cureus*. Published online October 5, 2018. doi:10.7759/cureus.3417
33. S.K. St Clair RPHPKPHJHSIBLEB. Current management of choroid plexus carcinoma in children. *Pediatr Neurosurg* . Published online 1999.
34. Wrede B, Hasselblatt M, Peters O, et al. Atypical choroid plexus papilloma: clinical experience in the CPT-SIOP-2000 study HHS Public Access. *J Neurooncol*. 2009;95(3):383-392. doi:10.1007/s11060-009-9936-y
35. Due-Tønnessen B, Helseth E, Skullerud K, Lundar T. *Choroid Plexus Tumors in Children and Young Adults: Report of 16 Consecutive Cases*. Vol 17.; 2001.
36. Mai PL, Best AF, Peters JA, et al. Risks of First and Subsequent Cancers Among TP53 Mutation Carriers in the National Cancer Institute Li-Fraumeni Syndrome Cohort. doi:10.1002/cncr.30248

Article topic: Bow Hunter Syndrome

Author: Hashem Bani Ata, Omar Alqudah**.**

Editor: Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: vertebrobasilar, compression, head rotation, doppler, dizziness, osteophytes, cervical, decompression.

Introduction

Bow hunter syndrome is a rare condition of transient vertebrobasilar symptoms as a result of reversible vertebrobasilar insufficiency caused by mechanical compression of the vertebral artery triggered by head rotation[1]. Symptoms include dizziness, visual abnormalities, vertigo, and syncope that improve when the head comes back[1]. Osteophytic compression is thought to be the most common etiology[2]. Diagnosis is made by doppler sonography, CTA, and MRA. Treatment could be conservative, or surgical such as cervical decompression, cervical spine fusion, and stent placement[3]. The name Bow Hunter's Syndrome came from the the position of bow hunter's head when they aim their bow[4].In 1978, the first scientific literature was established about bow hunter syndrome by Sorensen[5].

Epidemiology

Bow hunter syndrome is more common in males than females, typically in (5-7) the decade of life with a mean age of 53 years old, but it can present in any age group. Also, many comorbidities increase the risk of bow hunter syndromes such as diabetes, hyperlipidemia, hypertension, and coronary artery disease, as noticed in many case reports that a patient has two or more from the previous comorbidities.[6]

Etiologies and Pathogenesis

Many etiologies for bow hunter syndrome are recorded in many case reports however, every cause compresses the vertebral artery by certain mechanisms, compressive agents could be bone, ligament, disc[7], and muscle[8]. The most common etiology is osteophyte[9]. Spondylosis causes vertebral compression by overgrowth[10]. Also, hypertrophy of neck muscles[8], ligament disc[7], atlantoaxial hypermobility[4], and thyroid cartilage impingement[5]. Rare causes for bow hunter syndrome could be vascular, such as aneurysm, vertebral artery hypoplasia, vertebral artery dissection, atherosclerosis, or embolism[5].

Pathogenesis of bow hunter syndrome is depending on the compression of the vertebral artery, and the most common locations of compression are C1-2 and C5-C7 because of the hypermobility for these locations. Narrowing of the vertebral artery during head rotation is physiologic due to stretching, what happens in bow hunter syndrome is there is an offending agent such as osteophyte that exacerbates narrowing and stretching[7].

Clinical features

Bow hunter syndrome manifests with transient symptoms that are relieved when the head return to the neutral position and the angles at which symptoms are provoked are 30,45,60,80 and 90. The classic presentation of bow hunter is vertigo, dizziness, and nausea, but it can manifest with posterior circulation stroke[6]. These symptoms are illustrated with their prevalence in the table below[3]:

Symptom	Prevalence
Vertigo	28%
Syncope	26%
Lightheadedness	11%
Dizziness	
Nausea/vomiting	10%
Visual symptoms	8%
Tinnitus	7%
Focal neurological deficits	5%
Other symptoms	5%

Diagnosis

Comprehensive history and physical examination are the first step in the diagnosis of bow hunter syndrome and need high suspicion because of its rarity, after that, Imaging confirms the diagnosis[11]. Regardless of the technique employed to diagnose bow hunter syndrome, two positions are needed; one when the head is neutral to show the patent artery, and one when the head is rotated to show the compressed or stenotic artery. The diagnosis may involve a variety of techniques. The gold standard modality is digital subtraction angiography (DSA). Other techniques like computed tomography and angiography, magnetic resonance imaging, and angiography, are also option.[6].DSA

overweight CTA and MRA by its accuracy and quickness during the evaluation of the flow through the vertebral artery as the symptoms develop after seconds of head rotation. Also, the risk of posterior circulation infarction is increase with CTA and MRA. In contrast, CTA provides details about an offending agent and its effect on vascularity[6].

Other modalities are used such as transcranial Doppler (TSD) sonography, which confirms lesion the effectiveness of treatment and is used widely because it is considered safe and non-invasive at a lower cost. Cerebral blood flow scintigraphy, single-photon emission CT scanning, and Electrophysiological examinations are also used[6].

The accuracy of all modalities above in the diagnosis of bow hunter syndrome is recorded in table below[11]:

Modality	Accuracy
Dynamic angiography	100%
Ultrasound	36.4%
CTA	18.2%
MRA	18.2%

Treatment

There is no ideal management for bow hunter syndrome, and multiple management is available; conservative, surgery, and endovascular intervention. Depending on the desire of the patient and complications for each procedure, the decision will be[5,6].

Conservative therapy

This option includes explaining to the patient how to prevent eliciting symptoms by avoiding head rotation using a neck collar and using antiplatelet and anticoagulant drugs such as aspirin and warfarin. According to that this therapy avoids patient invasive procedures with variable complications, it can be considered a first-line treatment. The effectiveness of this therapy is variable from patient to patient, so some patients do not improve with this treatment and need another management[5,6].

Surgical treatment

Surgical decompression and cervical spine fusion are two possible surgical techniques, each one has its indication depending on the advantages and disadvantages, offending

agent, and patient conditions. Sometimes a surgery called decompression with effusion combines two operations[5,6].

Surgical decompression involves the removal of bone elements such as the transverse process that surround the vertebral artery. So, decompression doesn't affect on motion range of the head, and that makes it overweighs fusion which restricts head movements. The disadvantages of decompression are represented by the fact of removing the protective agent of the vertebral artery from adhesion with surrounding structures which increases the risk of restenosis; because in this procedure, some bony structures such as the transverse process and groove of the atlas are removed, which prevent adhesions.

Although decompression makes patients return to their daily living activities, they are at risk of recurrence, and some patients develop postoperative posterior circulation infarction, so some patients need fusion later. Depending on where the disease is, there are two ways to accomplish surgical decompression: an anterior approach and a posterior approach. The anterior approach is performed for lower cervical spine pathology and the posterior approach is for upper cervical spine[5,6].

Cervical spine fusion is adopting restricted neck motion to prevent vascular compression. Movement restriction is performed by bone graft fixed between the lamina of the axis and the posterior arch of the atlas. The risk of restenosis in this procedure is less than vascular decompression, but the problem is in head motion restriction and it reflect in daily living activities[5,6].

Endovascular procedure

In this procedure, a coil or stent is used in cases of atherosclerosis, aneurysms, or malformations. The effectiveness of this procedure isn't known until now[6].

References

1. Hernandez RN, Wipplinger C, Navarro-Ramirez R, et al. Bow Hunter Syndrome with Associated Pseudoaneurysm. *World Neurosurg*. 2019;122:53-57. doi:10.1016/j.wneu.2018.10.102
2. Khan NR, Elarjani T, Chen SH, Miskolczi L, Strasser S, Morcos JJ. Atlanto-Occipital Decompression of Vertebral Artery for a Variant of Bow Hunter's Syndrome: 2-Dimensional Operative Video. *Oper Neurosurg (Hagerstown, Md)*. 2021;21(4):E363-E364. doi:10.1093/ons/opab231
3. Rastogi V, Rawls A, Moore O, et al. Rare Etiology of Bow Hunter's Syndrome and Systematic Review of Literature. *J Vasc Interv Neurol*. 2015;8(3):7-16.
4. Montano M, Alman K, Smith MJ, Boghosian G, Enochs WS. Bow Hunter's Syndrome: A rare cause of vertebrobasilar insufficiency. *Radiol case reports*. 2021;16(4):867-870. doi:10.1016/j.radcr.2021.01.041
5. Schulz R, Donoso R, Weissman K. Rotational vertebral artery occlusion ("bow hunter syndrome"). *Eur spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc*. 2021;30(6):1440-1450. doi:10.1007/s00586-020-06680-5
6. Duan G, Xu J, Shi J, Cao Y. Advances in the Pathogenesis, Diagnosis and Treatment of Bow Hunter's Syndrome: A Comprehensive Review of the Literature. *Interv Neurol*. 2016;5(1-2):29-38. doi:10.1159/000444306

7. Zaidi HA, Albuquerque FC, Chowdhry SA, Zabramski JM, Ducruet AF, Spetzler RF. Diagnosis and management of bow hunter's syndrome: 15-year experience at barrow neurological institute. *World Neurosurg*. 2014;82(5):733-738. doi:10.1016/j.wneu.2014.02.027
8. Sarkar J, Wolfe SQ, Ching BH, Kellicut DC. Bow hunter's syndrome causing vertebrobasilar insufficiency in a young man with neck muscle hypertrophy. *Ann Vasc Surg*. 2014;28(4):1032.e1-1032.e10. doi:10.1016/j.avsg.2013.06.038
9. Davis DD, Kane SM. Rotation Vertebral Artery Syndrome. In: ; 2022.
10. Fleming JB, Vora TK, Harrigan MR. Rare case of bilateral vertebral artery stenosis caused by C4-5 spondylotic changes manifesting with bilateral bow hunter's syndrome. *World Neurosurg*. 2013;79(5-6):799.E1-5. doi:10.1016/j.wneu.2012.06.022
11. Strickland BA, Pham MH, Bakhsheshian J, Russin JJ, Mack WJ, Acosta FL. Bow Hunter's Syndrome: Surgical Management (Video) and Review of the Literature. *World Neurosurg*. 2017;103:953.e7-953.e12. doi:10.1016/j.wneu.2017.04.101

Title: Epidural Abscesses.

Author: Dana Alshawabkeh.

Editor: Rahmeh Adel.

Reviewer: Ethar Hazaimeh.

Keywords: ***epidural abscess, intracranial abscess, spinal abscess, brain abscess.***

Abbreviations:

ICEA=Intracranial Epidural Abscess, **SEA**= Spinal Epidural Abscess, **ESR**= Erythrocyte Sedimentation Rate, **CSF**= CerebroSpinal Fluid, **MRI**= Magnetic Resonance Imaging, **CT**= Computerized Tomography.

Abstract

Epidural abscess is an infection within epidural space anywhere in the brain or spinal cord.[5] It is a serious, potentially life-threatening central nervous system infection involving the intracranial or spinal compartments.[1]

Intracranial epidural abscesses (ICEAs) are uncommon lesions, being more frequent in older children and adults, they commonly result from direct extension of a pre-existing infection and rarely present with the focal deficit.[2]

Spinal epidural abscess (SEA) is a rare condition that occurs most commonly in adults in their fifth and sixth decades of age.[21] Despite advances in diagnostic medicine, early recognition of SEAs remains difficult.[3] Delay in early diagnosis may be related to increased morbidity and mortality,[6] wherefores once SEA was diagnosed in the patients, immediate treatment has to be initiated for all SEA patients.[7]

Overview

The sites of spinal epidural abscesses are variable. Only 20% occur anterior to the spinal cord. Abscesses in the cervical or upper thoracic region are common, the preponderance of lower thoracic and lumbar abscesses. Patients with a lumbar abscess may be misdiagnosed as having a herniated lumbar disc.[27]

So, in this article, we will discuss diagnosis epidemiology, risk factors, pathogenesis, clinical presentation, diagnosis, complications, and treatment of an epidural abscess.

Epidemiology

SEA is nine-time more common than ICEA and more likely to be acute. Although ICEA is not common, still the third most common focal pyogenic intracranial infection, after brain abscess and subdural empyema.[9]

The incidence of SEA is 0.2 to 1.2 cases per 10,000 hospital admissions [9] and the ratio of male to female is about [1: 0·56], which is associated with the higher prevalence of risk factors in men and boys and mortality rate from about 6% to 32%.[5]

SEAs are more prevalent in 30-year-old patients and older. However, they can affect younger people, even young children.[5]

The ICEA complications are more in children, adolescents, and young adults (7–20 years of age).[5]

Risk factors

Intracranial Epidural Abscess (ICEA)

The most common risk factors for ICEAs include frontal sinus infection, post-traumatic infection, recent intracranial, transnasal, or transmastoid surgical procedures, and congenital defects in the bone of the anterior cranial fossa which facilitate communication between the intracranial epidural space and the paranasal sinuses.[5]

Spinal Epidural Abscess (SEA)

Non-spinal infections were the most common cause of SEAs. Among them, the paravertebral abscess was the most cause, then skin and soft tissue abscesses. Additional risk factors include spinal procedures such as epidural injection for pain control, acupuncture treatment, and previous spine surgery after spinal trauma. Risk Factors such as diabetes mellitus, liver disease, and cancer were also found *(Table 1)*.[7]

There are other risk factors including penetrating injury to the spine, class III obesity, primary or iatrogenic immunosuppression, skin infections or abscesses, and transient bacteremia.[5] The organism was identified in 84% of cases, most commonly Staphylococcus aureus.[8]

Risk factor	Number of patients (%)
Paravertebral abscess	12 (35)
Skin & soft tissue infection	5 (14)
Perirenal abscess	1 (3)
Endocarditis	1 (3)
Epidural injection	2 (6)
Acupuncture	3 (8)
Previous spine surgery	1 (3)
Vertebral body fracture	3 (8)
Psoas muscle contusion	1 (3)
Diabetes mellitus	1 (3)
Liver disease	3 (8)
Cancer	1 (3)
No risk	1 (3)

Table 1: Associated predisposing factors of SEAs.7

Etiology and pathogenesis

ICEA

Streptococci (usually anaerobe forms like Peptostreptococcus) and other anaerobes such as Cutibacterium (part of the skin flora) are usually the causing organisms. Gram-negative bacilli or fungi can be a cause as well. They originate in the sinuses.

ICEA starts with an exogenous port of entry, either the paranasal sinuses or ears and can be a complication of neurosurgery. Also, the infection can spread inward from osteomyelitis of the skull or fetal monitoring probes applied to the cranium during birth.[9]

SEA

The infection enters the spinal epidural space by some 4 mechanisms:[20]

- Hematogenous spread from an existing infection is the most common mechanism.
- Through direct extension.
- Inoculation via spinal procedures.

- Trauma.

Hematogenous SEAs are primarily located in the posterior aspect of the spinal canal.[27] The second most common mechanism of infection is direct spread from an infected element of the vertebral column or paraspinal soft tissues. Most commonly, this takes the form of anterior SEAs in association with vertebral body osteomyelitis.[20]

Septic arthritis of a facet joint can cause a secondary infection of the posterior epidural space. Direct spread from other posterior structures such as retropharyngeal, psoas, or paraspinal muscle abscess may cause SEAs as well.[20]

Less frequent mechanisms include direct inoculation and trauma. Infection of the epidural space can occur in conjunction with spinal surgery, placement of an epidural catheter, or spinal injections. Hematoma secondary to an osseous or ligamentous injury can become seeded by bacteria, causing abscess formation.[20]

Clinical presentation

ICEA

The clinical presentation of brain abscess relies on the lesion's size and anatomic location, the causative pathogen's virulence, the host's immune status, and the presence of underlying systemic conditions.[1] Symptoms of ICEAs may include nausea, vomiting, fever, and headache. Neurologic deficits are common, but not always present.[24]

SEA

SEA should be suspected in the patient presenting with complaints of back pain or a neurologic deficit in association with fever or an elevated erythrocyte sedimentation rate.[22]

The typical features of spinal epidural abscess are recognizable clinically.[27] The classic triad of clinical manifestations of SEA includes localized back pain, progressive neurologic deficit, and fever.[18]

It occurred in only a minority of patients (37%). However, the coexistence of axial back pain and progressive neurologic symptoms remained the most reliable clinical indicator for the presence of SEA.[12]

Diagnosis

Imaging findings

Any patient presenting with purulent otorhinogenic, sinus, or dental infections with encephalopathy or focal neurologic deficits must undergo brain imaging with contrast.[1]

Plain radiographs are ineffective and lack specificity and sensitivity in diagnosing SEAs.[5] If there is a concern for SEAs, patients should undergo an immediate MRI of the whole spine. If MRI is not available, CT with IV contrast is a less sensitive alternative. Lumbar puncture is not necessary as it lends little diagnostic utility and has potential morbidity in the setting of spinal epidural abscess.[13]

CT scan

CT is less sensitive for detecting an epidural abscess than MRI is. Features of epidural abscess on CT include extra-axial location, isodense or hypodense to surrounding brain, biconvex shape, usually does not cross suture lines, may cross the midline, and strong peripheral enhancement with contrast.[25]

MRI

ICEAs

Characteristics of ICEAs on MRI include[25] *(as shown in figure 1)*

- T1: hyperintense
- T1 C+ (Gd): strong peripheral contrast enhancement
- T2/FLAIR: isointense or hyperintense
- PD: isointense or hyperintense
- DWI: area of restricted diffusion

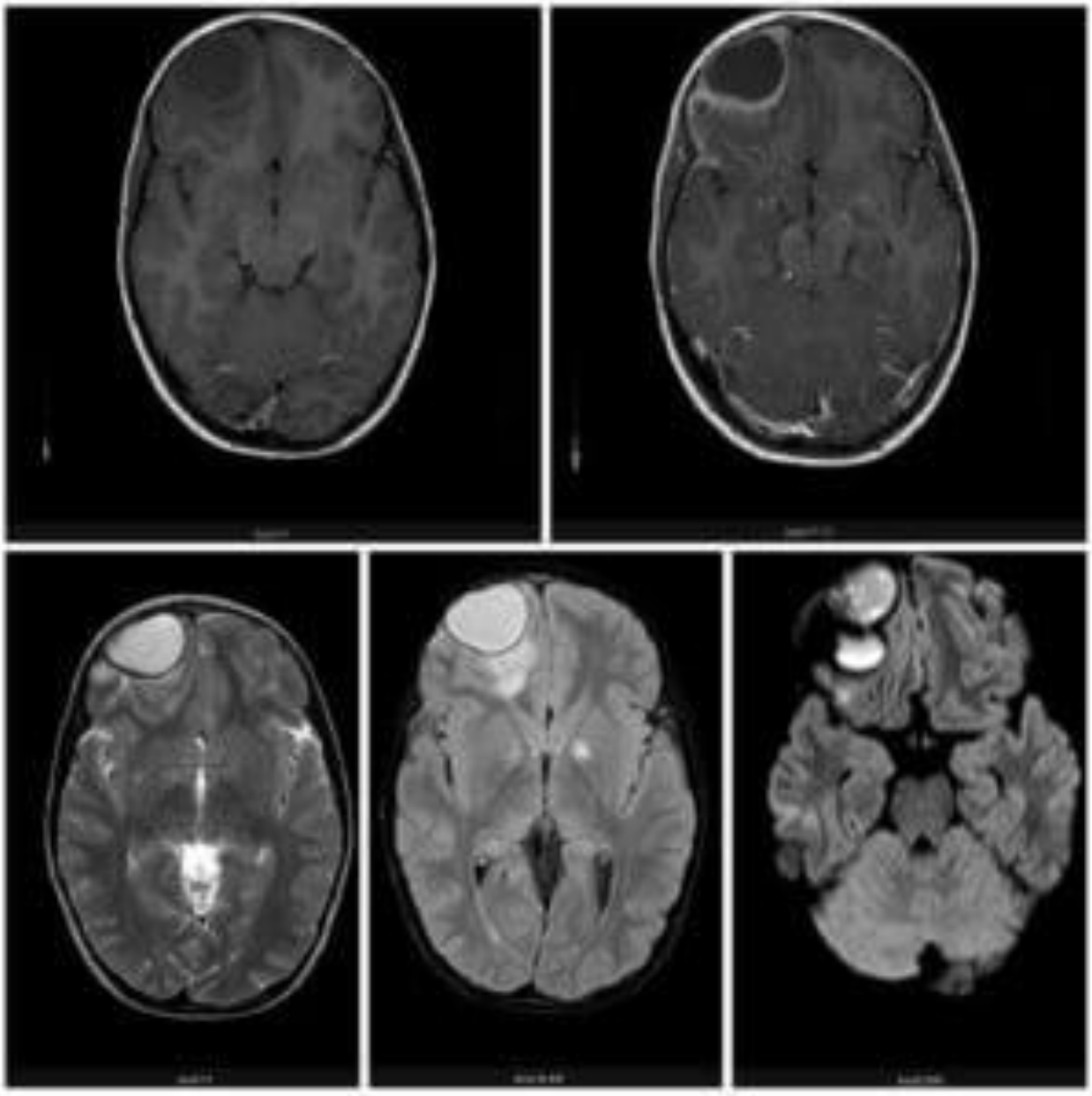


Figure 1. MRI shows the multiloculate morphology of the intracranial epidural collection located in the right supraorbital region. The collection is hypointense on T1-weighted and hyperintense on T2-weighted images, with a surrounding membrane that enhances with contrast administration.25

SEAs

Gadolinium-enhanced MRI is the imaging option for the diagnosis of spinal epidural infection. Diffusion-weighted sequences are helpful to confirm the condition.

There are two main manners, with distinct imaging appearances:

- Phlegmonous stage of infection results in a homogeneous enhancement of the abnormal area which correlates to granulomatous-thickened tissue with embedded micro-abscess without a significant pus collection.
- Liquid abscess surrounded by inflammatory tissue shows a varying degree of peripheral enhancement with gadolinium.

The key to relating liquid abscesses, which is usually a sufficient cause for surgical drainage, is the presence of a region of high T2 signal, with low T1 signal and without enhancement, usually surrounded by an edge of enhancement *(as shown in figure 2)*. DWI/ADC commonly demonstrates limited diffusion of the abscesses content.[26]

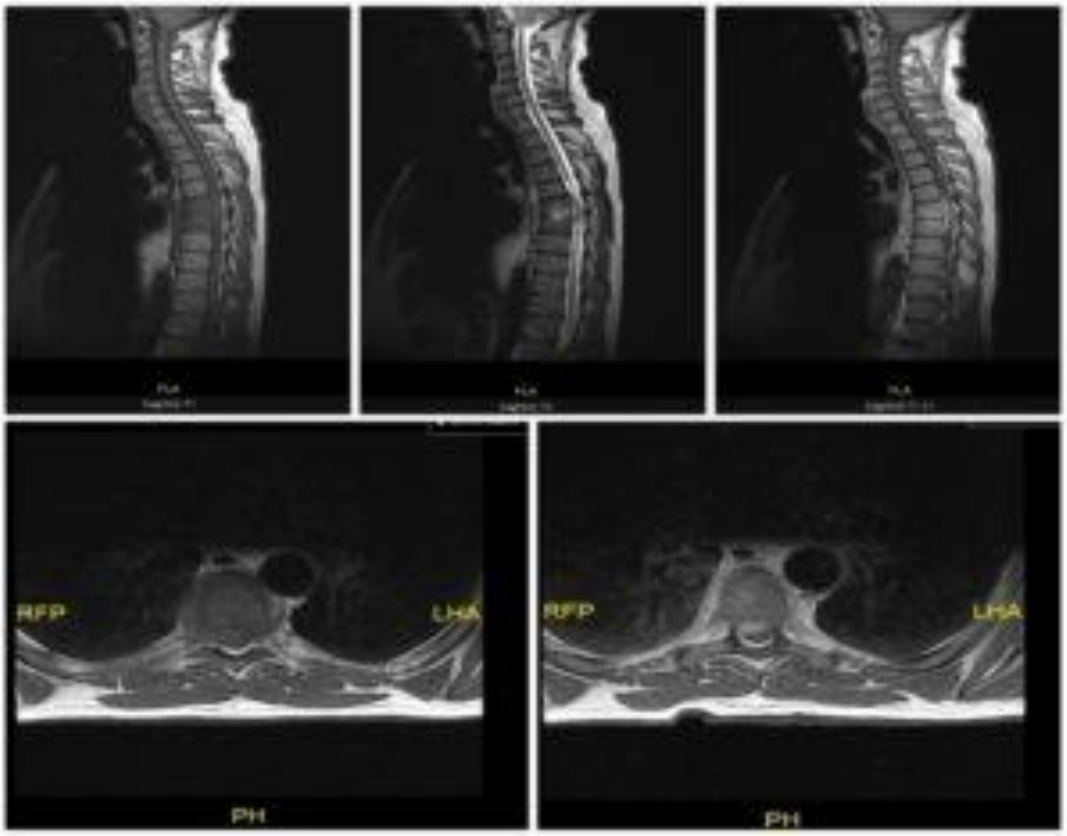


Figure 2. Changing signal and avid enhancement of the T6 and T7 vertebral bodies and intervening discs. Epidural abscess, canal stenosis, and thoracic cord compression at T6/T7 level. L4/L5/S1 degenerative change.[26]

Laboratory Findings

Sensitive tests such as (ESR) and (CRP) can help guide more investigation of epidural abscesses in such patients.[19]

In ICEA serum inflammatory markers, including (ESR) and (CRP) may be elevated. In one study, 73 of 90 patients (81%) had an elevated ESR and 23 of 25 patients (92%) had

a raised CRP.[1,14] Elevated markers of inflammation, although nonspecific, raise the degree of suspicion for infection, while normal measures do not rule out the presence of a brain abscess.[17] The presence of peripheral leucocytosis is highly variable but can be seen in 50% or more of cases.[15]

Lab evaluation for SEAs should include blood cultures, complete blood count, inflammatory markers, and coagulation studies. Although the ESR is often elevated in these patients, it does not rule out the diagnosis of a spinal epidural abscess (85% to 94% sensitivity). Positive cultures are found in 90% of abscess aspirates, 62% of blood specimens, and 19% of CSF specimens.[13]

The presence of leucocytosis is not sensitive nor specific for the diagnosis. While an elevated ESR and CRP are sensitive, they are not disease specific. Blood cultures are positive in almost 60% of SEAs.[18]

Histopathology

Blood cultures define the organisms and histopathology of SEAs. Staph aureus accounts for over 60% of the SEA. Polymicrobial SEAs are a rarity and blood cultures are positive in most patients.

This situation differs from that of IEAs in which blood cultures are positive in only 10% of patients; and even if positive, they do not represent the actual causative organism. Brain abscess pus often grows mixed organisms.[28]

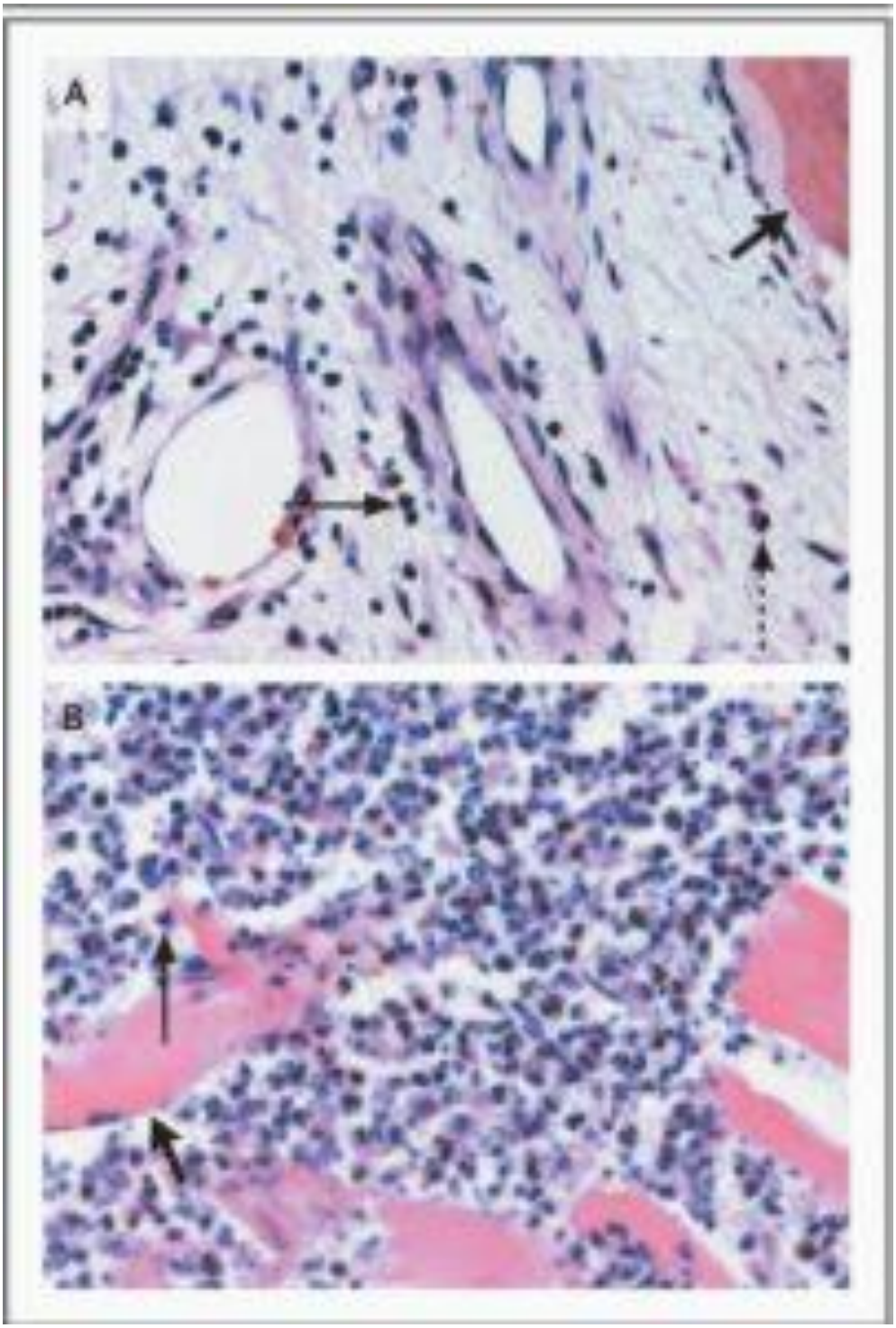


Figure 3.
Histopathological Findings in patients with SEAs.
Panel A, H&E stained vertebral-bone biopsy in chronic vertebral osteomyelitis that led to a SEA, shows chronic inflammatory cells, including lymphocytes (arrow) and plasma cells (dashed thin arrow) in the vicinity of trabecular bone (thick arrow).
Panel B, the spread of infection from the epidural space resulted in the formation of an acute psoas muscle abscess, and the infiltration of PMN cells (thin arrow) adjacent to striated muscle fibers (thick arrow) 16[/caption]

Complications

Complications of SEAs include meningitis or subdural infection if the needle traverses the epidural abscess, sepsis, neurologic deterioration if the lumbar puncture is performed below a complete spinal subarachnoid block, and irreversible paralysis which is the most fearsome complication of spinal epidural abscess and continues to affect 4 to 22% of patients.[16]

ICEA has a 10% mortality rate and may result in long-term neurologic deficits.[24]

Treatment and Management

The treatment of choice is usually urgent surgical debridement in combination with intravenous antibiotics.[8] SEA may be treated without surgery in cautiously selected patients.[20] Few studies have reported similar outcomes in patients who were treated with antibiotics alone and in patients who received both medical and surgical treatment.[16] The findings of blood cultures or CT-guided needle aspiration of the abscess must guide antibiotic treatment.[16]

ICEAs

ICEAs treatment usually requires a combination of a drainage procedure and antibiotic therapy, like most abscesses.

Physicians should choose antibiotics for Streptococcus, Hemophilus, and anaerobes to cover infections that have spread from the ear, sinuses or other areas of the head and neck. Third-generation Cephalosporins plus Vancomycin and Metronidazole is one regimen. They can then change treatment depending on cultures and sensitivities.[4]

Vancomycin does not cross the BBB; therefore, some authors advocate using Rifampin in its place while others may consider a short course of steroids. Linezolid and Daptomycin have also been used, but data on their efficacy are very limited.[4]

Antibiotic therapy is usually 6 to 8 weeks of intravenous agents since oral agents will not achieve a therapeutic level in CSF that is needed for a cure.[10]

SEAs

The treatment usually comprises decompressive surgery, drainage of the abscess, and Eradication of the primary underlying infectious focus (if detectable).

Drainage of the abscess is considered the gold standard under most circumstances. The surgeon usually places a drainage system and continues to irrigate the abscesses for several days post-surgery until the infection is entirely resolved.

Parenteral antibiotic therapy; targets potential etiologic agents such as coagulase-negative staphylococci (CoNS), and streptococci.

A combination of a third-generation Cephalosporin (Ceftriaxone) with another antimicrobial that exhibits anti-staphylococcal activity (Rifampicin, Nafcillin, or Fosfomycin) is recommended.

Physicians must treat patients with antibiotic therapy for 4 to 6 weeks unless there is associated osteomyelitis, in which case they should continue the treatment for 6 to 8 weeks.[1]

Prevention

The most critical factor in preventing permanent disability is early recognition and treatment.[11]

Recent updates

In recent years, the number of reported cases of SEAs has elevated.[23]

The incidence rate of SEAs during the period (2004-2014) of 5.1 cases per 10,000 admissions. Mortality rates among SEAs cases have improved over time from a mortality rate of 81% in the 1920s to 34% in 1954-1960, and 15% in 1991-1997. There was a 7% mortality rate reported in recent studies.[8]

References

1. Chow, F. (2018) “Brain and spinal epidural abscess,” CONTINUUM: Lifelong Learning in Neurology, 24(5), pp. 1327–1348. Available at: https://doi.org/10.1212/con.0000000000000649.
2. Fernández, L.M. et al. (2001) “Absceso epidural intracraneal en Neonato Secundario a catéter Cutáneo,” Neurocirugía, 12(4), pp. 338–341. Available at: https://doi.org/10.1016/s1130-1473(01)70691-4.
3. Sharfman, Z.T. et al. (2020) “Spinal epidural abscess: A review of presentation, management, and Medicolegal Implications,” Asian Spine Journal, 14(5), pp. 742–759. Available at: https://doi.org/10.31616/asj.2019.0369.
4. Lener, S. Et al. (2018) “Management of Spinal Infection: A review of the literature,” Acta Neurochirurgica, 160(3), pp. 487–496. Available at: https://doi.org/10.1007/s00701-018-3467-2.
5. Pradilla, G. Et al. (2009) “Epidural abscesses of the CNS,” The Lancet Neurology, 8(3), pp. 292–300. Available at: https://doi.org/10.1016/s1474-4422(09)70044-4.
6. Kitov, B. Et al. (2020) “Outcome of surgical treatment of spontaneous spinal epidural abscesses for a 10-year period,” Folia Medica, 62(3), pp. 482–489. Available at: https://doi.org/10.3897/folmed.62.e49902.
7. Ma, H.J. and Kim, I. (2012) “Clinical outcomes of spinal epidural abscess,” Korean Journal of Spine, 9(1), p. 6. Available at: https://doi.org/10.14245/kjs.2012.9.1.6.
8. Vakili, M. And Crum-Cianflone, N.F. (2017) “Spinal epidural abscess: A series of 101 cases,” The American Journal of Medicine, 130(12), pp. 1458–1463. Available at: https://doi.org/10.1016/j.amjmed.2017.07.017.

9. MB;, A.H.B. (no date) Epidural abscess, National Center for Biotechnology Information. U.S. National Library of Medicine. Available at: https://pubmed.ncbi.nlm.nih.gov/30571071/ (Accessed: October 31, 2022).
10. Ferrara, P. Et al. (2016) “Irrigation with liquid sevoflurane and healing of a postoperative, recurrent epidural infection: A potential cost-saving alternative,” World Neurosurgery, 90. Available at: https://doi.org/10.1016/j.wneu.2016.02.079.
11. Davis, D.P. et al. (2004) “The clinical presentation and impact of diagnostic delays on emergency department patients with spinal epidural abscess,” The Journal of Emergency Medicine, 26(3), pp. 285–291. Available at: https://doi.org/10.1016/j.jemermed.2003.11.013.
12. Rigamonti, D. et al. (1999) “Spinal epidural abscess: Contemporary trends in etiology, evaluation, and Management,” Surgical Neurology, 52(2), pp. 189–197. Available at: https://doi.org/10.1016/s0090-3019(99)00055-5.
13. FB;, A.M.A.K.T.L.M. (no date) Spinal epidural abscess, National Center for Biotechnology Information. U.S. National Library of Medicine. Available at: https://pubmed.ncbi.nlm.nih.gov/28722920/ (Accessed: October 31, 2022).
14. J;, S.K.F.G.T.A.P. (no date) Brain abscesses—the groote schuur experience, 1993-2003, South African journal of surgery. Suid-Afrikaanse tydskrif vir chirurgie. U.S. National Library of Medicine. Available at: https://pubmed.ncbi.nlm.nih.gov/16180392/ (Accessed: October 31, 2022).
15. Sharma, R., Mohandas, K. And Cooke, R.P. (2009) “Intracranial abscesses: Changes in epidemiology and management over five decades in Merseyside,” Infection, 37(1), pp. 39–43. Available at: https://doi.org/10.1007/s15010-008-7359-x.
16. Darouiche, R.O. (2006) “Spinal epidural abscess,” New England Journal of Medicine, 355(19), pp. 2012–2020. Available at: https://doi.org/10.1056/nejmra055111.
17. Helweg-Larsen, J. Et al. (2012) “Pyogenic brain abscess, a 15 year survey,” BMC Infectious Diseases, 12(1). Available at: https://doi.org/10.1186/1471-2334-12-332.
18. Kolinsky, D.C. and Liang, S.Y. (2018) “Musculoskeletal infections in the emergency department,” Emergency Medicine Clinics of North America, 36(4), pp. 751–766. Available at: https://doi.org/10.1016/j.emc.2018.06.006.
19. Allencherril, R. And Joseph, L. (2020) “Pneumococcal epidural abscess in an asplenic patient presenting after mild hip trauma,” Cureus [Preprint]. Available at: https://doi.org/10.7759/cureus.7494.
20. DeFroda, S.F. et al. (2015) “Evaluation and management of spinal epidural abscess,” Journal of Hospital Medicine, 11(2), pp. 130–135. Available at: https://doi.org/10.1002/jhm.2506.
21. Chima-Melton, C., Pearl, M. and Scheiner, M. (2017) Diagnosis of spinal epidural abscess: A case report and literature review, Spinal cord series and cases. U.S. National Library of Medicine. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5382353/ (Accessed: December 2, 2022).
22. Tompkins, M. Et al. (2010) “Spinal epidural abscess,” The Journal of Emergency Medicine, 39(3), pp. 384–390. Available at: https://doi.org/10.1016/j.jemermed.2009.11.001.
23. “Spinal epidural abscess: A review highlighting early diagnosis and management” (2019) JMA Journal [Preprint]. Available at: https://doi.org/10.31662/jmaj.2019-0038.
24. Edlund, W. Et al. (2020) “Intracranial epidural abscess in a 9-year-old boy with precocious puberty and use of continuous positive airway pressure,” Journal of Child Neurology, 35(8), pp. 509–511. Available at: https://doi.org/10.1177/0883073820912047.
25. Neto, A.R.de A. (2022) Intracranial epidural abscess: Radiology case, Radiopaedia Blog RSS. Radiopaedia.org. Available at: https://radiopaedia.org/cases/intracranial-epidural-abscess?lang=gb (Accessed: October 31, 2022).
26. Weerakkody, Y. (2022) Spinal epidural abscess: Radiology reference article , Radiopaedia Blog RSS. Radiopaedia.org. Available at: https://radiopaedia.org/articles/spinal-epidural-abscess?lang=gb (Accessed: October 31, 2022).
27. Mackenzie, A.R. et al. (1998) “Spinal epidural abscess: The importance of early diagnosis and treatment,” Journal of Neurology, Neurosurgery & Psychiatry, 65(2), pp. 209–212. Available at: https://doi.org/10.1136/jnnp.65.2.209.
28. Akhondi H, Baker MB. Epidural Abscess. 2022 May 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 30571071.

Article topic: Intraventricular Central Neurocytoma.

Author: Abdallah Arabyat.

Editor: Rahmeh Adel.

Reviewer: Ethar Hazaimeh.

keywords: Central neurocytoma, Histopathology, Management.

Overview

Central neurocytoma is a rare intraventricular brain tumor, that typically appears in young adults with elevated intracranial pressure as a result of obstructive hydrocephalus.

The Ventricular System

The lateral, third, and fourth ventricles make up the ventricular system of the brain. These are just little cavities in the brain that are connected by tiny ducts and canals (*as shown in Figure 1*). The choroid plexus, which is found in each lateral ventricle and resembles a tuft, is primarily responsible for producing cerebrospinal fluid.[1]

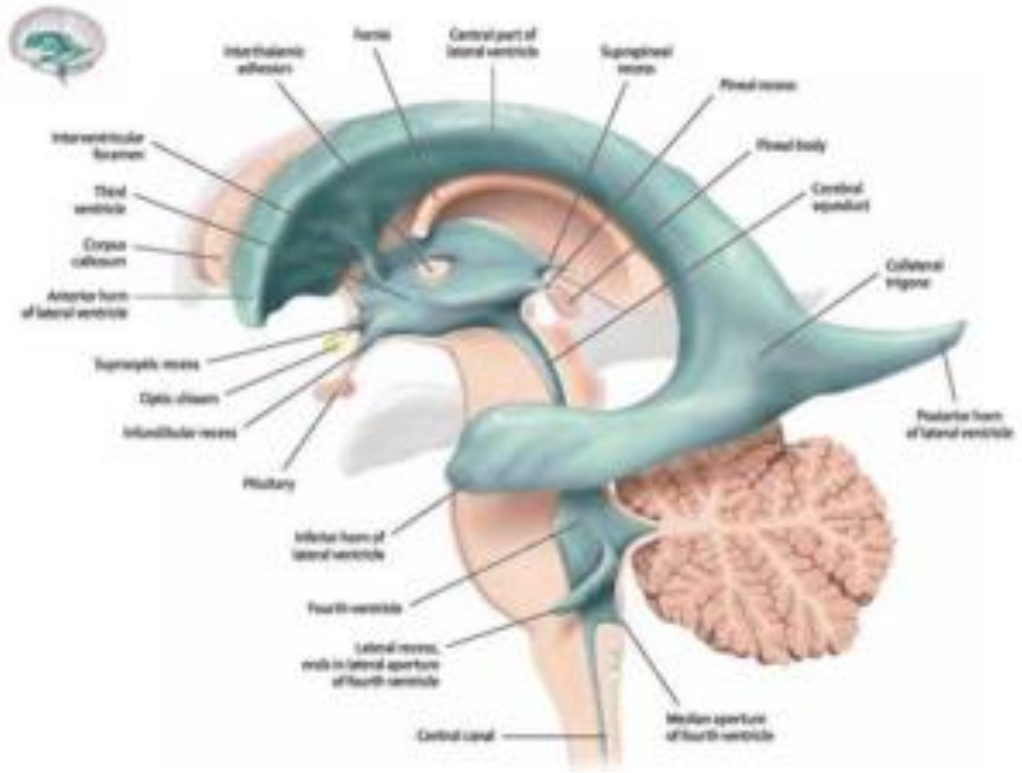


Figure (1), The ventricular system of the brain 2[/caption]

Each hemisphere has a pair of lateral ventricles. Each one is a C-shaped cavity that can be separated into an inferior horn that extends into the temporal lobe and anterior, posterior, and inferior horns that are each located in the frontal, occipital, and parietal lobes, respectively. The intraventricular foramen, also known as the foramen of Monro, connects the lateral ventricle to the third ventricle. On its medial side, the lateral ventricle's choroid plexus extends into the hollow.[1]

Between the thalami, there is a small slit which is the third ventricle. Additionally, it has a connection to the fourth ventricle via the cerebral aqueduct or the aqueduct of Sylvius. The choroid plexuses are found above the roof of the ventricle.[1]

The fourth ventricle is located behind the pons and the upper half of the medulla and anterior to the cerebellum. It is continuous superiorly with the cerebral aqueduct and the central canal below. The fourth ventricle has a floor, two lateral walls, and a tent-shaped ceiling. The two lateral foramina of Luschkea and the median foramen of Magendie are the fourth ventricle's three tiny apertures. The cerebrospinal fluid enters the subarachnoid area through these holes.[1]

The fourth ventricle's choroid plexus features a T-shape. The cerebrospinal fluid is transported by the ventricular system (*as shown in Figures 1 & 2*). Cerebrospinal fluid is actively secreted by the choroid plexuses of the ventricles, while part of the fluid may come from tissue fluid generated in the brain matter.[1]

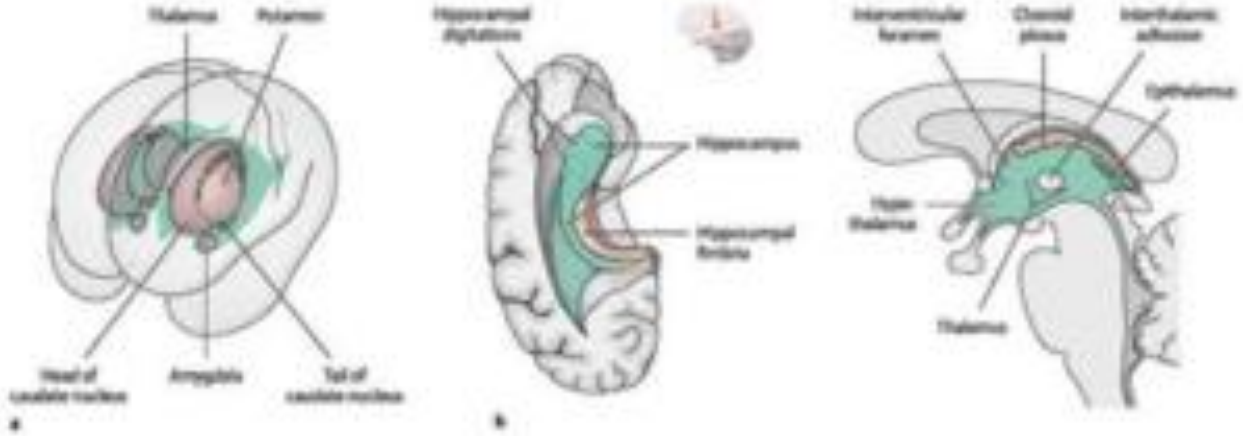


Figure (2), the ventricular system of the brain 2.

Disease Entity

The lateral ventricles of the central nervous system (CNS) are the major location of Central Neurocytoma (CN), a benign primary neuronal tumor. Less than 1% of brain tumors are CN, which primarily affects young adults. [3] CN is a grade II brain tumor, according to the World Health Organization (WHO) classification. Though its cause is uncertain, central neurocytoma is thought to develop from subependymal cells of the lateral ventricles and neuronal cells of the septum pellucidum.[4]

Epidemiology

Hassoun first reported CN et al. in 1982, and it is still a rare diagnosis. Small series and lone case reports account for a substantial portion of the information we have regarding CN. Asian people have reported more incidences of CN than Caucasian ones, with higher rates in Korea, India, and Japan.[6] CN tends to affect both men and women equally, primarily affecting individuals in their second or third decade of life. [7]

Pathology

A homogenous population of spherical cells with little cytoplasm in a fibrillary backdrop make up central neurocytomas. The nuclei have punctate nucleoli and finely specked chromatin. There is often a fragile capillary vascular network (*as shown in figure 3*).[8] The tumor cells are immunoreactive for synaptophysin, NSE, and other neural markers and exhibit ultrastructural signs of neural development. Rare, atypical forms with enhanced mitotic activity, necrosis, and cytologic atypia have been observed. Ependymomas and intraventricular oligodendrogliomas are frequently included in the differential diagnosis. [8]

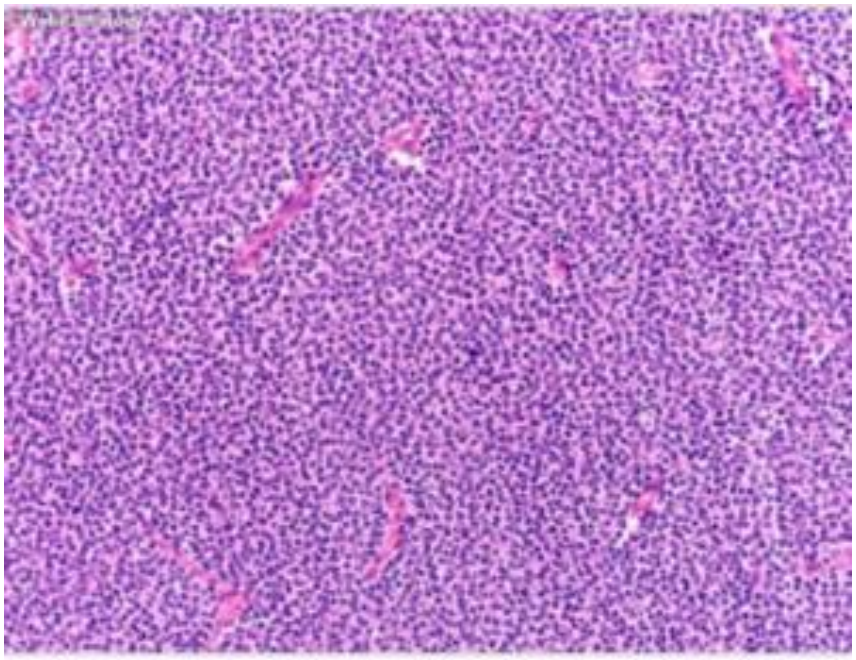


Figure 3, A uniform population of round cells with scant cytoplasm in a fibrillary background.[8]

Synaptophysin, a transmembrane glycoprotein present in presynaptic neuronal vesicles, is the most trustworthy diagnostic marker.[9]

Western blotting or immunohistochemistry is used to measure synaptophysin reactivity. However, it is important to remember that the lack of synaptophysin does not rule out the diagnosis of CN. According to studies, it is possible to distinguish between CN and other CNS neoplasms using an immunohistochemical panel that includes the Epithelial Membrane Antigen (EMA), vimentin, and neuronal nuclear protein (NeuN). When EMA and vimentin are negative and NeuN is positive, CN is more likely to be diagnosed than ependymoma or oligodendroglioma.[3]

Imaging Features

General

Intraventricular mass in the supratentorial region that appears cystic or bubbly. Near the foramen of Monro, it is frequently found with a lateral ventral frontal horn or body attached to the septum pellucidum or lateral ventricular wall, either with or without third ventricular extension. It often displays calcification.

CT scan

Heterogeneous density intraventricular mass due to solid and cystic components with and without calcification.

MRI

T1: heterogeneous but predominantly isointense. Figure (4)

T2: usually hyperintense with cystic or bubbly appearance; ±flow voids. Figure (5)

FLAIR: heterogeneously hyperintense. Figure (6)

T2*/GRE/SWI: black signal blooming in foci of calcification

T1WI+C: heterogeneous enhancement. Figure (7)

MRS: increased Cho, decreased NAA; glycine peak at 3.55

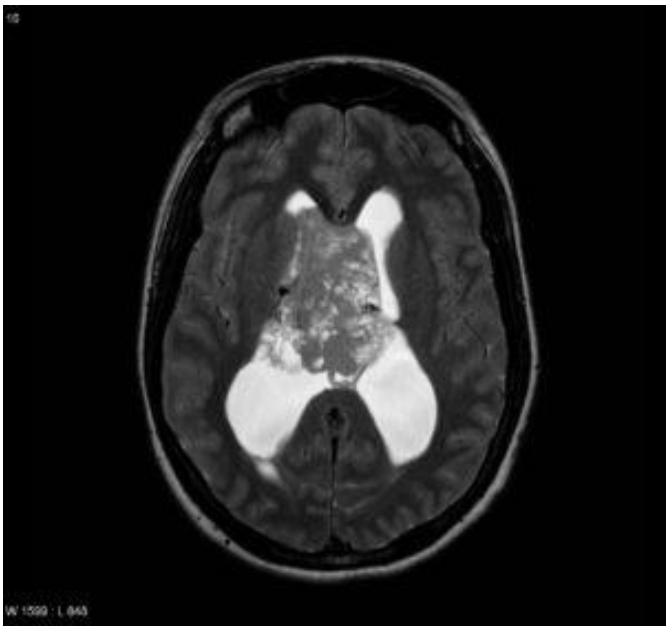


Figure (4) Axial T1

Figure (5) Axial T2

Figure (6) Axial FLAIR

Figure (7) Axial T1 C+

Earlier Figures are selected images from MRI of the brain including post-contrast sequences that demonstrate a large intraventricular mass filling and expanding the body of the right lateral ventricle. It has a high T2 signal, and wispy regions of intermediate T1 signal giving it a bubbly appearance. Following contrast administration only minimal heterogeneous enhancement is present.[10]

Clinical presentations

Due to the interventricular foramen obstruction, patients may have elevated intracranial pressure and hydrocephalus.[17]

Headaches, seizures, nausea, vomiting, and changes in memory or vision are just a few of the possible side effects that patients may face.[18,19]

Treatment

Institutional case studies provide a guide for managing CN. The standard of care for treating CNs is gross total resection (GTR) surgery, which is successful in 30 to 50% of cases and has a 5-year survival rate of 99% according to studies.[5] Patients with subtotal resection (STR) have a higher chance of recurrence and are given radiosurgery or adjuvant radiotherapy as treatment. Studies have been inconclusive as to whether adjuvant fractionated radiotherapy or adjuvant stereotactic radiosurgery is better for local tumor control, but both have proved to be better when GTR cannot be achieved.[9]

Prognosis

CNs often have low rates of local recurrence and are benign tumors amenable to surgical resection. According to specific research, the five-year survival rate for CN following GTR can reach 99%, but the five-year survival rate for CN merely reaching STR is 86%. [9]

Reference

1. Russell J. Love Ph.D., Wanda G. Webb Ph.D., in Neurology for the Speech-Language Pathologist, 1992
2. Atlas of Anatomy. Head and Neuroanatomy. Michael Schuenke 13. Ventricular System and Cerebrospinal Fluid
3. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathol. 2007;114(2):97-109. doi:10.1007/s00401-007-0243-4
4. Choudhari KA, Kaliaperumal C, Jain A, et al. Central neurocytoma: A multidisciplinary review. British Journal of Neurosurgery. 2009;23(6):585-595. doi:10.3109/026886909032543
5. Hassoun J, Soylemezoglu F, Gambarelli D. Central neurocytoma: a synopsis of clinical and histological features. Brain Pathol 1993; 3:297-306.
6. Sharma MC, Deb P, Sharma S, Sarkar C. Neurocytoma: a comprehensive review. Neurosurg Rev. 2006;29(4):270-285; discussion 285. doi:10.1007/s10143-006- 0030-z
7. Choudhari KA, Kaliaperumal C, Jain A, et al. Central neurocytoma: A multi-disciplinary review. British Journal of Neurosurgery. 2009;23(6):585-595. doi:10.3109/02688690903254350
8. https://www.webpathology.com/image.asp?n=2&Case=633
9. Lee SJ, Bui TT, Chen CHJ, et al. Central Neurocytoma: A Review of Clinical Management and Histopathologic Features. Brain Tumor Res Treat. 2016;4(2):49-57. doi:10.14791/btrt.2016.4.2.49 .
10. Case courtesy of Frank Gaillard, Radiopaedia.org. From the case rID: 4355
11. Kocaoglu M, Ors F, Bulakbasi N, et al. Central neurocytoma: proton MR spectroscopy and diffusion-weighted MR imaging findings. Magn Reson Imaging 2009;27:434–440. doi.org/10.1016/j.mri.2008.07.012.
12. Osborn AG, Salzman KL, Jhaveri MD. Diagnostic Imaging (3rd ed). Elsevier, Philadelphia, PA; 2016.
13. Patel DM, Schmidt RF, Liu JK. Update on the diagnosis, pathogenesis, and treatment strategies for central neurocytoma. J Clin Neurosci 2013;20:1193–1199. doi.org/10.1016/j.jocn.2013.01.001.
14. Schmidt MH, Gottfried ON, von Koch CS, et al. Central neurocytoma: a review. J Neurooncol 2004;66:377–384. doi.org/10.1023/b:neon.0000014541.87329 .3b.
15. Tlili-Graiess K, Mama N, Arifa N, et al. Diffusion-weighted MR imaging and proton MR spectroscopy findings of central neurocytoma with pathological correlation. J Neuroradiol 2014;41:243–250. doi.org/10.1016/j.neurad.2013.09.004.
16. Yeh IB, Xu M, Ng WH, et al. Central neurocytoma: typical magnetic resonance spectroscopy findings and atypical ventricular dissemination. Magn Reson Imaging 2008;26:59–64. doi.org/10.1016/j.mri.2007.04.005.
17. Lee SJ et al. Central neurocytoma: a review of clinical management and histopathologic features. Brain Tumor Res Treat 2016;4(2):49–57.
18. Yang I et al. Clinical manifestations of central neurocytoma. Neurosurg Clin N Am 2015;26(1):5–10.
19. Wang M et al. Clinical features, treatment, and long-term outcomes of central neurocytoma: a 20-year experience at a single center. World Neurosurg 2017.

Article Title: Encephalocele.

Author: Mohammad Al Jamal.

Editor: Aseel Rabadi, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: Cerebrospinal fluid, Congenital brain abnormality, Neural tube defect, Occipital encephalocele.

Overview

Encephalocele is a type of congenital neural tube defect (NTD) in which a sac containing the brain, meninges, and cerebrospinal fluid (CSF) forms outside the skull due to a defect in the bone. Trauma, tumors, or iatrogenic injury can all cause acquired encephaloceles. [1] Depending on the intracranial content protruding through the skull opening, encephalocele defects are divided into four types: meningoencephaloceles (*herniations of cerebrospinal fluid (CSF), brain tissue, and meninges*); meningoceles (*herniations of the meninges and CSF*), glioceles (*glial-lined cyst containing CSF*) and atretic cephaloceles (*forming of the dura, fibrous tissue and degenerated brain tissue*). [2] Occipital encephalocele is the most common form of this congenital disorder and is manifested as a midline swelling of different sizes over the occipital bone. [3]

Repairing an encephalocele is not an emergency, and only individuals with skin ulcers or CSF leaks require immediate surgery to avoid complications such as meningitis. Surgery can be performed as early as two months of age but is often postponed for months to several years due to newborns limited total blood volume. The surgical goals are to close the skull defect with a watertight Dural closure and to restore the bone deficit. [4]

Figure (1): Encephalocele.

Etiology

The cause of encephalocele is not completely understood, and is multifactorial, including both genetic and environmental factors. Individuals with a family history of NTDs (spina bifida, anencephaly) have a higher risk to develop encephalocele. The presence of the gene associated with certain disorders does not assure the development of the anomaly. However, the presence of some factors (e.g. environmental) might trigger the disease. [5] Researchers have emphasized that non-specific environmental factors (such as hyperthermia, aflatoxins, genetic background, mother's lack of nutrition, or other environmental factors) are involved in the development of encephalocele. [6] Maternal levels of folate and its relevance for encephalocele is still 'not clear.' [7] However, the use of folic acid (400 micrograms of folic acid daily) in the diet of pregnant women might lower the risk of some NTDs. [4]

Pathophysiology

Encephaloceles are a type of NTDs series caused by neurulation failure, such as the failure of neural tube closure. [8,9] This theory, however, does not explain the existence of well-formed neural structures within the prolapsed sac because brain tissue is formed after the neural tube is closed. As a result, some authors propose that an encephalocele is a post-neurulation event. [10][11]

According to these post-neurulation ideas, failure of mesodermal migration into the midline results in brain matter herniation. The deformed, stretched appearance of the

neuroparenchyma next to the calvarial defect is best explained by this notion. Many cases, particularly occipital kinds, showed the stretched and distorted appearance of the brain next to the cranial vault defect, supporting the post-neurulation idea. Skull base encephaloceles can be caused by a primary osseous defect, a failure of bone induction due to a defective neural tube closure, a lack of fusion of ossification centers, or a persistent cricopharyngeal canal. [12,13]

Clinical presentation and complications

Encephalocele is frequently evident and detectable at birth as a deformity in the midline of the skull with a big projecting mass. There will be no apparent mass if it is located in the nasopharynx, but the infant may have breathing issues due to airway obstruction. [14]

The size and location of the encephalocele influence whether the newborn develops properly or has any malformations or growth difficulties. When a frontal encephalocele extends into one of the eye orbits, proptosis might happen. Occipital encephalocele, on the other hand, can result in blindness and cognitive disability.

Still, the most common encephalocele complications are irregular CSF circulation and meningitis. Other complications to consider are: [14]

- CSF leak
- Seizures
- Hydrocephalus
- Endoscopic recurrence
- Developmental delay
- Developmental impairment

Workup and Evaluation

The cornerstone imaging demonstrating a fluid-filled sac through a skull defect is prenatal ultrasonography, which is commonly conducted between the 9th and 11th weeks of gestation. [15, 16] By 13 weeks, it will be clear whether the abnormality is a meningocele (*without brain matter herniation*) or an encephalocele. [17]

Prenatal magnetic resonance imaging (MRI) will have easily revealed the problem, but the fetus must be sedated in order to be imaged so it is not commonly used. Postnatal brain MRI is preferred, showing the defect, its contents, brain tissue, and any accompanying anomalies. To assess the skull defect, bone anomalies, and hydrocephalus, a computed tomographic (CT) scan of the head is performed. [18] Angiography can be used if the defect is close to the Dural sinuses. MRI with magnetic

resonance angiography (MRA) is a beneficial method to visualize the contents of the sac and its relationship to venous sinuses. [19]

CT scan in fetal life, particularly in the first two trimesters, is not recommended because of the side effects of radiation. [20] The significant value of postnatal CT scan comes from its excellent ability in showing the details of bony defects. [21] Yet, compared to MRI, CT scan is less effective in depicting soft tissue components in encephaloceles. [20]

Management and Treatment

Treating these defects necessitates the collaboration of a multidisciplinary team of neurosurgeons, neuro anesthetists, pediatricians, maxillofacial surgeons, and plastic surgeons. These anomalies should be treated in the first few months of life if possible because identifying the intracranial connection would be technically easier, and the Dural defect would be completely fixed. The goal of the procedure is to close the internal defect with a watertight Dural closure (intradural repair is recommended over extradural repair), close the skull defect, resect the sac, and restore the exterior bony deformity (titanium mesh or Osteopore bone scaffold filler). [22] **Figure (2)**.

The reconstruction goals are:

(a) To close open skin defects preventing infection and desiccation of viable brain tissue.

(b) To remove or invaginate nonfunctional extracranial cerebral tissue.

(c) To close the dura and do a craniofacial reconstruction with focusing on accurate skeletal reconstruction. [23]

Early surgical correction is necessary for children with frontoethmoidal encephalocele to treat and avoid facial abnormalities, binocular vision impairment, swelling that worsens due to secondary herniation of intracranial contents, and the possibility of infections of the central nervous system. The treatment of accompanying brain malformations (such as hydrocephalus) should come first, followed by a one-stage reconstructive operation. [22, 24-26]

Frontoethmoidal encephaloceles appear to have a favorable prognosis than occipital or parietal meningoencephaloceles, with an overall mortality rate of 7%-20% and a fair developmental outcome. [24, 27] The occurrence of concomitant hydrocephalus or other congenital brain abnormalities determines the prognosis. [28]

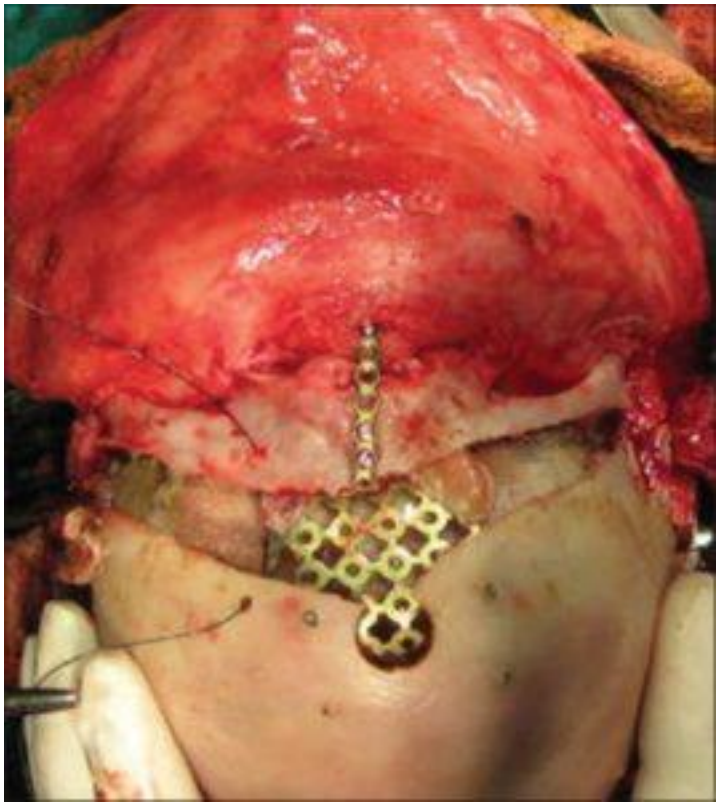


Figure (2): Intraoperative photograph showing reconstruction of the skull defect by titanium mesh [29]

Prognosis

Many factors influence an encephalocele's prognosis, including its location, size, the amount of brain tissue and Dural sinuses inside the sac, and the presence of hydrocephalus. [30,31] Patients with frontoethmoidal encephaloceles have a better prognosis than those with occipital or parietal encephaloceles. The occurrence of additional congenital brain abnormalities markedly influences the prognosis. A research paper assessing the clinical predictors found that seizures, microcephaly, and brain tissue in the sac were all associated with poor prognosis. Whereas hydrocephalus and the existence of other intracranial abnormalities were found to be significant predictors of developmental delay. [32] Hydrocephalus exists in 34% of all patients prior to surgical correction of the defect and develops in 4% of them after the defect is closed. [33]

A long-term study of children with encephaloceles revealed that 48% developed normally, 11% had mild impairment, 16% had a substantial impairment, and 25% had severe impairment. [32] Due to seizures and hydrocephalus, occipital encephaloceles have a poorer prognosis than frontal encephaloceles. Approximately half of the occipital encephalocele patients are unable to live independently in society. [34]

References

[1] Gump WC. Endoscopic Endonasal Repair of Congenital Defects of the Anterior Skull Base: Developmental Considerations and Surgical Outcomes. J Neurol Surg B Skull Base. 2015 Aug;76(4):291-5
[2] Ugras M., Kavak O., Alpay F., Karabekir S.H., Bicer S. New Born Children with Encephalocele Journal of Neurology and Neuroscience. 2016;7(73):1–4.
[3] Markovic I, Bosnjakovic P, Milenkovic Z. Occipital Encephalocele: Cause, Incidence, Neuroimaging and Surgical Management. Curr Pediatr Rev. 2020;16(3):200-205. doi: 10.2174/1573396315666191018161535. PMID: 31656152; PMCID: PMC8193807.
[4] Matos Cruz AJ, De Jesus O. Encephalocele. [Updated 2022 Sep 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562168/#
[5] NORD https://rarediseases.org/rare-diseases/encephalocele/
[6] Agthong S., Wiwanitkit V. Encephalomeningocele cases over 10 years in Thailand: a case series. BMC Neurol. 2002;2:3. doi: 10.1186/1471-2377-2-3.
[7] Siffel C., Wong L.Y., Olney R.S., Correa A. Survival of infants diagnosed with encephalocele in Atlanta, 1979-98. Paediatr. Perinat. Epidemiol. 2003;17(1):40–48. doi: 10.1046/j.1365-3016.2003.00471.x.
[8] Wen S., Ethen M., Langlois P.H., Mitchell L.E. Prevalence of encephalocele in Texas, 1999-2002. Am. J. Med. Genet. A. 2007;143A(18):2150–2155. doi: 10.1002/ajmg.a.31907.
[9] Sadewa A.H., Sutomo R., Istiadjid M., et al. C677T mutation in the MTHFR gene was not found in patients with frontoethmoidal encephalocele in East Java, Indonesia. Pediatr. Int. 2004;46(4):409–414. doi: 10.1111/j.1442-200x.2004.01927.x.
[10] Nakatsu T, Uwabe C, Shiota K (2000) Neural tube closure in humans initiates at multiple sites: evidence from human embryos and implications for the pathogenesis of neural tube defects. Anat Embryol (Berl) 201(6):455–466.
[11] Marin-Padilla M (1980) Morphogenesis of experimental encephalocele (cranioschisis occulta). J Neurol Sci 46(1):83–99.
[12] Gluckman TJ, George TM, McLone DG (1996) Postneurulation rapid brain growth represents a critical time for encephalocele formation: a chick model. Pediatr Neurosurg 25(3):130–136.
[13] Bhagwati SN, Mahapatra AK (1999) Encephalocele and anomalies of the scalp. In: Choux M, Di Rocco C, Hockley AD, Walker JL (eds) Pediatric neurosurgery. Churchill Livingstone, London, pp 101–120
[14] Thompson HM, Schlosser RJ, McCarty Walsh E, Cho DY, Grayson JW, Karnezis TT, Miller PL, Woodworth BA. Current management of congenital anterior cranial base encephaloceles. Int J Pediatr Otorhinolaryngol. 2020 Apr;131:109868
[15] Ong AGJ, Rolnik DL, Menezes M, Meagher S. Early Diagnosis and Differences in Progression of Fetal Encephalocele. J Ultrasound Med. 2020 Jul;39(7):1435-1440.[PubMed][Reference list]
[16] Budorick NE, Pretorius DH, McGahan JP, Grafe MR, James HE, Slivka J. Cephalocele detection in utero: sonographic and clinical features. Ultrasound Obstet Gynecol. 1995 Feb;5(2):77-85.[PubMed][Reference list]
[17] Ong AGJ, Rolnik DL, Menezes M, Meagher S. Early Diagnosis and Differences in Progression of Fetal Encephalocele. J Ultrasound Med. 2020 Jul;39(7):1435-1440.[PubMed][Reference list]
[18] Matos Cruz AJ, De Jesus O. Encephalocele. [Updated 2022 Sep 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562168/
[19] Walia B., Bhargava P., Sandhu K. Giant Occipital EncephaloceleMed J Armed Forces India. 2005;61:293–294. doi: 10.1016/S0377-1237(05)80181-9.
[20] MEDSCAPE https://emedicine.medscape.com/article/403308-overview#a2
[21] Franco A., Jo S.Y., Mehta A.S., Pandya D.J., Yang C.W. A Rare Triad of Giant Occipital Encephalocele with Lipomyelomeningocele, Tetralogy of Fallot, and Situs Inversus. J. Radiol. Case Rep. 2016;10(3):36–46. doi: 10.3941/jrcr.v10i3.2718.
[22] Smit CS, Zeeman BJ, Smith RM, de V Cluver PF. Frontoethmoidal meningoencephaloceles: A review of 14 consecutive patients. *J Craniofac Surg*. 1993;4:210–4. [PubMed] [Google Scholar] [Ref list]
[23] Velho V, Naik H, Survashe P, Guthe S, Bhide A, Bhople L, Guha A. Management Strategies of Cranial Encephaloceles: A Neurosurgical Challenge. Asian J Neurosurg. 2019 Jul-Sep;14(3):718-724. doi: 10.4103/ajns.AJNS_139_17. PMID: 31497091; PMCID: PMC6703041.
[24] Macfarlane R, Rutka JT, Armstrong D, Phillips J, Posnick J, Forte V, et al. Encephaloceles of the anterior cranial fossa. *Pediatr Neurosurg*. 1995;23:148–58.[PubMed] [Google Scholar][Ref list]
[25] David DJ. Cephaloceles: Classification, pathology, and management – A review. *J Craniofac Surg*. 1993;4:192–202.[PubMed] [Google Scholar][Ref list]
[26] Forcada M, Montandon D, Rilliet B. Frontoethmoidal cephaloceles: Transcranial and transfacial surgical treatment. *J Craniofac Surg*. 1993;4:203–9.[PubMed] [Google Scholar][Ref list]
[27] Holmes AD, Meara JG, Kolker AR, Rosenfeld JV, Klug GL. Frontoethmoidal encephaloceles: Reconstruction and refinements. *J Craniofac Surg*. 2001;12:6–18.[PubMed] [Google Scholar][Ref list]
[28] Hoving EW, Vermeij-Keers C. Frontoethmoidal encephaloceles, a study of their pathogenesis. *Pediatr Neurosurg*. 1997;27:246–56.[PubMed] [Google Scholar][Ref list]
[29] Velho V, Naik H, Survashe P, Guthe S, Bhide A, Bhople L, Guha A. Management Strategies of Cranial Encephaloceles: A Neurosurgical Challenge. Asian J Neurosurg. 2019 Jul-Sep;14(3):718-724. doi: 10.4103/ajns.AJNS_139_17. PMID: 31497091; PMCID: PMC6703041.
[30] Siffel C, Wong LY, Olney RS, Correa A. Survival of infants diagnosed with encephalocele in Atlanta, 1979-98. Paediatr Perinat Epidemiol. 2003 Jan;17(1):40-8.[PubMed][Reference list]
[31] Nath HD, Mahapatra AK, Borkar SA. A giant occipital encephalocele with spontaneous hemorrhage into the sac: A rare case report. Asian J Neurosurg. 2014 Jul-Sep;9(3):158-60.[PMC free article] [PubMed][Reference list]

[32] Lo BW, Kulkarni AV, Rutka JT, Jea A, Drake JM, Lamberti-Pasculli M, Dirks PB, Thabane L. Clinical predictors of developmental outcome in patients with cephaloceles. J Neurosurg Pediatr. 2008 Oct;2(4):254-7.[PubMed][Reference list]
[33] Rehman L, Farooq G, Bukhari I. Neurosurgical Interventions for Occipital Encephalocele. Asian J Neurosurg. 2018 Apr-Jun;13(2):233-237.[PMC free article] [PubMed][Reference list]
[34] Bui CJ, Tubbs RS, Shannon CN, Acakpo-Satchivi L, Wellons JC, Blount JP, Oakes WJ. Institutional experience with cranial vault encephaloceles. J Neurosurg. 2007 Jul;107(1 Suppl):22-5.[PubMed][Reference list]
Figure 1: Jahangir Moini, Pirouz Piran, in Functional and Clinical Neuroanatomy, 2020
Figure 2: Velho V, Naik H, Survashe P, Guthe S, Bhide A, Bhople L, Guha A. Management Strategies of Cranial Encephaloceles: A Neurosurgical Challenge. Asian J Neurosurg. 2019 Jul-Sep;14(3):718-724. doi: 10.4103/ajns.AJNS_139_17. PMID: 31497091; PMCID: PMC6703041.

Article topic: Brainstem Cavernoma.

Author: Ali Ifraitekh.

Editors: Rawan Hamamreh, Yasmeen Alabdallat.

Reviewer: Adam M. Abdallah.

keywords: Cavernous Hemangioma, Cavernoma, angioma, malformation, Brainstem, Vascular malformation

Overview

Cavernoma, Cavernous angioma, cavernous hemangioma, cavernous malformation, and cerebral cavernous malformations are all terms describing the same disease (2). A cavernoma usually presents in the CNS, particularly in the brain, they can also affect the spinal cord and other areas of the body. Cavernomas are quite common but rarely symptomatic, it is thought that they can affect 1 in 200 people but only about one in 10 will develop symptoms (3).

A symptomatic cavernoma can present with a wide variety of mainly neurological symptoms some of which include headaches, focal neurological deficits, seizures, and hemorrhage or it can even be discovered incidentally (that is, while looking for another anomaly). The most common finding was found to be seizures though (4). Cavernomas represent 15% of cerebrovascular malformations. Cavernomas are usually associated with other vascular malformations, most notably venous malformations.

The incidence rate of cavernomas was found to be 0.15-0.56 per 100 000 persons per year. The annual hemorrhage rate was found to be between 0.6% and 11% per patient per year (5).

Pathology

Cavernomas are abnormal vascular structures made up of bubble-like cavities termed Caverns. Venous blood flows through them. Their walls are thin and can leak blood. They range from being microscopic to being several inches in diameter. The cause is often unknown although up to 20% are familial in origin (6). Cavernomas are often described to look like a berry. The enlarged closely packed vessels of cavernomas have no interposition of the brain parenchyma and are usually surrounded by hemosiderin and gliosis. The cause of cavernomas is unknown although 20% of cases are familial in origin (6). The remaining 80% are sporadic. The inheritance pattern of familial cases is autosomal dominant with incomplete penetrance. Lesions in the brain are divided based

on their location relative to the tentorium cerebelli into supra and infratentorial lesions. Brainstem cavernomas are infratentorial. Approximately 70% of cases are supratentorial and 30% are infratentorial, particularly in the brainstem (7).

Diagnosis

The diagnostic modality of choice is the MRI while the CT scan lacks specificity when compared to the MRI (8). On MRI cavernomas appear as well-circumscribed (it is demarcated by a layer of signal loss owing to it being surrounded by a layer of hemosiderin) popcorn-like lesions that have multiple foci with different signal intensities. The variation in signal intensity is due to them representing bleeding at different stages of evolution (9). Cavernomas are usually not associated with edema or mass effect. Figure (1)

Different MRI sequences used and the results they give:

- **T1:**
    - Varied signal intensity depends on the age of the blood products, small fluid-fluid levels may be present. Figure (2)
- **T2**
    - Hypointense rim is visible
    - Varied signal intensity depending on the age of blood products
    - If a recent bleed has occurred, edema surrounding the lesion may be present
- **GRE T2*/SWI**
    - Shows prominent blooming
    - Can be used for detecting smaller lesions that would otherwise be missed by conventional spin echo sequences, particularly in patients with familial or multiple cavernous malformations
- **T1 C+ (Gd):** using gadolinium contrast usually shows no enhancement

It is important to note that angiography is usually not the preferred method to diagnose cavernomas since they are angiographically occult due to the low speed at which blood flows through them (4). Angiography (digital subtraction angiography) does play a role however in differentiating between a cavernoma and an arteriovenous malformation (10).

Figure (2): Axial T2, Evidence of well-demarcated rounded lesion at the pontomedullary junction, on the posterior medial aspect. (13)

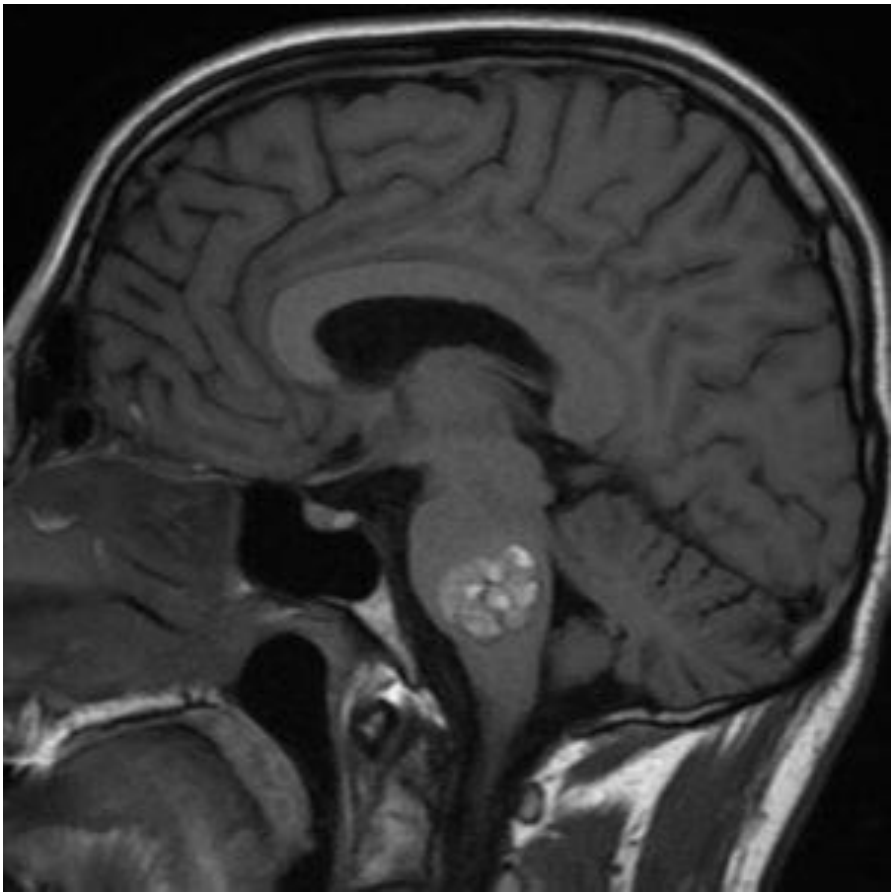


Figure (2): Sagittal T1, Large pontine cavernous malformation demonstrating fluid-fluid levels and surrounding edema in keeping with episodic hemorrhage. (14)[/caption]

Treatment

In 1928 Walter Dandy was the first to operate on a pontine brain stem cavernoma. This was of course found after operating on the patient since diagnostic modalities weren't advanced enough back then to diagnose such a lesion (1).

Treatment options include following the lesion up over time, and surgical removal which is a choice reserved for lesions causing significant symptoms interfering with the patient's life. Surgical removal is relatively simple due to the lesion being surrounded by a layer of gliosis which naturally demarcates it. The risk of bleeding is also lower due to the lower speeds at which blood flows through these lesions further simplifying their resection. Brainstem cavernomas however have an eloquent location owing to the vitality and importance of the brainstem which renders these lesions technically difficult to resect.

Indications for surgery include a single hemorrhage when it is not located in an eloquent area, intractable epilepsy, progressive neurological deficit, multiple hemorrhages when

it is located in eloquent areas, severe symptoms such as cardiac or respiratory instability, and the presence of a cavernoma within 2 mm from the pial surface. The following situations might also be indications of surgery in brainstem cavernomas (8,11):

- Patients are treated with steroids to limit the edema.
- Progressive neurological deficits caused by recurrent bleeding
- In case developmental venous anomalies (DVA) associated with the cavernoma are present, resection is usually avoided due to the risk of venous infarction that is caused by resecting the DVA.
- Exsanguinated blood is seeping into brain tissue surrounding the angioma. This includes acute or subacute bleeding visible on MRI whether inside or outside the cavernoma and which is causing mass effect.
- The cavernous angioma is causing considerable compression of surrounding tissue (visible compression)
- The lesion is in contact with the brain stem surface
- Stereotactic radiosurgery can be considered in patients with surgically inaccessible lesions. However, studies have reported a high risk of complications such as recurrence of hemorrhage, permanent neurological deficits, and radiation-induced adverse effects.
- In cases where aborting further bleeding or the development of seizures is required, resection is warranted. Postoperative MRI within 72 hours of the operation to detect any rebleeding is needed.
- Coma, respiratory or cardiac instability as clinical presentations of cavernomas is not considered surgical contraindications due to the fact that emergent surgical evacuation might achieve satisfactory outcomes in relieving these grave symptoms.
- Stable lesions (not growing) that have not reached the brain stem surface causing minimum neurological manifestations ought not to be operated on but rather followed up conservatively.

Cavernomas in the brainstem is in an eloquent position, the slightest increase in size or bleeding (which increases size indirectly) can press on important nerves or nuclei and cause severe symptoms, this risk should be balanced by the risks associated with the intricate surgery that would be performed to remove such lesions. It is also worth noting that repeated hemorrhages worsen the neurological deficits which in turn affects the clinical picture of the patient, furthermore, surgically removing the lesion after such repeated hemorrhage will also become technically more difficult (11).

Resecting brainstem cavernomas can be achieved by using one of the four standard skull-base approaches, and those are retrosigmoid suboccipital (with or without telovelar approach), supracerebellar infratentorial, orbitozygomatic, and far lateral (12).

References

1. Paulo Henrique Pires de Aguiar, Carlos Alexandre Martins Zicarelli, Gustavo Isolan, Ápio Antunes, Rogério Aires, Sérgio Murilo Georgeto, Adriana Tahara, Fahd Haddad. Brainstem cavernomas: a surgical challenge. Einstein. 2012;10(1):67-73
2. PACIFIC STROKE & NEUROVASCULAR CENTER 2021, accessed 15 December 2021, <https://www.pacificneuroscienceinstitute.org/stroke-neurovascular/conditions-and-treatments/brain-vascular-malformation/cavernoma/>
3. Cleveland Clinic 2021, accessed 15 December 2021, <https://my.clevelandclinic.org/health/diseases/21594-cavernous-hemangioma>
4. Zyck S, Gould GC. Cavernous Venous Malformation. [Updated 2021 Jul 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526009/
5. Goldstein HE, Solomon RA. Epidemiology of cavernous malformations. Handb Clin Neurol. 2017;143:241-247.
6. Mayoclinic 2021, accessed 15 December 2021, <https://www.mayoclinic.org/diseases-conditions/cavernous-malformations/symptoms-causes/syc-20360941>
7. Anatomie pathologique des cavernomes du système nerveux central [Histopathology of central nervous system cavernomas]. Neurochirurgie. 2007 Jun;53(2-3 Pt 2):131-5.
8. Bokhari MR, Al-Dhahir MA. Brain Cavernous Angiomas. [Updated 2021 Sep 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430871/
9. Hallam DK, Russell EJ. Imaging of angiographically occult cerebral vascular malformations. Neuroimaging Clin N Am. 1998 May. 8(2):323-47.
10. Akers A, Al-Shahi Salman R, A Awad I et al. Synopsis of Guidelines for the Clinical Management of Cerebral Cavernous Malformations: Consensus Recommendations Based on Systematic Literature Review by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel. Neurosurgery. 2017;80(5):665-80.
11. Wang CC, Liu A, Zhang JT, Sun B, Zhao YL. Surgical management of brain-stem cavernous malformations: report of 137 cases. Surg Neurol. 2003 Jun;59(6):444-54; discussion 454.
12. Abla AA, Turner JD, Mitha AP, Lekovic G, Spetzler RF. Surgical approaches to brainstem cavernous malformations. Neurosurg Focus. 2010 Sep;29(3):E8.
13. Case courtesy of Gaurav Som Prakash Gupta, Radiopaedia.org. From the case rID: 25939
14. Case courtesy of Frank Gaillard, Radiopaedia.org. From the case rID: 10224

Article topic: Subclavian Steal Syndrome.

Author: Samia Sulaimain.

Editors: Miramar Haddad, Haneen A. Banihani.

Reviewer: Hala Qaryouti.

Overview

Subclavian steal syndrome (SSS) is a condition characterized by abnormal blood flow in arteries due to occlusion or stenosis of the subclavian artery, causing retrograde flow in the ipsilateral vertebral artery and ensuing symptoms of cerebral ischemia. While many patients with SSS may be asymptomatic, some patients present with manifestations of arterial insufficiency, which impact the brain and upper extremities of the body supplied by the subclavian artery.[3] SSS may manifest as syncope or presyncope related to cerebral hypoperfusion, which can occur while using the arm, often during exercise.[2]

Epidemiology

According to the Joint Study of Extracranial Arterial Occlusion by Fields et al., only 168 out of 6534 patients (2.5%) who have arteriographic evidence of subclavian or innominate stenosis with >30% occlusion show symptoms of subclavian steal syndrome. Of which, only 5.3% experienced neurological symptoms [1]. However, the exact prevalence remains unknown [2].

The left subclavian artery, which supplies the left upper limb via the axillary artery, is commonly the most affected by atherosclerosis. As a result, it is involved in subclavian steal syndrome three times more frequently than the right subclavian artery [9]. On the right side, disease or occlusion of the innominate, also known as brachiocephalic, artery may lead to occlusion in the subclavian artery origin [4].

Subclavian steal syndrome occurs most commonly in people over the age of 50 years. There is a greater male predilection with a 2:1 male-to-female ratio. The reasoning behind this being the increasing likelihood of atherosclerotic disease in older males [3,4].

Risk Factors

Given the fact that atherosclerosis is the main etiology of SSS, risk factors involved in the development of fatty plaques are considered a direct contributor to subclavian steal. These risk factors are divided into modifiable and non-modifiable [9].

Modifiable risk factors are related to cigarette smoking, diabetes mellitus, hypertension, hypercholesterolemia and hyperhomocysteinemia. Whereas non-modifiable risks include aging, male gender and a positive family history of SSS [9].

Other relatively rare risk factors involved with subclavian steal syndrome include: [1-3]

-
- ***Takayasu arteritis***, a type of large vessel granulomatous vasculitis, found classically in middle-aged women of Asian descent.
- ***Presence of a cervical rib***, an “extra” rib originating from the seventh cervical vertebra
- ***Neuromuscular compression*** of the subclavian artery in the thoracic outlet, a presentation more common in athletes
- ***Surgical repair of coarctation of the aorta***
- ***Rare anatomical factors***, including aortic dissection, external vertebral artery compression, and vertebral artery congenital malformations
- ***Congenital abnormalities*** include right aortic arch with isolated left subclavian, preductal aortic arch, or an interrupted aortic arch.

Etiology and Pathogenesis

Significant subclavian artery occlusion results in a decrease in arterial pressure distal to the occlusion site. If the lesion is proximal to the origin of the vertebral artery, the pronounced pressure drop may reverse or 'steal' the blood flow in the ipsilateral vertebral artery to ensure adequate flow to the ipsilateral arm [4].

SSS is classified into three grades based upon the hemodynamic alteration of the vertebral artery:[2]

-
  - **Grade 1:** decreased (antegrade) mid-systolic blood flow in the vertebral artery.
  - **Grade 2:** retrograde blood flow in the vertebral artery by ipsilateral arm hyperemia test.
  - **Grade 3:** permanently retrograde vertebral artery blood flow

While identifying the grade can help grasp better knowledge regarding the prognosis, no linear relationship relating to the prognosis and the extent to which symptoms are seen

has been noticed, making it unclear whether higher grade is related to more extreme manifestations. It has been noted, however, that patients with grade 2 tend to present with more symptoms than the two other groups.[2]

Clinical Presentation

SSS is often asymptomatic, and diagnosis may be incidental in cases necessitating ultrasound testing for coronary or carotid artery disease, or when a blood pressure difference is detected between the arms during physical examination [2].

When symptomatic, patients may complain from arm pain or claudication, numbness, paresthesia, or fatigue secondary to upper extremity ischemia exacerbated during activity or vigorous exercise [1]. Patients may also present with neurological symptoms as a result of vertebrobasilar insufficiency, including dizziness, hearing loss, tinnitus, ataxia, vertigo, syncope, and disequilibrium [2]. In addition, visual symptoms include blurry vision, inability to focus and monocular and binocular visual loss [9].

Dizziness and vertigo are relatively more common symptoms seen in over 50% of patients, followed by diplopia in 19% of cases, syncope (18%) and dysarthria (12.5%).[9]

Workup and Diagnosis

In case of clinical suspicion of SSS, physical examination findings include a difference in pulses and brachial systolic blood pressure between the upper extremities, where a difference of at least 15 mmHg is noticed. In addition, recurrent angina pectoris after successful grafting using LIMA may also indicate stenosis in the left subclavian artery [7].

Imaging techniques considered for the diagnosis of SSS include duplex ultrasonography (DUS), computed tomography (CT) and computed tomography angiography (CTA), magnetic resonance angiography (MRI), digital subtraction angiography (DSA), four-vessel cerebral arteriography, and chest radiography. Electrocardiography could also be taken into consideration. [1,3,8]

Duplex ultrasound is the most important test of the subclavian, extracranial carotid and vertebral arteries. DUS is used to show retrograde blood flow and any significant occlusive lesions.

CTA is considered the first-line test and has high sensitivity and specificity. It identifies subclavian artery stenosis and/or occlusion, delayed enhancement of the ipsilateral vertebral artery, and other lesions in arch vessels, yet cannot determine the direction of flow in the ipsilateral vertebral artery.

MRA identifies subclavian artery stenosis and/or occlusion, delayed enhancement of the ipsilateral vertebral artery, other lesions in arch vessels, and flow direction in the ipsilateral vertebral artery.

Digital subtraction angiography is performed during the endovascular intervention to identify subclavian artery stenosis, delayed filling of the ipsilateral vertebral artery, and other extracranial and intracranial cerebral vascular lesions. ***DSA*** is a confirmatory test of choice if stenting is chosen as the proper treatment.

Differential Diagnosis [2]

Posterior Circulation Stroke: Although infarction of the posterior cerebral artery can present with symptoms similar to SSS (i.e., syncope, dizziness, ataxia, or blurring of vision), imaging such as MR or CT angiography can differentiate between the disease.

Peripheral Artery Disease (PAD) of upper extremities: this may only present with asymmetric blood pressure but can also cause exercise-induced pain or pain at rest and digit ulceration. PAD could be differentiated from SSS by its lack of neurological manifestations.

Aortic Stenosis: Ruling out cardiac causes is an essential step in patients with syncope. A systolic ejection murmur in the aortic region is highly suggestive, but the definitive diagnosis for aortic stenosis is established using an echocardiogram.

Peripheral Neuropathy: Peripheral neuropathy may be suggested by the "glove-and-stocking" pattern and diagnosed by electromyography.

Management

No intervention is required in many asymptomatic or mild cases that improve over time. However, since subclavian steal syndrome is a marker for atherosclerotic disease, patients must follow secondary preventive measures to control their blood pressure, cut off smoking, achieve glycemic control in diabetes mellitus and treat dyslipidemia to avoid any complications. [1]

Limiting physical activity in the involved extremity is also helpful in preventing provoked episodes [1,2]. Moreover, routine evaluation of blood pressure and detailed physical examination of patients who are at higher vascular risk, such as in cases of dyslipidemia, diabetes, and hypertension, could assist in the early detection of SSS [5].

A treatment option for symptomatic SSS is *open surgical bypass,* and the most frequent choice is extra-anatomic revascularization [6]. As for patients with short proximal

stenosis or occlusion, *endovascular intervention* may be the more appropriate consideration. Around 10% of patients with <70% recurrent stenosis and only 5% of those require surgery and may benefit from repeat angioplasty.[2]

Some patients may have high surgical risk or unfavorable anatomy for surgery; therefore, *antiplatelet therapy* and *oral anticoagulation* may be chosen despite the lack of studies on their effectiveness.

Complications

SSS is considered a benign condition, and no long-term complications are reported. However, reversing blood flow through the internal mammary graft from coronary to subclavian circulation may cause myocardial ischemia. Vertebrobasilar insufficiency may lead to patients suffering from syncope and experiencing falls, leading to serious head injuries. [5,9]

Prognosis

Secondary preventive and early detection measures significantly help improve prognosis and avoid the risk atherosclerosis imposes on the individual and which may lead to myocardial ischemia or stroke [2].

Patients who undergo angioplasty, stenting, or open surgical bypass, usually have a good prognosis and over 95% sustain resolution of ischemic symptoms, and the target vessel does not require further reintervention [2].

Recent Updates and Further Reading

Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis - PubMed (nih.gov)

Subclavian steal syndrome: neurotological manifestations - PMC (nih.gov)

Coronary subclavian steal syndrome: an extracoronary cause of acute coronary syndrome - PubMed (nih.gov)

Prevalence and impact of the subclavian steal syndrome - PubMed (nih.gov)

Long-term results of endovascular therapy for proximal subclavian arterial obstructive lesions - PubMed (nih.gov)

References

1. Osiro S, Zurada A, Gielecki J, Shoja MM, Tubbs RS, & Loukas M. A review of subclavian steal syndrome with clinical correlation. Medical Science Monitor : International Medical Journal of Experimental and Clinical Research 2012;18(5):RA57–63. https://doi.org/10.12659/msm.882721.
2. Shankar KN, Nagalli S. Subclavian Steal Syndrome. Treasure Island (FL): StatPearls Publishing; 2022.
3. D'Souza D, El-Feky M BD. Subclavian steal syndrome. Radiopaedia 2022. https://doi.org/10.53347/rID-5012.
4. Olsen KG, Lund C. Subclavian Steal Syndrome. Tidsskrift for Den Norske Laegeforening : Tidsskrift for Praktisk Medicin, Ny Raekke 2006;126(24):3259–62.
5. Amano Y, Watari T. Asymptomatic Subclavian Steal Syndrome. Cureus 2021;13(10). https://doi.org/10.7759/cureus.19109.
6. Sonoda LY, Hawerroth MDGL, ,, Vargas, T T, Santos LBS, Diniz TR, Oliveira WA, et al. Carotid Subclavian Bypass for the Treatment of Coronary Subclavian Steal Syndrome. Brazilian Journal of Cardiovascular Surgery 2022;37(5):780–3. https://doi.org/10.21470/1678-9741-2020-0609.
7. Cua B, Mamdani N, Halpin D, Sunny Jhamnani SJ, Mena-Hurtado C. Review of coronary subclavian steal syndrome. Journal of Cardiology 2017;70:432–7. https://doi.org/10.1016/j.jjcc.2017.02.012.
8. Sheehy N, MacNally S, Smith CS, Boyle G, Al E, 04. RMHAO. Contrast-Enhanced MR Angiography of Subclavian Steal Syndrome: Value of the 2D Time-of-Flight "Localizer" Sign Read More: https://www.ajronline.org/doi/10.2214/ajr.04.1130. American Journal of Roentgenology 2005;184:1069–73.
9. Bayat I, Cheuen J, Fong J. Subclavian Steal Syndrome. Medscape 2021.
10. Clark CE, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis. Lancet 2012;379(9819). https://doi.org/10.1016/S0140-6736(11)61710-8.
11. Psillas G, Kekes G, Constantinidis J, Triaridis S, Vital V. Subclavian steal syndrome: neurotological manifestations. Acta Otorhinolaryngol Ital 2007;27(1).
12. Schatzl S, Karnik R, Gattermeier M. Coronary subclavian steal syndrome: an extracoronary cause of acute coronary syndrome. Wiener Klinische Wochenschrift 2013;125(15-16):437–8. https://doi.org/10.1007/s00508-013-0386-3.
13. Labropoulos N, Nandivada P, Bekelis K. Prevalence and impact of the subclavian steal syndrome. Annals of Surgery 2010;252(1):166–70. https://doi.org/10.1097/SLA.0b013e3181e3375a
14. Wang KQ, Wang ZG, Yang BZ, Yuan C, Zhang WD, Yuan B, et al. Long-term results of endovascular therapy for proximal subclavian arterial obstructive lesions. Chinese Medical Journal 2010;123(1):45–50.

Article title: Dysembryoplastic Neuroepithelial Tumor (DNET).

Author: Samia Sulaiman.

Editor: Miramar Haddad, Haneen A. Banihani.

Reviewer: Lobana Mahdawi, Ethar Hazaimeh.

Abbreviations

DNET: dysembryoplastic neuroepithelial tumor
LEAT: long-term epilepsy-associated tumors
SGNE: specific glioneuronal element
GFAP: glial fibrillary acidic protein
PXA: pleomorphic xanthoastrocytoma

Overview

Dysembryoplastic neuroepithelial tumors (DNETs), first elucidated in 1988 by Daumas-Duport, could be described as indolent, slow-growing, mixed neuronal-glial grade 1 neoplasm and are usually diagnosed in children and young adults and localized to the primary site of origin. [1]

DNETs could arise from deep grey matter or cortical matter. In up to 80% of cases, they are frequently associated with cortical dysplasia, which accompanies unimodular or multinodular lesions. [2,5], they arise from secondary germinal layers and usually cause characteristic intractable focal seizures or may remain asymptomatic. [2, 18]

The etiologies and risk factors of DNETs are still poorly understood, yet ongoing research aims to develop a better understanding of DNETs and ease their diagnosis.[4] Researchers believe that a combination of genetic, environmental, and occupational factors may lead to the development of DNETs. [18]

This article will discuss the epidemiology, clinical presentation, histopathology, immunopathology, molecular pathology, diagnosis, and treatment and prognosis of DNETs.

Epidemiology

DNETs are comparatively rare as they amount to only 1-2% of all tumors and correspond to 13.5% of histological findings in children undergoing epilepsy surgery while contributing to 12% in adults undergoing epilepsy surgery. [4, 5]. Although nine

years is the average age of diagnosis and despite it being mainly diagnosed in children and young adults, DNETs may still develop at any age.[4]

There has been a male predominance noticed in DNETs. [5] Furthermore, an association with Noonan syndrome, a genetic disorder characterized by developmental abnormalities, has been proposed. [2,3].

Clinical Presentation

Most patients present with a history of focal seizures that may or may not lead to hindered awareness and may progress to chronic drug-resistant epilepsy.[8] This led to the introduction of the term "long-term epilepsy-associated tumors" (LEAT), which also includes other tumors.[9] Furthermore, the symptoms accompanying DNETs depend on the location of the tumors.[18] Therefore, the symptoms vary significantly among individuals, making diagnosing it difficult.[18] The most prominent symptom is persistent convulsions,[18] and other frequently observed symptoms of DNETs include:

- Chronic headaches
- Nausea and vomiting
- Numbness and tingling sensations
- Muscle weakness; weakness in arms and legs
- Neck pain
- Impaired vision, such as blurred vision, double vision, or poor eyesight
- Hearing impairment or hearing loss
- Speech problems
- Insomnia or loss of sleep, or excessive sleepiness (usually during daytime)
- Tremors
- Lack of coordination; unsteadiness and loss of balance (vertigo)
- Dizziness and fainting
- Confusion
- Changes in one's behavior, personality changes
- Mental impairment
- Memory loss
- Seizures or convulsions, which may be any of the following types:

1. Myoclonic seizures
2. Grand mal (tonic-clonic) seizures
3. Sensory seizures
4. Complex partial seizures

The temporal lobe is the most common location where DNETs develop. Nevertheless, all CNS sites containing grey matter are still considered potential locations for DNETs to develop, as shown in *Table 1*.[2]

Location	
Temporal Lobe	Over 65% of cases
Frontal Lobe	About 20% of cases
Caudate Nucleus	
Cerebellum	More commonly present with ataxia rather than seizures
Pons	

Table 1: Locations of DNETs in the brain and epidemiology involved with each location.[2]

Occasional presentation in the context of Neurofibromatosis 1 (NF1), a genetic disorder leading to the growth of tumors in nerve tissue, and XYY syndrome have been reported as well. [5,7]

Histopathology

Gross description:

DNETs may appear as expanded and elevated “macro gyri” that vary in size from millimeters to multiple centimeters.[5]. They may also sometimes appear with an exophytic component and demonstrate a heterogenous, gelatinous, cut surface with firmer tissue nodules upon sectioning.[2]. DNETs may also contain solid, mucoid, or cystic components.[6]

Microscopic (histologic) description

Characteristically, a specific glioneuronal element (SGNE) which refers to columnar bundles of axons surrounded by oligodendrocyte-like cells - oriented perpendicularly to the overlying cortical surface - is noticed. Floating neurons (mature ganglion cells) and stellate astrocytes between these columns are found in pools of mucin between columns, as shown in Figure 1.[2]

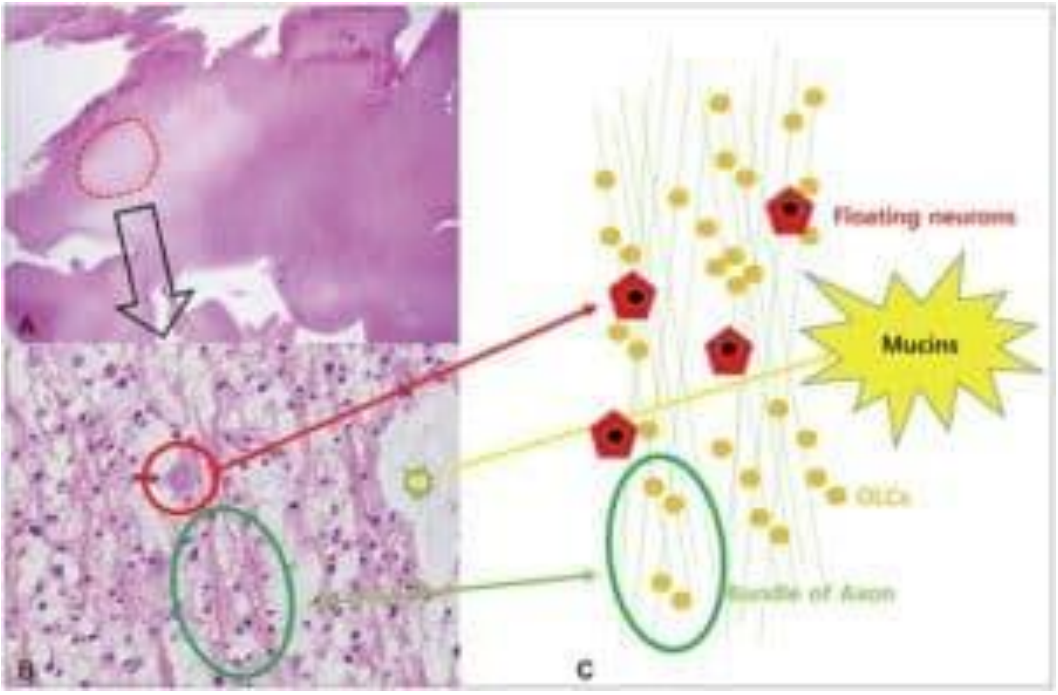


Figure 1: A. Histological features of the multinodular pattern of DNETs. B: Glioneuronal elements with floating neurons. C: Diagram of the DNET architecture and components.8

There are three histological forms:[5]

1. Simple form: SGNE only
2. Complex form: SGNE with glial nodules and multinodular architecture
3. Nonspecific form: no SGNE yet the same clinical and neuroimaging features as the complex form

The characteristic histological features of DNETs contributed to upgrading the term "long-term epilepsy-associated tumors" (LEAT) to introducing the more specific term "low-grade, developmental, epilepsy-associated" brain tumors.[8]

Immunohistochemistry

Alcian blue is positive for the extracellular component.[6] An astrocytic component is identified by the glial marker called glial fibrillary acidic protein (GFAP) through immunostaining and is negative in oligodendroglial-like cells.[2]The oligodendrocyte-like cells are S100, OLIG2, and PDGFRA positive and may express myelin-oligodendrocyte glycoprotein and NOGO-A.[2] The floating neurons are positive for NeuN.[6]

Moreover, negative stains include MAP2 in oligodendroglial-like cells in about 76.5% of cases.[6]

Molecular Pathology

Remarkably, DNETs do not show 1p19q co-deletion and are negative for IDH and TP53 mutations. These features are essential in distinguishing DNETs from oligodendrogliomas (IDH mutated and 1p19q co-deleted) and astrocytomas (typically IDH mutations).[2] The differential diagnosis of DNETs is further discussed later in this article.

In almost 30-50% of DNETs, BRAF V600E mutations have been noticed, yet it remains unclear whether BRAF V600E positivity and the presence of pilocytic astrocytoma are correlated in cases of DNETs.[5]. Moreover, when located outside of the cerebellum and shared by pilocytic astrocytomas, DNETs show fibroblast growth factor receptor tyrosine kinase domain duplication (FGFR1-TKDD).[2]

Diagnosis

DNETs may remain undiagnosed for long periods as they are generally asymptomatic and slow growing. Diagnosis usually occurs when there is sudden worsening of symptoms, ongoing epileptic seizures at a young age, or upon radiological observation for unrelated health concerns. [18]

CT scan

DNETs appear as low-density masses with no or slight enhancement. To an extent, the cranial fossa may be enlarged in some cases. In cortical DNETs, which is the typical case, the inner table of the skull vault appears to be remodeled yet with no erosion. Calcification is visible in about 30% of cases and typically seen in the deepest portions of the tumor, next to the enhancing or hemorrhagic regions.[2]. This is shown in Figure 3.

MRI

DNETs usually appear as cortical lesions, scarcely with any vasogenic edema.[5]

-
  - **T1:** hypointense compared with adjacent brain[2]
  - **T1 C+ (Gd):** 20-30% of cases show enhancement which could be heterogeneous or a mural nodule[2]
  - **T2:** high signal “bubbly appearance”[2]
  - **T2/FLAIR:** mixed-signal intensity with bright rim sign, partial suppression of “bubbles”[2]
  - **T2*:** frequent calcification, hemosiderin is uncommon as bleeding is only seen occasionally in DNETs[2]

- **DWI:** no restricted diffusion[2]
- **MR spectroscopy:** nonspecific, yet lactate may be present[2]

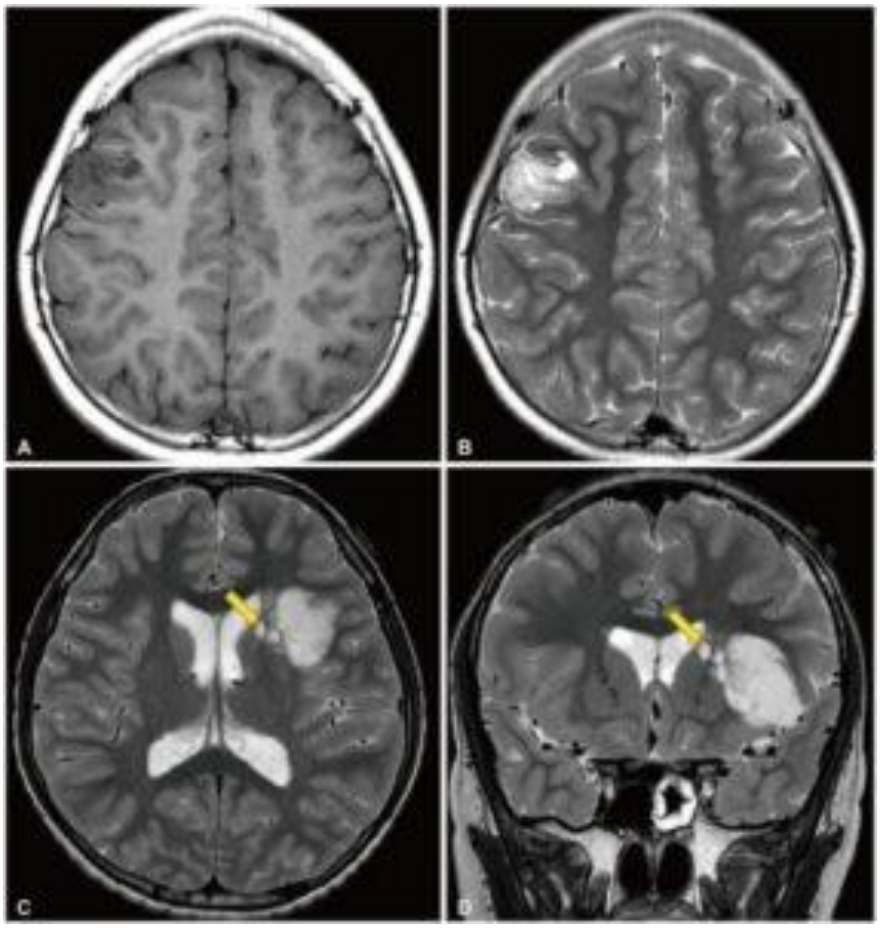


Figure 2: Radiological features of dysembryoplastic neuroepithelial tumor. A and B: T1-weighted and T2-weighted magnetic resonance images of a 10-year-old girl who presented with recurrent focal seizures. In the right middle frontal gyrus, a multinodular mass is seen. C and D: T2-weighted axial and coronal images of a 12-year-old boy who presented with chronic epilepsy. A large tumor is positioned in the insular and left inferior frontal lobes. Several satellite lesions (shown with the yellow arrows) are seen on the medial side of the mass, in the caudate nucleus and internal capsule.8

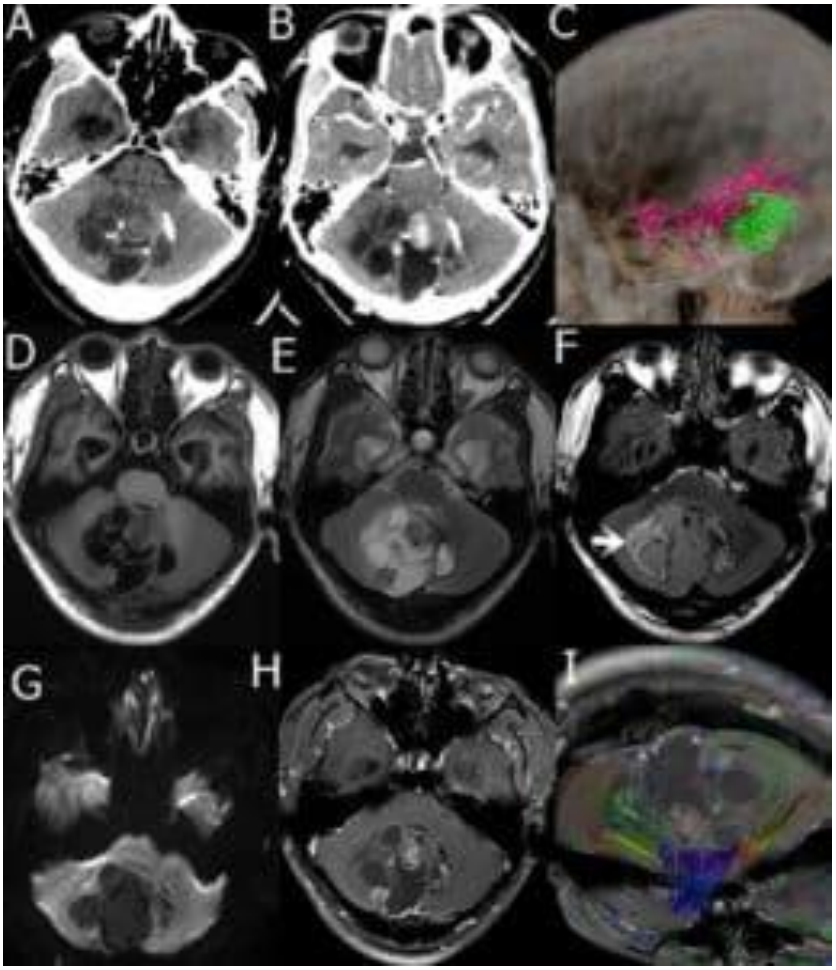


Figure 3: A 29-year-old male presented with a DNET in the cerebellar vermis. A: Plain CT scan of cerebellar vermis showing scattered calcification and low, slightly high mixed density; B: enhanced CT scan showed low-density areas without enhancement, solid nodules, septa, and cyst wall showed uneven enhancement; C: Computed Tomography Angiography (CTA) branching arteries were noticed at the edge of tumors; D: T1WI tumor shows a low and iso-mixed signal on T1WI; E: T2WI tumor shows a high and iso- signal on T2WI; F. FLAIR tumor shows slightly hyperintensity, surrounded by high signal (arrow); G: DWI tumor shows low signal; H: Enhanced MRI the solid nodules, septa, and cyst walls were heterogeneously enhanced; I: DTI white matter fiber bundles were compressed and displaced.17[/caption]

Differential Diagnosis

As DNETs may be challenging to diagnose, differential diagnosis is extremely significant. The main differential diagnosis is that in the features of another cortical tumor that make each distinctive from the other, as shown in Table 2.[2]

Cortical tumor type	Characteristic features
Ganglioglioma	- More common contrast enhancement - Calcification in about 50% of cases - Absence of a “bubbly” appearance
Pleomorphic xanthoastrocytoma	- Prominent contrast enhancement - Dural tail sign is seen often
Diffuse low-grade astrocytoma	- IDH mutation - No SGNE
Oligodendroglioma	- IDH mutated and 1p19q co-deleted - No SGNE
Desmoplastic infantile astrocytomas and ganglioglioma	- Prominent dural involvement - Large, multiple lesions

Table 2: Differential diagnosis of DNETs and cortical tumors according to distinguishing features [2]

Moreover, the differential diagnosis may also depend on the location of the tumor:

Location	Condition	
Temporal lobe	Tumors (in order of decreasing frequency)	- ganglioglioma - DNET - pilocytic astrocytoma - diffuse astrocytoma - oligodendroglioma - pleomorphic xanthoastrocytoma (PXA)
	Cysts	- neuroepithelial cyst - choroid fissural cyst
	Other	- herpes simplex encephalitis - mesial temporal sclerosis (MTS)

		- limbic encephalitis
Cortical	Tumors	- ganglioglioma - low-grade astrocytoma - pleomorphic xanthoastrocytoma (PXA) - Taylor dysplasia oligoastrocytoma/oligodendroglioma

Table 3: Differential diagnosis of DNETs according to the location in the brain [2]

Treatment and prognosis

Treatment is achieved through surgical resection to remove the tumor completely.[18] Irrespective of the extent of the seizures' pharmacoresistance, surgery avoids the consequences of prolonged pharmacological therapy and the rare risk of malignant transformation.[12]

As the tumors are well-circumscribed and demonstrate no growth over time, they are regarded benign and often completely removed safely. [2] No evidence of progression following subtotal resection or recurrence following total resection has been shown after long-term follow-up with patients.[5] However, in cases where the tumor recurs, it is recommended to undergo a second surgery to remove the tumor. [3] Seizures also frequently cease, even in patients undergoing incomplete resection.[2]

Radiation therapy may be used if tumor removal is not an option for specific patients or after surgery to destroy any remaining meningioma cells. Chemotherapy is not recommended except in higher-grade tumors. [18]

Complications

Complications related to DNETs include disability with undetected large tumors, severe memory loss, dementia, emotional and mental stress, problems with concentrations, peritumoral brain edema, and rarely, high-grade malignant transformation into anaplastic DNETs [18]

Possible surgical complications include wound infections, damage to muscles, nerves, blood vessels, and unaffected brain tissue during surgery, and rarely, tumor recurrence. [18]

Current Research

The development of malignancy and the pursuit of misinterpreting DNETs with other diagnoses, such as gangliogliomas, is currently being explored.[9] Moreover, complications, including intratumoral bleeding, are also being studied in voluminous tumors and in tumors that may undergo malignant transformation and have mutations such as FGFR1.[11]

Recent and extensive restructuring of DNET classification has also occurred in the past 5-10 years as genomic alterations are being further explored.[10]

In general, some predisposing factors and preventive measures associated with tumors are further discussed in the fifth article in the "Further Reading" list below.

References

1. S, Elia A, Del Maestro M, Elbabaa S, Carnevale S, Guerrini F, et al. Dysembryoplastic Neuroepithelial Tumors: What You Need to Know. World Neurosu [Internet]. 2019 Apr 11;127(2019):255–65. Available from: https://www.sciencedirect.com/science/article/pii/S1878875019310484
2. Gaillard F, Weerakkody Y, Sharma R E al. Dysembryoplastic neuroepithelial tumor [Internet]. Radiopedia. 2008 [cited 2023 Feb 7]. Available from: https://radiopaedia.org/articles/dysembryoplastic-neuroepithelial-tumour#nav_pathology
3. Noonan syndrome [Internet]. National Center for Advancing Translational Sciences. 2023 [cited 2023 Feb 6]. Available from: https://rarediseases.info.nih.gov/diseases/10955/noonan-syndrome
4. DNET Tumor Treatment for Children [Internet]. Children's Minnesota. 2023 [cited 2023 Feb 6]. Available from: https://rb.gy/x6hhy3
5. Adesina A, Fuller C, Hunter J, Illner A, Koy Y, Mohila C, et al. Atlas of Pediatric Brain Tumors. Switzerland : Springer International Publishing; 2010.
6. Dampier C, Cimino PJ. Pathology Outlines - Dysembryoplastic neuroepithelial tumor [Internet]. Pathologyoutlines.com, Inc. 2022 [cited 2023 Feb 6]. Available from: https://www.pathologyoutlines.com/topic/cnstumorDNET.html
7. Cimino PJ, Gutmann DH. Neurofibromatosis type 1. Handbook of clinical neurology. 2018;148:799–801.
8. Phi JH, Kim SH. Dysembryoplastic Neuroepithelial Tumor: A Benign but Complex Tumor of the Cerebral Cortex. Brain tumor research and treatment [Internet]. 2022 Jul 28;10(3):144–50. Available from: http://dx.doi.org/10.14791/btrt.2022.0015
9. Chassoux F, Daumas-Duport C. Dysembryoplastic neuroepithelial tumors: Where are we now? Epilepsia [Internet]. 2013 Dec 12;54:129–34. Available from: https://onlinelibrary.wiley.com/doi/10.1111/epi.12457
10. P, Debily MA, Fina F, Jones DTW, Saffroy R, Castel D, et al. The genomic landscape of dysembryoplastic neuroepithelial tumours and a comprehensive analysis of recurrent cases. Neuropathology and applied neurobiology [Internet]. 2022;48. Available from: http://dx.doi.org/10.1111/nan.12834
11. Takita H, Shimono T, Uda T, Ikota H, Kawashima T, Horiuchi D, et al. Malignant transformation of a dysembryoplastic neuroepithelial tumor presenting with intraventricular hemorrhage. Radiology case reports, [Internet]. 2022;17(3):939–43. Available from: http://dx.doi.org/10.1016/j.radcr.2022.01.014
12. Giulioni M, Marucci G, Martinoni M, Marliani AF, Toni F, Bartiromo F, et al. Epilepsy associated tumors: Review article. World journal of clinical cases [Internet]. 2014;2(11):623–41. Available from: https://pubmed.ncbi.nlm.nih.gov/25405186/
13. Uno T, Kinoshita M, Furuta T, Miyashita K, Sabit H, & Nakada M. Volumetric growth analysis of an insular dysembryoplastic neuroepithelial tumor over a 10-year follow-up. Surgical neurology international [Internet]. 2016;7:1154–7. Available from: https://pubmed.ncbi.nlm.nih.gov/28194304/
14. Rheims S, Rubi S, Bouvard S, Bernard E, Streichenberger N, Guenot M, et al. Accuracy of distinguishing between dysembryoplastic neuroepithelial tumors and other epileptogenic brain neoplasms with [^{11}C]methionine PET. Neuro-oncology [Internet]. 2014;16(10):1417–26. Available from: https://pubmed.ncbi.nlm.nih.gov/24598358/
15. Sukheeja D, Mehta J. Dysembryoplastic neuroepithelial tumor: A rare brain tumor not to be misdiagnosed [Internet]. 2014. Available from: https://pubmed.ncbi.nlm.nih.gov/27057233/
16. Liao DW, Zheng X, Feng QQ, & Xia T. Association of CT and MRI Manifestations with Pathology in Dysembryoplastic Neuroepithelial Tumors. Journal of the Belgian Society of Radiology [Internet]. 2022;106(1):135. Available from: https://pubmed.ncbi.nlm.nih.gov/36590378/

17. Sampetrean O, Maehara T, Arai N, Nemoto T. Rapidly growing dysembryoplastic neuroepithelial tumor: case report. Neurosurgery [Internet]. 2006;59(6). Available from: https://journals.lww.com/neurosurgery/Abstract/2006/12000/RAPIDLY_GROWING_DYSEMBRYOPLASTIC_NEUROEPITHELIAL.24.aspx
18. Tangella K. Dysembryoplastic Neuroepithelial Tumor [Internet]. DoveMed. 2020 [cited 2023 Sep 2]. Available from: https://www.dovemed.com/diseases-conditions/dysembryoplastic-neuroepithelial-tumor/#:~:text=%28Etiology%29%20The%20exact%20cause%20of%20development%20of%20Dysembryoplastic,several%20factors%20including%20genetic%2C%20environmental%2C%20and%20occupational%20factors.

Article topic: Glioblastoma Multiforme (GBM).

Author: Randa Shahwan.

Editor: Hamza Aljarrah, Rahmeh Adel.

Reviewer: Adam M. Abdallah.

Keywords: glioblastoma, GBM, astrocytoma, glioma, brain tumor.

Abbreviations: GMB: Glioblastoma Multiforme, MRI: Magnetic resonance imaging, FLAIR: fluid-attenuated inversion recovery, PET: Positron emission tomography.

Abstract

Glioblastoma multiforme (GBM) is a very aggressive and incurable malignant primary brain tumor, with high morbidity and mortality rates, which make it known for its poor prognosis. It is a grade IV astrocytoma. GBM is relatively rare, however, it's the most common primary malignant brain tumor in adults. Signs and symptoms of GBM vary greatly, but common symptoms are headache, seizures, neurological deficits, and cognitive impairment. It's often diagnosed by different modalities of neuroimaging, such as MRI and CT scan, along with biopsy. Treatment of GBM is typically multidisciplinary, including surgical resection, radiotherapy, and chemotherapy.

Introduction

The nervous system is made of two main types of cells: neurons and glial cells. Neurons are electrically excitable cells that generate and transmit action potentials to various parts of the body. Glial cells support neurons structurally, they provide neurons with nutrients and protection, they form myelin, and they maintain homeostasis.

While neurons are the basic functional unit of the nervous system, glial cells are more numerous than neurons. There are 6 major types of glial cells (**Figure 1**) in both the central nervous system (CNS) and the peripheral nervous system (PNS), which are: astrocytes, ependymal cells, oligodendrocytes, microglia, satellite cells, and Schwann cells. Each type of glial cell has its specific function. In this article, we'll focus on astrocytes.

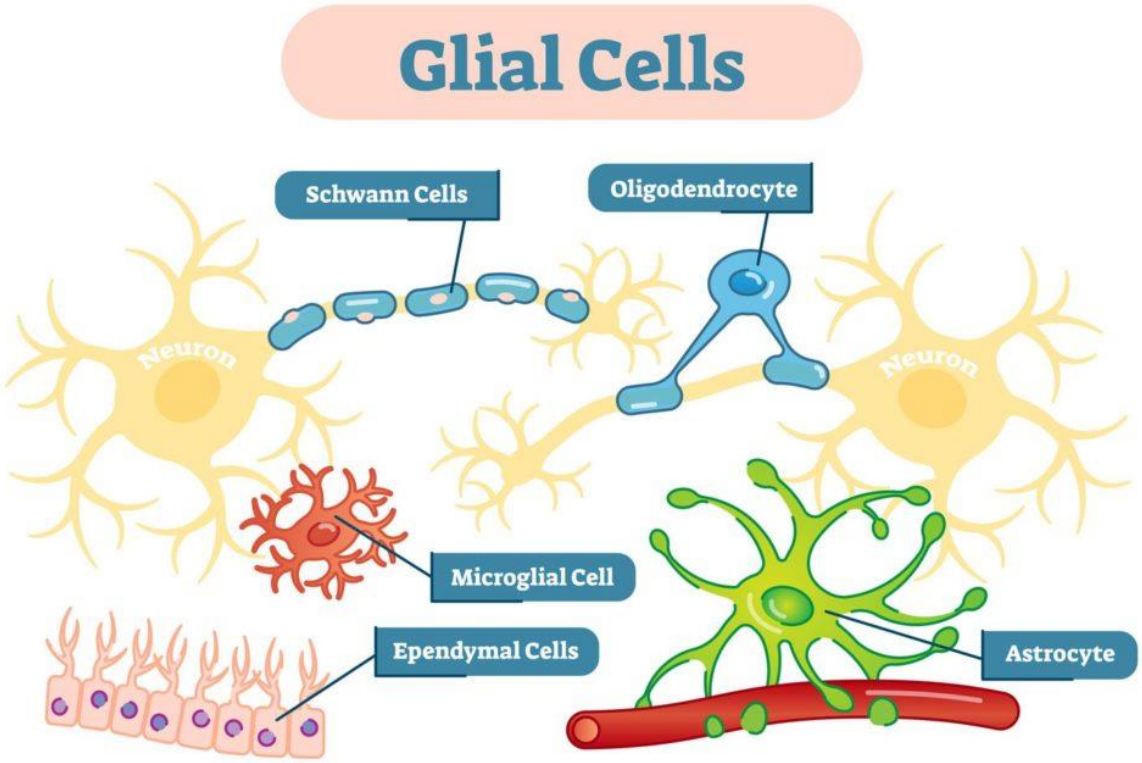


Figure 1: There are 6 major types of glial cells in both the central nervous system (CNS) and the peripheral nervous system (PNS). 15

Astrocytes are considered to be the most numerous glial cells in the CNS. Astrocytes' roles include structural and metabolic support, maintenance of the blood-brain barrier (BBB), regulation of cerebral blood flow, and inflammatory reactivity after injury.[1]

When a tumor originates from any type of glial cells, it's considered a "glioma". Based on the specific cell type from which the tumor originates, there are three major types of gliomas: astrocytoma, ependymoma, and oligodendroglioma. Considering their growth pattern and infiltrating capacity, gliomas are classified according to the World Health Organization (WHO) by Grades (I-IV). The grade a tumor has is correlated with its aggressiveness.[2]

Definition

Glioblastoma multiforme is an astrocytoma and a grade 4 glioma based on the (WHO) grading system. Although it is the most common primary malignant brain tumor in adults, it's a rare malignant tumor overall. It is also the most aggressive primary malignant brain tumor.[3] Although it's overly aggressive it rarely metastasizes. It also rarely occurs in children. It is more common in males than females.[4] Generally, it has an

extremely poor prognosis and is rarely cured.[3] It most commonly forms in the frontal lobe, followed by the temporal, parietal, and occipital lobes.[3]

Risk factors

The exact cause of GBM is unknown. However, there are some risk factors related to GBM. Risk factors found to be associated with GMB include some genetic disorders, such as Li-Fraumeni syndrome, neurofibromatosis, and Lynch syndrome; previous radiation therapy;[5] and impaired immunity.[6]

It is suggested that in some cases, there is a genetic component, which in turn, may run in families.[4] Most commonly, GBMs arise de novo, but in rare cases, a lower-grade brain tumor can transform into a GBM.[7]

Clinical presentation

Symptoms of GBMs are nonspecific. The clinical presentation of GBM varies depending on the location of the tumor, its size, and the anatomic brain structures infiltrated by the tumor.[3]

GBMs often cause symptoms due to mass effect, or increased intracranial pressure, these symptoms include headache, nausea, and vomiting, change in personality, slowly progressive focal neurologic deficits, double or blurred vision, depression, and loss of appetite.[3]

Diagnosis

The diagnosis of GBM relies on a full medical history and physical examination - focusing on neurological examination to check if there's any neurological impairment- imaging modalities including MRI, CT,[3] and PET scan[9], and biopsy.

Magnetic resonance imaging

MRI with and without contrast is considered the gold standard in the diagnosis of GBM. On MRI (**Figure 2**), GBM appears as a poorly circumscribed mass with contrast enhancement at its margins. The center of the mass appears hypointense on T1-weighted scans. It is surrounded by edema which looks hyperintense on T2-weighted and FLAIR scans.[8]

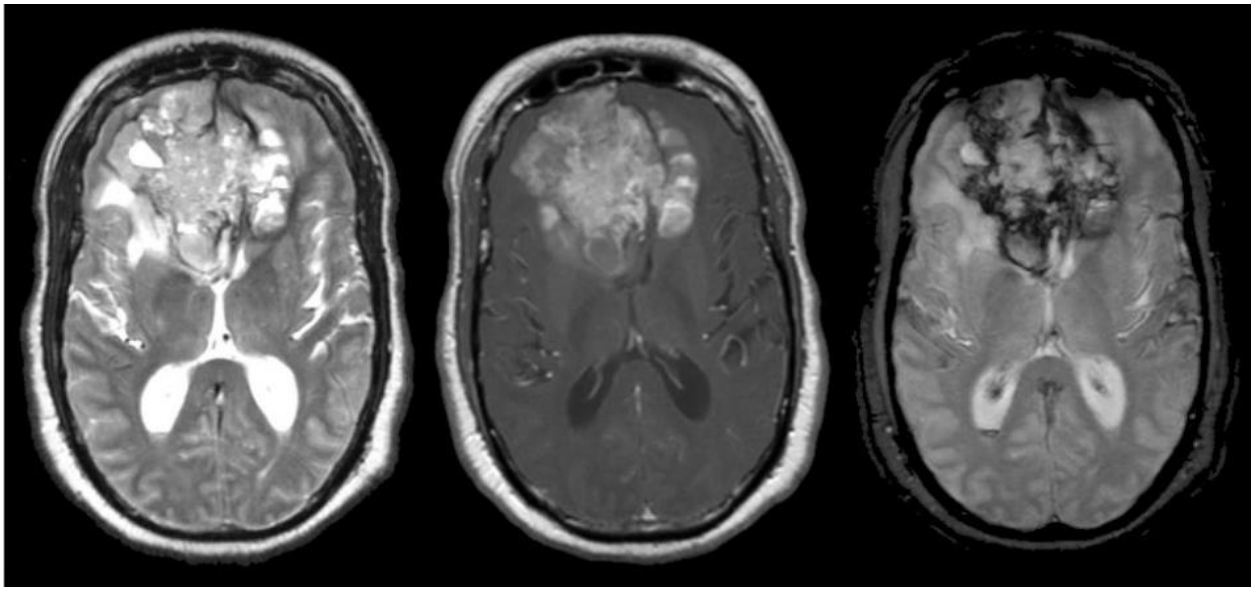


Figure 2: Glioblastoma Multiforme (Frontal Lobe).14

Biopsy

A biopsy mostly confirms the diagnosis. GBM is characterized histologically by the hypercellularity of bizarre giant cells with marked atypia, numerous mitoses, microvascular proliferation, and necrosis.[10]

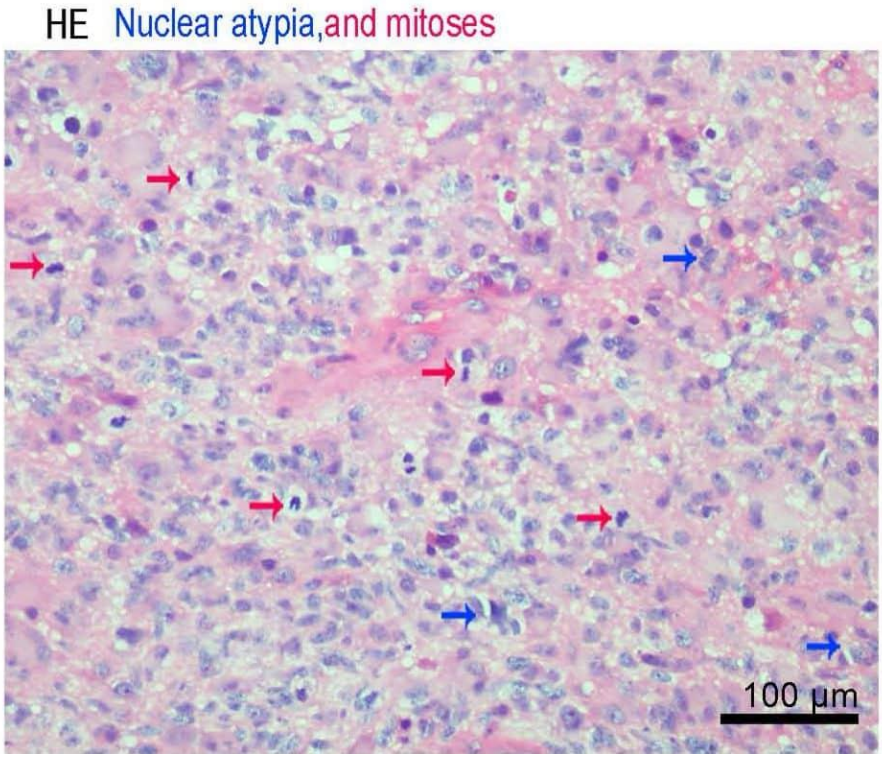


Figure 3: Nuclear Atypia and Mitosis 17

a. Open surgical biopsy

b. Stereotactic biopsy

It is considered a minimally invasive, safe, and accurate procedure. It is preferred if the lesion is deep, or critically hard to reach. It is also done when other procedures are considered risky for the patient.[16]

Biopsy techniques:
1. Core Needle Biopsy
2. Fine Needle Aspiration (FNA)

Prognosis

GBM has a 7.2% 5-year survival rate.[11] Without therapy, GBMs have a median survival of 3 months. If managed with optimal management, they have a median survival of approximately 15 months.[4] Primary GBMs generally have a worse prognosis than secondary GBMs.[3] Overall, GBM has a very poor prognosis, whether treated or not.

Treatment

If glioblastoma is recently diagnosed, it must be managed with a multidisciplinary approach. There are several treatment options currently, which include surgical resection, chemotherapy, and radiation.[3] Standard therapy involves maximal safe surgical resection, then radiotherapy concomitant with temozolomide (an oral chemotherapy medication), followed by adjuvant chemotherapy with temozolomide.[3] This combination of radiotherapy and chemotherapy is known as the Stupp regimen. However, in older patients, shorter courses of radiotherapy, or only chemotherapy with temozolomide may be considered. After the radiation therapy, chemotherapy with temozolomide is done.[3]

A radical resection of glioblastoma is not curative, because it is a highly invasive tumor, so most likely, infiltrating tumor cells will remain within the surrounding brain tissue.[12]

New treatment modalities such as tumor-treating fields and immunotherapy options are currently under trial.[3] Immunotherapy options against GBM include dendritic cell vaccines, peptide vaccines, checkpoint inhibitor therapy, chimeric antigen receptor T cells, and oncolytic virotherapy.[13]

Unfortunately, despite all treatment options available, until now, GBM remains incurable.[12]

References

1.. Freeman MR, Rowitch DH. Evolving Concepts of Gliogenesis: A Look Way Back and Ahead to the Next 25 Years. Neuron [Internet]. 2013 Oct 10 [cited 2023 Aug 14];80(3):613. Available from: /pmc/articles/PMC5221505/
2. Marquet G, Dameron O, Saikali S, Mosser J, Burgun A. Grading glioma tumors using OWL-DL and NCI Thesaurus. AMIA Annual Symposium Proceedings [Internet]. 2007 [cited 2023 Aug 14];2007:508. Available from: /pmc/articles/PMC2655830/
3. Davis ME. Glioblastoma: Overview of disease and treatment. Clin J Oncol Nurs. 2016 Oct 1;20(5):1–8.
4. Grochans S, Cybulska AM, Simińska D, Korbecki J, Kojder K, Chlubek D, et al. Epidemiology of Glioblastoma Multiforme–Literature Review. Cancers (Basel) [Internet]. 2022 May 1 [cited 2023 Aug 14];14(10). Available from: /pmc/articles/PMC9139611/
5. Gallego O. Nonsurgical treatment of recurrent glioblastoma. Current Oncology [Internet]. 2015 Aug 20 [cited 2023 Aug 14];22(4):e273. Available from: /pmc/articles/PMC4530825/
6. Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, et al. Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev [Internet]. 2014 Oct 1 [cited 2023 Aug 14];23(10):1985–96. Available from: https://pubmed.ncbi.nlm.nih.gov/25053711/
7. Nguyen HS, Best B, Doan NB, Gelsomino M, Shabani S, Awad AJ, et al. Glioblastoma in the setting of prior lower grade gliomas – insights from SEER database. Oncotarget [Internet]. 2018 Sep 9 [cited 2023 Aug 14];9(70):33271. Available from: /pmc/articles/PMC6161794/
8. Gilard V, Tebani A, Dabaj I, Laquerrière A, Fontanilles M, Derrey S, et al. Diagnosis and management of glioblastoma: A comprehensive perspective. J Pers Med [Internet]. 2021 [cited 2023 Aug 14];11(4):258. Available from: /pmc/articles/PMC8065751/
9. Bernstock JD, Gary SE, Klinger N, Valdes PA, Ibn Essayed W, Olsen HE, et al. Standard clinical approaches and emerging modalities for glioblastoma imaging. Neurooncol Adv [Internet]. 2022 Jan 1 [cited 2023 Aug 14];4(1). Available from: /pmc/articles/PMC9268747/
10. D'Alessio A, Proietti G, Sica G, Scicchitano BM. Pathological and Molecular Features of Glioblastoma and Its Peritumoral Tissue. Cancers (Basel) [Internet]. 2019 Apr 1 [cited 2023 Aug 14];11(4). Available from: /pmc/articles/PMC6521241/
11. Wu W, Klockow JL, Zhang M, Lafortune F, Chang E, Jin L, et al. Glioblastoma Multiforme (GBM): An overview of current therapies and mechanisms of resistance. Pharmacol Res [Internet]. 2021 Sep 1 [cited 2023 Aug 14];171:105780. Available from: /pmc/articles/PMC8384724/
12. Wilson TA, Karajannis MA, Harter DH. Glioblastoma multiforme: State of the art and future therapeutics. Surg Neurol Int [Internet]. 2014 [cited 2023 Aug 14];5(Supplement). Available from: /pmc/articles/PMC4078454/
13. Huang B, Li X, Li Y, Zhang J, Zong Z, Zhang H. Current Immunotherapies for Glioblastoma Multiforme. Front Immunol [Internet]. 2020 Mar 9 [cited 2023 Aug 14];11. Available from: /pmc/articles/PMC7986847/
14. Glioblastomaf3a [Internet]. [cited 2023 Aug 15]. Available from: https://case.edu/med/neurology/NR/glioblastomaf3a.htm
15.https://www.verywellhealth.com/thmb/JfmurUsZk6doDldg3usx1B6BRlo=/1500x0/filters:no_upscale():max_bytes(150000):strip_icc():format(webp)/glialcellsillustration-5a94d585642dca00362568c4.jpg
16. Barnett GH, Miller DW, Weisenberger J. Frameless stereotaxy with scalp-applied fiducial markers for brain biopsy procedures: experience in 218 cases. *Journal of Neurosurgery* 1999; 91(4), 569–576. doi:10.3171/jns.1999.91.4.0569
17. https://www.spandidos-publications.com/4789/downloadSupplementary

Neurology

Article Title: Parkinson's Disease.

Author: Farah Moh'd Sbeih Fuad Awayes.

Editors: Yaman Oudat, Aroob Awwad.

Reviwer: Ethar Hazaimeh.

Keywords: Parkinson's disease, Parkinsonism, Lewy bodies.

Overview

Parkinson's disease (PD) is the most common chronic, progressive movement disorder of the central nervous system and is the second most common neurodegenerative disease after Alzheimer's disease. [1][2] It involves the degeneration of the dopaminergic neurons in the substantia nigra pars compacta (SNpc), where it manifests mostly as non-motor symptoms that precede the classical motor symptoms. [3] The motor symptoms usually appear after the degeneration of 50-70% of the SNpc neurons. [4]

PD is named after the British physician James Parkinson, who wrote "An Essay on the Shaking Palsy" in 1817 and described it as a neurological syndrome. Later, in 1872, Jean-Martin Charcot suggested naming it differently to differentiate it from other disorders, especially multiple sclerosis, and since then, it has been called Parkinson's disease. [5][6][7]

Epidemiology

1-2 per 1000 are affected at any time; [2] studies recognized an increase in PD incidence, with increasing age occupying 1% of people above 65 years of age. [8] Also, it was noticed that women have a lower incidence rate and higher age at which symptoms would appear, as there may be a protective factor from female sex hormones. [9] Men are twice more prone to PD than women, and it was found that Hispanics have the highest susceptibility in the US. [10]

Pathogenesis

PD revolves around neuron degeneration in the SNpc and pigment loss. Another crucial hallmark is the falsely folded α-synuclein protein following a mutation in the *SNCA* gene [11]; when misfolded, they become insoluble and accumulate intracellularly to form what we call Lewy bodies. Lewy bodies can also be found in the spinal cord and

peripheral nervous system, including the vagus nerve, salivary glands, sympathetic ganglia, cardiac plexus, enteric nervous system, adrenal medulla, and sciatic nerve. [12]

Etiology

The cause of PD remains unknown, yet it is believed to be multifactorial. Genetics contribute to 5% of PD cases; six main genes are responsible for the autosomal dominant forms of Parkinson's disease: *SNCA, LRRK2, VPS35, EIF4G1, DNAJC13,* and *CHCHD2*. [3] *LRRK2* mutations account for 4% of familial PD and 1% of sporadic PD and are considered the most common PD-causing mutation. [13] *LRRK2* normally encodes the leucine-rich repeat kinase 2, a large multi-domain protein involved in various cellular processes and has a part in innate immunity. Therefore, a mutation in *LRRK2* will cause a Gly2019Ser amino acid substitution, thus increasing the kinase activity. [14][15]

The environment also plays a key role; some examples are infections, MPTP, heavy metals, pesticides, and herbicides exposure, living in rural areas, head trauma, drinking well water, and others. MPTP exposure has been specifically linked to PD as it crosses the blood-brain barrier and is then taken up by dopaminergic cells, destroying them after being converted to MPP+ by astrocytes. [16][17] Strangely, cigarette smoking and caffeine intake have been inversely linked to PD. [18][19]

Clinical Presentation

Progression of early PD undergoes three phases, according to The Movement Disorder Task Force. The first is the preclinical phase, where patients have no clinical symptoms, but neurodegeneration occurs. Second is the prodromal phase, where symptoms, often non-motor symptoms, begin to appear but are not PD-specific and are inadequate for diagnosis. Third is the clinical phase, where symptoms are obvious for PD diagnosis. [20][21][22]

The classical motor symptoms arise unilaterally and asymmetrically; PD has four cardinal symptoms: tremor, bradykinesia or akinesia, muscular rigidity, and postural instability. [23]

1. **Tremor** is usually the first motor symptom to appear, and it is defined as an involuntary continuous shaking when muscles are at rest or relaxed; although most PD patients develop resting tremors, 50% also experience tremors with extended arms after latency. [20] It is characterized by supination and pronation, or pill-rolling.
2. **Bradykinesia** is the decline in voluntary or spontaneous movement, while akinesia means loss of movement. [24]

3. **Rigidity** means muscle stiffness and difficulty in motion when moved passively.
4. **Postural instability** is the inability to maintain an upright, balanced position; it usually appears later in the disease course. It is considered the least responsive to levodopa therapy and the most threatening symptom contributing to increased falls, hip fractures, and dependency. [25]

The course of progression can be seen in Figure 1.

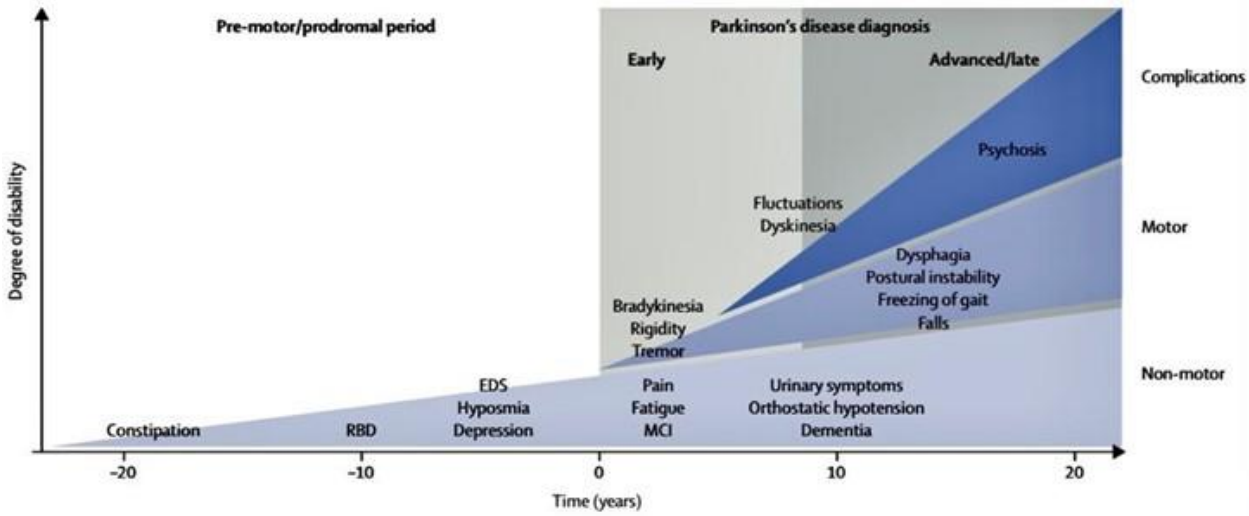


Figure 1: Clinical symptoms and time course of PD progression. [3] EDS = Excessive Daytime Sleepiness. MCI = Mild Cognitive Impairment. RBD = REM sleep Behavior Disorder.

As mentioned earlier, non-motor symptoms precede motor symptoms in most cases and can last up to 20 years or more; these symptoms include:

- Autonomic symptoms like orthostatic hypotension, constipation, fecal incontinence, nausea and vomiting. [25]
- Neuropsychiatric symptoms include depression, hallucinations, psychosis, and panic attacks. [25]
- Cognitive symptoms like dementia and memory loss. [25]
- Sleep disturbances include excessive daytime sleepiness (EDS) and rapid eye movement sleep behavior disorder (RBD). [25]
- Sensory abnormalities like pain, numbness, and anosmia. [25]

There are also premotor symptoms, which are RBD, constipation, depression, and anosmia. [26][27]

Workup and Diagnosis

Diagnosis of PD is quite challenging, especially in the early stages, since it has overlapping signs and symptoms with other Parkinsonian syndromes. The definite diagnosis is post-mortem when autopsied in 76% of cases. [28]

Clinical diagnosis relies primarily on history and neuropathological assessment to identify the presence of the cardinal motor signs; it can also be assisted by response to levodopa therapy, also called the levodopa test. [29]

In the UK, they improved the diagnostic sensitivity and specificity to 98.6% and 91.1%, respectively, with the use of the UK Parkinson's Disease Society Brain Bank (UKPDSBB) clinical criteria shown in Figure 2. [23]

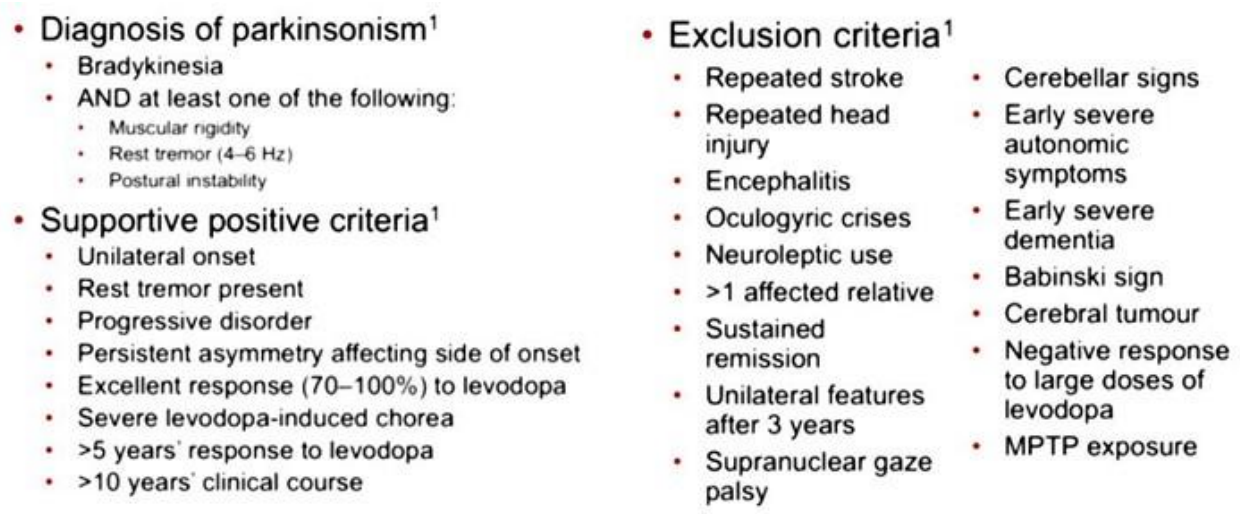


Figure 2: UK Parkinson's Disease Society Brain Bank criteria [23]

Furthermore, Braak and colleagues established disease staging to reflect the location of Lewy body deposition in different brain parts; this guides in determining the disease progression; only 10-20% of cases are exceptions that opposed this staging scheme. [30]

Stage 1 is when Lewy bodies deposit in the olfactory bulb and/or the glossopharyngeal and vagal nerves, followed by stage 2, where they develop in the medulla oblongata and the pontine tegmentum. Stage 3, when motor symptoms start to show, is when the α-synuclein inclusions begin to appear in the amygdala and the substantia nigra. Stage 4, Lewy bodies reach the temporal cortex. Finally, stages 5 and 6 are where cognitive alterations are noticed when they reach the neocortex. [31] Figure 3 shows immunohistochemical staining for α-synuclein in different brain regions.

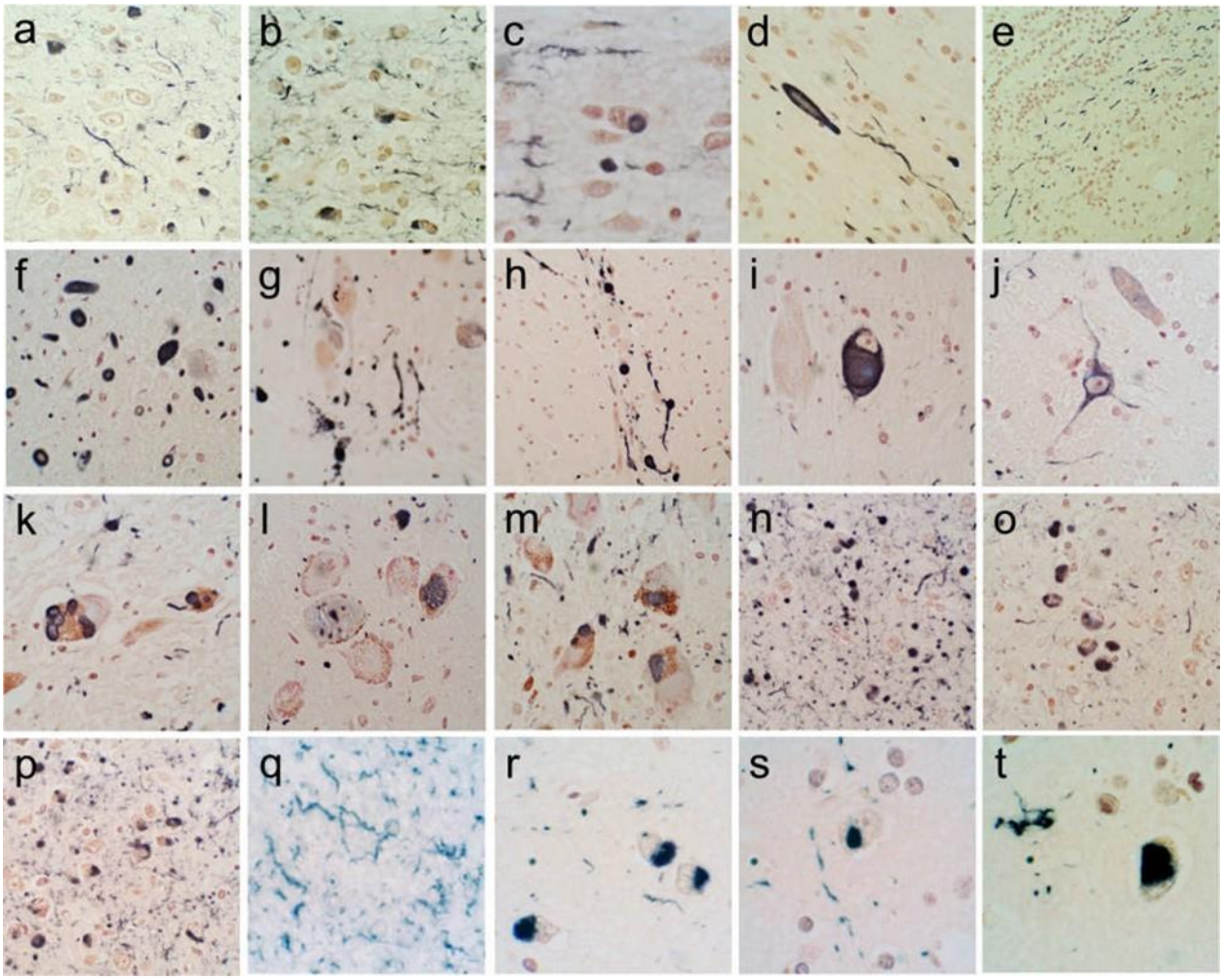


Figure 3: Immunohistochemical staining for α-synuclein in different brain regions. positive immunostaining is black; the counterstain is neutral red. (a–e) The olfactory bulb tract. An enlarged, abnormal neurite within the olfactory tract is shown in (d). positive fibers coursing in parallel array through the internal plexiform layer shown in (e). (f–j) The anterior medulla. The dorsal motor nucleus of the vagus nerve is shown in (f), the raphe nucleus in (g) and (i), the internal tract of the glossopharyngeal nerve in (h), and the lateral reticular nucleus in (j). (k–m) The locus coeruleus in the pons. (n–p) The amygdala. (q) The cingulate gyrus. (r) The middle temporal gyrus. (s) The middle frontal gyrus. (t) The inferior parietal lobule. [32]

Moreover, imaging aids in confirming the diagnosis and further understanding pathophysiology. Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) measures the loss of SNpc dopaminergic nerves and provides a biochemical marker for disease progression. [33]

Differential Diagnosis

Due to the complexity of PD diagnosis, misdiagnosis has been found in almost 25% of patients. The differential diagnosis of Parkinson's disease includes:

- Essential tremor is either an action tremor when doing simple tasks or a postural tremor that arises bilaterally and symmetrically in most cases with absent bradykinesia, rigidity, and postural instability; misdiagnosis occur when essential tremor is unilateral or is a resting tremor. [34][35]
- Progressive Supranuclear Palsy or Steel Richardson-Olszewski syndrome is a multisystem degenerative disorder; gaze palsy is the typical clinical picture that distinguishes it from PD easily; confusion arises in the early stages when symptoms overlap. [36]
- Multisystem Atrophy is a multisystem degenerative disorder that involves α-synuclein accumulation in the CNS with different degrees of autonomic involvement. The parkinsonian variant, or the MSA-p, is usually misdiagnosed with PD. [37]
- Dementia with Lewy bodies is a degenerative dementia that affects cognition, attention and causes visual hallucinations and parkinsonian signs that makes it difficult to differentiate. [38]
- Drug-induced parkinsonism is the most common secondary parkinsonism that may result in confusion at diagnosis especially with patients that have an unclear drug history. Various anti-dopaminergic drugs, mainly anti-psychotics and anti-emetics, induce this secondary parkinsonism. [39]

Management

There is no definite treatment for PD as all available options work as symptomatic relievers.

Levodopa/Carbidopa remains the gold standard therapy; Levodopa is transported to the brain and is then converted to dopamine as a striatal dopamine substitute while Carbidopa prevents its breakdown peripherally and decreases nausea. [40] Chronic use of levodopa causes dyskinesia and motor fluctuation.

Dopamine agonists can also be used such as Apomorphine that has both D1 and D2 receptor activity and same potency as Levodopa with less motor complications. Other Dopamine agonists include pramipexole, ropinirole and rotigotine. [41][42] Common side-effects of dopamine agonists and less commonly Levodopa include nausea, hypotension, oedema, hallucinations, impulse control disorders and sudden sleep attacks.

Catechol-O-Methyl Transferase (COMT) inhibitors including Entacapone and Tolcapone.

Monoamine Oxidase Type B (MAO-B) inhibitors, like Selegiline and Rasagiline as they increase dopamine synaptic concentration.

COMT inhibitors and MAO-B inhibitors are both used along Levodopa to increase its half-life and bioavailability. [33][35]

Amantadine, a N-Methyl-D-aspartate (NMDA) receptor antagonist, is used for levodopa-induced dyskinesia. [45]

Cholinesterase inhibitors such as Rivastigmine are used in dementia caused by PD. [46] Autonomic dysfunction is treated mainly with mineralocorticoid and fludrocortisone; Droxidopa is used with orthostatic hypotension. [45][47] Depression is treated with Selective Serotonin Reuptake Inhibitor (SSRI) since Tricyclic antidepressants can worsen orthostatic hypotension. [48]

Surgical intervention is used with severe motor complications and dyskinesias that do not respond well to medications; Deep Brain Stimulation (DBS) mimics ablative surgery by implanting a pacemaker-like device that generates electrical impulses targeting either the subthalamic nucleus, the thalamus' ventral intermediate nucleus or the globus pallidus interna. [49] Patients who do not respond to dopaminergic therapy do not typically respond to DBS, therefore, to obtain maximal results, patients must be carefully selected preoperatively, and implantation must be done accurately. [50] There are also side effects for DBS, but they are found to be reversible; they include paresthesia, ataxia, dysarthria, and frequent mood changes. [25] DBS electrodes are shown in CT images in Figure 4.

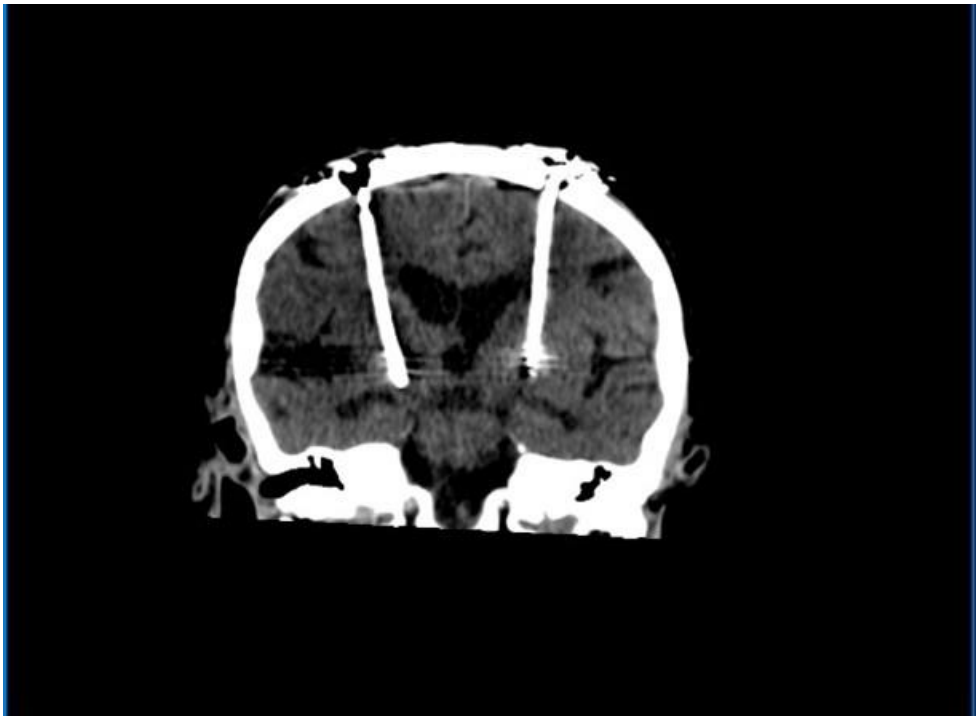


Figure 4: CT images show bilateral deep brain stimulation electrodes extending to the region of the subthalamic nuclei. Stimulator is housed on the chest wall. Case courtesy of Dr. Bruno Di Muzio [51]

Risk Factors

Many risk factors were mentioned throughout this paper; to summarize the main factors they include:

- Age is the main risk factor. Incidence and risk increase with age.
- Males are more susceptible than females (2:1).
- Race/ethnicity. In the US, Hispanics had the highest risk, followed by Whites, Asians, and Blacks. [10]
- Genetics, mostly *SNCA* and
- Environmental factors include exposure to pesticides, heavy metals, and others with dietary intake of free radical inducers such as iron and fat.

Prevention

Studies proved that regular exercise, including aerobic exercises with balance training and moderate intake of caffeine, can play a role in diminishing the risk of developing PD. [52][19] Another study stated that the use of non-steroidal anti-inflammatory drugs (NSAIDs) can also reduce PD risk. [53] Moreover, diet has a part in prevention, such as consuming antioxidants like vitamin E, which can neutralize free radicals, thus decreasing oxidative damage [54]; on the other hand, dietary fat and iron induce free radicals and increase the risk of PD. [55][56]

Prognosis

PD itself is not fatal, but the complications that come along with it may decrease life expectancy. These complications include increased falls and trauma due to postural instability, recurrent infections, and choking due to swallowing problems. [57][58] It was also noticed that developing dementia and the onset of which a patient does contributes to a poor outcome. [57]

References

[1] M. T. Hayes, "Parkinson's Disease and Parkinsonism.," *Am. J. Med.*, vol. 132, no. 7, pp. 802–807, Jul. 2019, doi: 10.1016/j.amjmed.2019.03.001.
[2] O.-B. Tysnes and A. Storstein, "Epidemiology of Parkinson's disease.," *J. Neural Transm.*, vol. 124, no. 8, pp. 901–905, Aug. 2017, doi: 10.1007/s00702-017-1686-y.
[3] L. V Kalia and A. E. Lang, "Parkinson's disease.," *Lancet (London, England)*, vol. 386, no. 9996, pp. 896–912, Aug. 2015, doi: 10.1016/S0140-6736(14)61393-3.
[4] P. K. Morrish, J. S. Rakshi, D. L. Bailey, G. V Sawle, and D. J. Brooks, "Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [18F] dopa PET.," *J. Neurol. Neurosurg. Psychiatry*, vol. 64, no. 3, pp. 314–319, Mar. 1998, doi: 10.1136/jnnp.64.3.314.
[5] J. Parkinson, "An Essay on the Shaking Palsy," *Whittingham Rowl. Sherwood, Needly Jones*, 1817.
[6] C. J-M, *De la paralysie agitante*. 1872.

[7] C. G. Goetz, "The history of Parkinson's disease: early clinical descriptions and neurological therapies.," *Cold Spring Harb. Perspect. Med.*, vol. 1, no. 1, p. a008862, Sep. 2011, doi: 10.1101/cshperspect. a008862.
[8] C. M. Tanner and S. M. Goldman, "Epidemiology of Parkinson's disease.," *Neurol. Clin.*, vol. 14, no. 2, pp. 317–335, May 1996, doi: 10.1016/S0733-8619(05)70259-0.
[9] C. A. Haaxma *et al.*, "Gender differences in Parkinson's disease.," *J. Neurol. Neurosurg. Psychiatry*, vol. 78, no. 8, pp. 819–824, Aug. 2007, doi: 10.1136/jnnp.2006.103788.
[10] S. K. Van Den Eeden *et al.*, "Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity.," *Am. J. Epidemiol.*, vol. 157, no. 11, pp. 1015–1022, Jun. 2003, doi: 10.1093/aje/kwg068.
[11] M. H. Polymeropoulos *et al.*, "Mutation in the alpha-synuclein gene identified in families with Parkinson's disease.," *Science*, vol. 276, no. 5321, pp. 2045–2047, Jun. 1997, doi: 10.1126/science.276.5321.2045.
[12] D. G. Beach, T. G., Adler, C. H., Sue, L. I., Vedders, L., Lue, L., Walker, "Multi-organ distribution of phosphorylated a-synuclein histopathology in subjects with Lewy body disorders," *Acta Neuropathol*, vol. 119, no. 6, pp. 689–702, 2010.
[13] D. G. Healy *et al.*, "Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study.," *Lancet. Neurol.*, vol. 7, no. 7, pp. 583–590, Jul. 2008, doi: 10.1016/S1474-4422(08)70117-0.
[14] M. R. Cookson, "Cellular effects of LRRK2 mutations.," *Biochem. Soc. Trans.*, vol. 40, no. 5, pp. 1070–1073, Oct. 2012, doi: 10.1042/BST20120165.
[15] N. Dzamko and G. M. Halliday, "An emerging role for LRRK2 in the immune system.," *Biochem. Soc. Trans.*, vol. 40, no. 5, pp. 1134–1139, Oct. 2012, doi: 10.1042/BST20120119.
[16] J. W. Langston, P. Ballard, J. W. Tetrud, and I. Irwin, "Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis.," *Science*, vol. 219, no. 4587, pp. 979–980, Feb. 1983, doi: 10.1126/science.6823561.
[17] B. R. Ransom, D. M. Kunis, I. Irwin, and J. W. Langston, "Astrocytes convert the parkinsonism inducing neurotoxin, MPTP, to its active metabolite, MPP+.," *Neurosci. Lett.*, vol. 75, no. 3, pp. 323–328, Apr. 1987, doi: 10.1016/0304-3940(87)90543-x.
[18] D. M. Morens, A. Grandinetti, D. Reed, L. R. White, and G. W. Ross, "Cigarette smoking and protection from Parkinson's disease: false association or etiologic clue?" *Neurology*, vol. 45, no. 6, pp. 1041–1051, Jun. 1995, doi: 10.1212/wnl.45.6.1041.
[19] G. W. Ross *et al.*, "Association of coffee and caffeine intake with the risk of Parkinson disease.," *JAMA*, vol. 283, no. 20, pp. 2674–2679, May 2000, doi: 10.1001/jama.283.20.2674.
[20] J. A. Obeso *et al.*, "Past, present, and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy.," *Mov. Disord.*, vol. 32, no. 9, pp. 1264–1310, Sep. 2017, doi: 10.1002/mds.27115.
[21] D. Berg *et al.*, "Changing the research criteria for the diagnosis of Parkinson's disease: obstacles and opportunities.," *Lancet. Neurol.*, vol. 12, no. 5, pp. 514–524, May 2013, doi: 10.1016/S1474-4422(13)70047-4.
[22] M. B. Stern, A. Lang, and W. Poewe, "Toward a redefinition of Parkinson's disease.," *Mov. Disord.*, vol. 27, no. 1, pp. 54–60, Jan. 2012, doi: 10.1002/mds.24051.
[23] A. J. Hughes, S. E. Daniel, L. Kilford, and A. J. Lees, "Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases.," *J. Neurol. Neurosurg. Psychiatry*, vol. 55, no. 3, pp. 181–184, Mar. 1992, doi: 10.1136/jnnp.55.3.181.
[24] A. Berardelli, J. C. Rothwell, P. D. Thompson, and M. Hallett, "Pathophysiology of bradykinesia in Parkinson's disease.," *Brain*, vol. 124, no. Pt 11, pp. 2131–2146, Nov. 2001, doi: 10.1093/brain/124.11.2131.
[25] T. A. Zesiewicz, "Parkinson Disease.," *Continuum (Minneap. Minn).*, vol. 25, no. 4, pp. 896–918, Aug. 2019, doi: 10.1212/CON.0000000000000764.
[26] R. B. Postuma *et al.*, "Identifying prodromal Parkinson's disease: premotor disorders in Parkinson's disease.," *Mov. Disord.*, vol. 27, no. 5, pp. 617–626, Apr. 2012, doi: 10.1002/mds.24996.
[27] T. K. Khoo *et al.*, "The spectrum of nonmotor symptoms in early Parkinson disease.," *Neurology*, vol. 80, no. 3, pp. 276–281, Jan. 2013, doi: 10.1212/WNL.0b013e31827deb74.
[28] E. Tolosa, G. Wenning, and W. Poewe, "The diagnosis of Parkinson's disease.," *Lancet. Neurol.*, vol. 5, no. 1, pp. 75–86, Jan. 2006, doi: 10.1016/S1474-4422(05)70285-4.
[29] C. D. Ward and W. R. Gibb, "Research diagnostic criteria for Parkinson's disease.," *Adv. Neurol.*, vol. 53, pp. 245–249, 1990.
[30] H. Braak *et al.*, "Pathology associated with sporadic Parkinson's disease--where does it end?" *J. Neural Transm. Suppl.*, no. 70, pp. 89–97, 2006, doi: 10.1007/978-3-211-45295-0_15.
[31] H. Braak, K. Del Tredici, U. Rüb, R. A. I. de Vos, E. N. H. Jansen Steur, and E. Braak, "Staging of brain pathology related to sporadic Parkinson's disease.," *Neurobiol. Aging*, vol. 24, no. 2, pp. 197–211, 2003, doi: 10.1016/s0197-4580(02)00065-9.
[32] T. G. Beach *et al.*, "Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction.," *Acta Neuropathol.*, vol. 117, no. 6, pp. 613–634, Jun. 2009, doi: 10.1007/s00401-009-0538-8.
[33] D. J. Brooks and N. Pavese, "Imaging biomarkers in Parkinson's disease.," *Prog. Neurobiol.*, vol. 95, no. 4, pp. 614–628, Dec. 2011, doi: 10.1016/j.pneurobio.2011.08.009.
[34] O. Cohen, S. Pullman, E. Jurewicz, D. Watner, and E. D. Louis, "Rest Tremor in Patients with Essential Tremor: Prevalence, Clinical Correlates, and Electrophysiologic Characteristics," *Arch. Neurol.*, vol. 60, no. 3, pp. 405–410, Mar. 2003, doi: 10.1001/archneur.60.3.405.
[35] E. D. Louis, G. Levy, L. J. Côte, H. Mejia, S. Fahn, and K. Marder, "Clinical correlates of action tremor in Parkinson disease.," *Arch. Neurol.*, vol. 58, no. 10, pp. 1630–1634, Oct. 2001, doi: 10.1001/archneur.58.10.1630.
[36] E. Tolosa, F. Valldeoriola, and F. Cruz-Sánchez, "Progressive supranuclear palsy: clinical and pathological diagnosis," *Eur. J. Neurol.*, vol. 2, no. 4, pp. 259–273, 1995, doi: https://doi.org/10.1111/j.1468-1331.1995.tb00129.x.
[37] S. Gilman *et al.*, "Consensus statement on the diagnosis of multiple system atrophy.," *J. Neurol. Sci.*, vol. 163, no. 1, pp. 94–98, Feb. 1999, doi: 10.1016/s0022-510x (98)00304-9.
[38] I. G. McKeith *et al.*, "Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop.," *Neurology*, vol. 47, no. 5, pp. 1113–1124, Nov. 1996, doi: 10.1212/wnl.47.5.1113.

[39] F. J. Jiménez-Jiménez *et al.*, "Drug-induced parkinsonism in a movement disorders unit: A four-year survey.," *Parkinsonism Relat. Disord.*, vol. 2, no. 3, pp. 145–149, Jul. 1996, doi: 10.1016/1353-8020(96)00013-2.
[40] P. A. LeWitt and S. Fahn, "Levodopa therapy for Parkinson disease: A look backward and forward.," *Neurology*, vol. 86, no. 14 Suppl 1, pp. S3-12, Apr. 2016, doi: 10.1212/WNL.0000000000002509.
[41] J. Jankovic and W. Poewe, "Therapies in Parkinson's disease.," *Curr. Opin. Neurol.*, vol. 25, no. 4, pp. 433–447, Aug. 2012, doi: 10.1097/WCO.0b013e3283542fc2.
[42] J. P. Frankel, A. J. Lees, P. A. Kempster, and G. M. Stern, "Subcutaneous apomorphine in the treatment of Parkinson's disease.," *J. Neurol. Neurosurg. Psychiatry*, vol. 53, no. 2, pp. 96–101, Feb. 1990, doi: 10.1136/jnnp.53.2.96.
[43] T. Müller, "Catechol-O-methyltransferase inhibitors in Parkinson's disease.," *Drugs*, vol. 75, no. 2, pp. 157–174, Feb. 2015, doi: 10.1007/s40265-014-0343-0.
[44] L. V Kalia, J. M. Brotchie, and S. H. Fox, "Novel nondopaminergic targets for motor features of Parkinson's disease: review of recent trials.," *Mov. Disord.*, vol. 28, no. 2, pp. 131–144, Feb. 2013, doi: 10.1002/mds.25273.
[45] S.-41. https://doi. org/10. 1002/mds. 2382. Fox, Susan HFox, S. H., Katzenschlager, R., Lim, S.-Y., Ravina, B., Seppi, K., Coelho, M., Poewe, W., Rascol, O., Goetz, C. G., & Sampaio, C. (2011). The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the motor symptoms of *et al.*, "The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the motor symptoms of Parkinson's disease.," *Mov. Disord.*, vol. 26 Suppl 3, pp. S2-41, Oct. 2011, doi: 10.1002/mds.23829.
[46] M. Emre *et al.*, "Rivastigmine for dementia associated with Parkinson's disease.," *N. Engl. J. Med.*, vol. 351, no. 24, pp. 2509–2518, Dec. 2004, doi: 10.1056/NEJMoa041470.
[47] S. Perez-Lloret, M. V. Rey, A. Pavy-Le Traon, and O. Rascol, "Emerging drugs for autonomic dysfunction in Parkinson's disease.," *Expert Opin. Emerg. Drugs*, vol. 18, no. 1, pp. 39–53, Mar. 2013, doi: 10.1517/14728214.2013.766168.
[48] W. M. McDonald, I. H. Richard, and M. R. DeLong, "Prevalence, etiology, and treatment of depression in Parkinson's disease.," *Biol. Psychiatry*, vol. 54, no. 3, pp. 363–375, Aug. 2003, doi: 10.1016/s0006-3223(03)00530-4.
[49] S. K. Kalia, T. Sankar, and A. M. Lozano, "Deep brain stimulation for Parkinson's disease and other movement disorders.," *Curr. Opin. Neurol.*, vol. 26, no. 4, pp. 374–380, Aug. 2013, doi: 10.1097/WCO.0b013e3283632d08.
[50] A. L. Benabid, P. Pollak, E. Seigneuret, D. Hoffmann, E. Gay, and J. Perret, "Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias.," *Acta Neurochir. Suppl. (Wien).*, vol. 58, pp. 39–44, 1993, doi: 10.1007/978-3-7091-9297-9_8.
[51] Radiopaedia, "DBS." https://radiopaedia.org/cases/deep-brain-stimulation-for-parkinson-disease?lang=gb.
[52] B. E. Fisher *et al.*, "The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease.," *Arch. Phys. Med. Rehabil.*, vol. 89, no. 7, pp. 1221–1229, Jul. 2008, doi: 10.1016/j.apmr.2008.01.013.
[53] H. Chen *et al.*, "non-steroidal anti-inflammatory drugs and the risk of Parkinson disease.," *Arch. Neurol.*, vol. 60, no. 8, pp. 1059–1064, Aug. 2003, doi: 10.1001/archneur.60.8.1059.
[54] M. C. de Rijk *et al.*, "Dietary antioxidants and Parkinson disease. The Rotterdam Study.," *Arch. Neurol.*, vol. 54, no. 6, pp. 762–765, Jun. 1997, doi: 10.1001/archneur.1997.00550180070015.
[55] A. A. Farooqui and L. A. Horrocks, "Lipid peroxides in the free radical pathophysiology of brain diseases.," *Cell. Mol. Neurobiol.*, vol. 18, no. 6, pp. 599–608, Dec. 1998, doi: 10.1023/a:1020625717298.
[56] K. M. Powers, T. Smith-Weller, G. M. Franklin, W. T. J. Longstreth, P. D. Swanson, and H. Checkoway, "Parkinson's disease risks associated with dietary iron, manganese, and other nutrient intakes.," *Neurology*, vol. 60, no. 11, pp. 1761–1766, Jun. 2003, doi: 10.1212/01.wnl.0000068021.13945.7f.
[57] C. H. Williams-Gray *et al.*, "The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort.," *J. Neurol. Neurosurg. Psychiatry*, vol. 84, no. 11, pp. 1258–1264, Nov. 2013, doi: 10.1136/jnnp-2013-305277.
[58] K. B. Mark Edwards, Niall Quinn, "Parkinson's Disease and Other Movement Disorders," 2e ed., Oxford University Press, 2008, pp. 18–34.

Article Title: Spinal Cord Infarction.

Author: Mahmoud Mohammed Hamed Abukhashab.

Editors: Yaman Oudat, Aroob Awwad.

Reviwer: Ethar Hazaimeh.

Keywords: Spinal cord injury; Myelopathies; Vascular disorder.

Overview and Epidemiology

Myelopathy is a term that refers to a pathology leading to a neurologic deficit related to the spinal cord [1]. Spinal cord infarction is a rare but aggressive disorder caused by a wide range of pathologic states. Patients usually present with acute paraparesis or quadriparesis, depending on the spinal cord level that is involved. The diagnosis is often made clinically with neuroimaging studies to confirm the diagnosis and exclude other conditions. Spinal cord infarction accounts for 1%-2% of all ischemic strokes and 5%-8% of all acute myelopathies **[2]**. The total occurrence rate of stroke in the United States ranges from 540,000 to 780,000 per year. It is expected that 5000 to 8000 cases of spontaneous spinal cord infarction occur each year **[3,4]**. These figures may be underestimated, as they do not include spinal cord infarction complicating major surgery, which is the most common cause of spinal cord infarction. Spinal cord infarction usually occurs in adults whose mean age is 64 years; this is expected as it is a complication of atherosclerotic vascular disease **[5]**. However, children and neonates in specific circumstances can develop spinal cord infarction **[6]**. Patients at risk may include those having operations between T6 and L2, open surgical repair, acute aortic dissection, prior abdominal aortic aneurysm surgery, elderly, and vascular risk factors; some of the associated risks include hypertension **[7]**, smoking, hyperlipidemia, and diabetes mellitus **[8]**, and the presence of aortic atheroma **[9]**.

Vascular anatomy of the spinal cord

Three major vessels arise from the vertebral arteries in the neck and supply the spinal cord **[10]**. One anterior spinal artery (ASA) and two posterior spinal arteries (PSAs) (Fig. 1). The ASA, as its name implies, supplies the anterior two-thirds of the spinal cord. The ASA and PSAs anastomose at the conus medullaris **[11]**. The spinal arteries receive their blood supply from other regional arteries: C1-T3 is supplied by the vertebral arteries, T3-T7 receives a branch from the intercostal arteries, T8 to the medullary conus is supplied by the Adamkiewicz artery **[11].** The artery of Adamkiewicz is the largest of these and typically arises from T9 to T12 and supplies the lumbar enlargement of the spinal cord (Fig. 2). The watershed area in the middle to the upper thoracic cord is

unproven, therefore; the majority of cases are due to hypoperfusion that occurs in the lower thoracic cord [13,14].

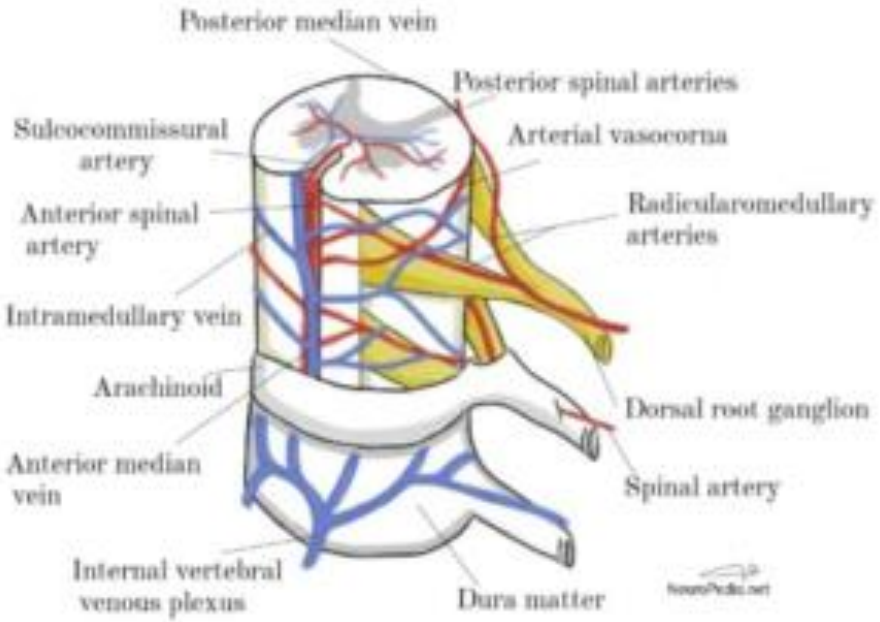


Figure1; spinal cord vascular anatomy.

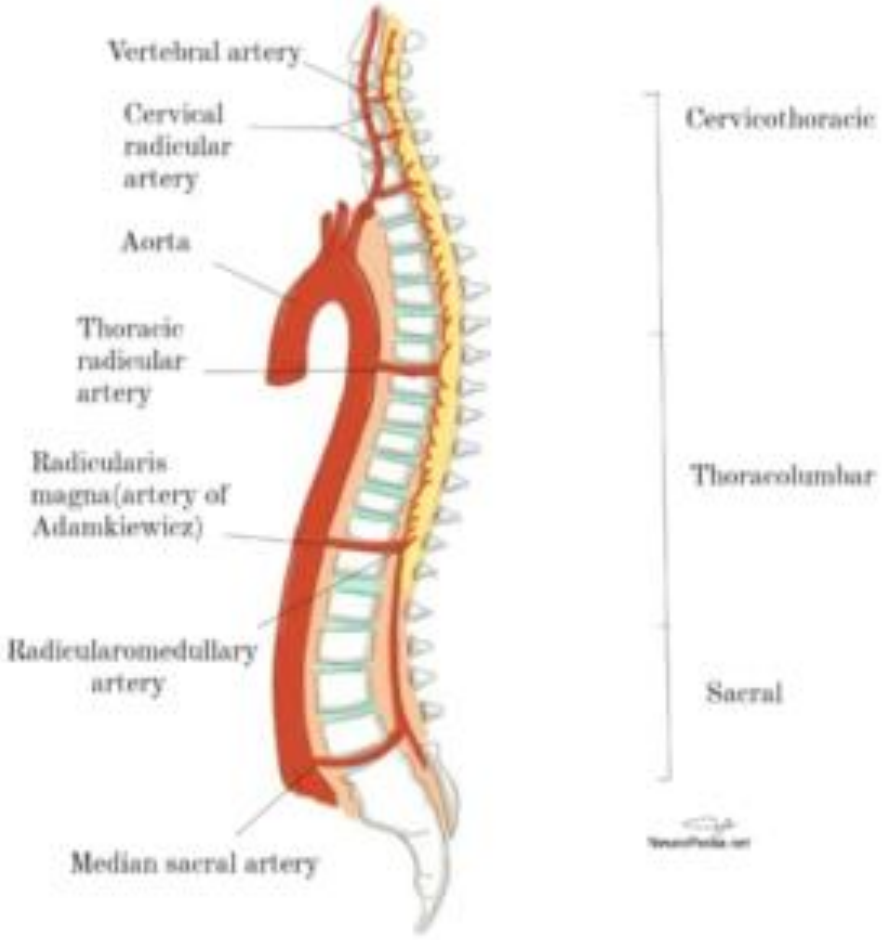


Figure 2: Origins of the vessels supplying the spinal cord from the aorta at various vertebral levels.

Pathogenesis and Etiology

There will be a blood flow restriction to either the white or grey matter of the spinal cord. This will lead to insufficient delivery of oxygen and glucose, leading to a metabolic failure of affected spinal cord tissue. The etiologies of infarction include atherosclerosis, aortic dissection, infection, systemic hypotension, emboli, vasculitis, decompression sickness, and coagulopathy [14].

Clinical presentation and complications

Spinal cord infarction presents with a typical sudden onset of pain weakness, flaccid initially with absent reflexes and/or loss of sensation, most commonly at level T10 [14,15]. Typically, upper motor neuron signs will develop, but if anterior horn cells have a significant involvement, they may not develop. In approximately one-third of patients, there will often be a radicular and may be transient back or neck pain that localizes to the level of infarction [16]. The sudden onset of symptoms that are associated with pain may mimic angina or myocardial infarction [17]. More broadly, clinical presentation depends mainly on the location and extent of the infarction. ASA and PSAs supply the spinal cord, so any abruption of blood flow to these arteries will lead to some syndromes.

In anterior spinal artery syndrome, [18] which is the most common clinical presentation of spinal cord infarction, there will be a loss of motor function and pain/temperature sensation bilaterally; the vibration and proprioception sensation below the lesion level is usually spared. The acute stages of the syndrome are characterized by flaccid paralysis and loss of deep tendon reflexes; spasticity and hyperreflexia may develop after days and weeks. We will also have autonomic dysfunction that may be present as hypotension (either orthostatic or frank hypotension), sexual dysfunction, and/or fecal and urinary incontinence. We may have respiratory failure if the lesion is in the rostral (toward the head) cervical cord. Ischemia is sometimes localized to the level of the anterior horns, which we call **Incomplete Syndrome of the Spinal Artery Syndrome** [18]. The presentation, in this case, will be:

1) Acute paraplegia (pseudo-polio myelitic form) without loss of sensation or sphincter dysfunction.

2) Painful bilateral brachial diplegia, “stiffness, weakness, or lack of mobility in muscle groups” in the case of a cervical lesion (the man-in-the-barrel syndrome) [19].

3) chronic lesions of the anterior horns will lead to progressive distal amyotrophy, which may be misdiagnosed as lateral amyotrophic sclerosis.

Moving to **Posterior Spinal Artery Syndrome** [18]. The manifestation will be loss of vibration and proprioception sensation below the level of the injury (The opposite of what we mentioned about ASA syndrome) and total anesthesia at the level of the injury. Typically, the weakness is mild and transient. Involvement is unilateral, which is more common, but bilateral presentations have also been described [15].

Workup and Diagnosis

As we said, the diagnosis is often made clinically with neuroimaging studies that include Magnetic Resonance Imaging (MRI) and Computed tomography (CT). MRI is the imaging modality of choice in a case where we suspect spinal cord ischemia, but unfortunately, it may appear entirely normal in up to 24% of acutely symptomatic patients [8]. In the MRI protocol, we should do both sagittal and axial T1 and T2-weighted sequences, diffusion-weighted imaging (DWI), and post-contrast imaging [20]. DWI MRI is sensitive for detecting cord ischemia and shows a characteristic high signal indicating cytotoxic edema and reduced free water diffusivity [21]. Now, to support the diagnosis of spinal cord ischemia, we have some characteristic MRI "signs"; sagittal T2-weighted MRI may show a pencil-like (Fig. 3) zone of signal abnormality, while sagittal T1-weighted image may show a focal elevation signal that represents hemorrhagic transformation, or can show a segmental cord swelling [20,21] (Fig. 4, B). If the watershed zone of the gray matter of the anterior horns is affected, then the classic "owl's eyes" or "snake eyes" sign can develop on T2 axial MRI [22,23,24] (Fig. 3). We can also do a Lumbar Puncture which is not helpful in the initial workup, but the CSF may show elevation in protein concentration which is non-specific [8,15].

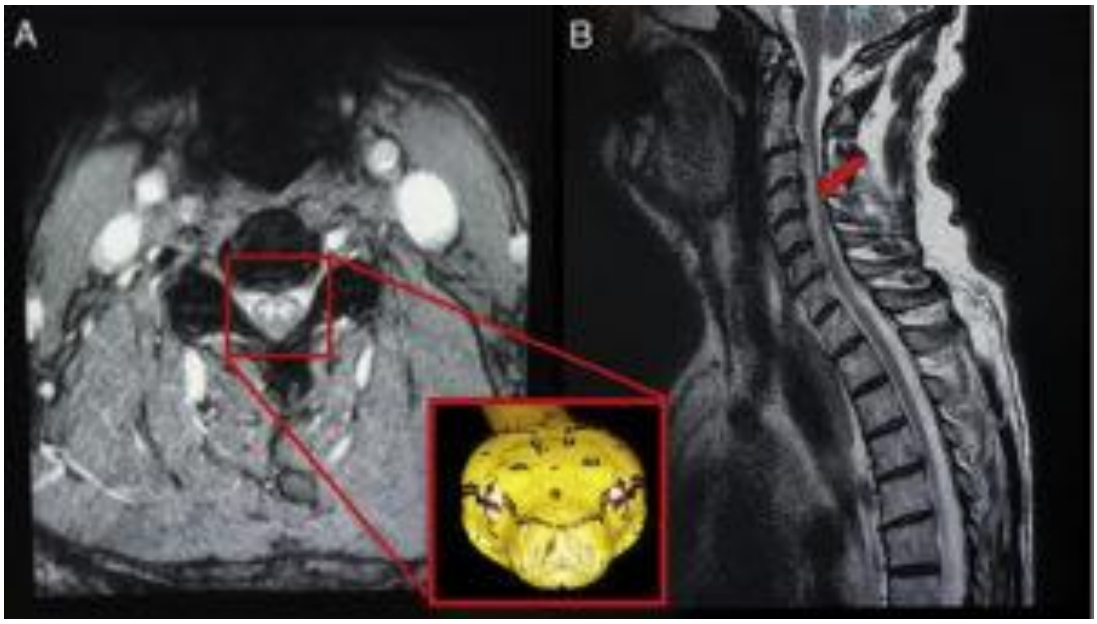


Figure 3 T2-weighted MRI images. The axial slice shows a snake eye-lesion that suggests spinal cord infarction

Figure 4 T1-weighted MRI images. The sagittal slice shows pencil-like signal hyperintensity [25].

Treatment and management

If ischemia is left untreated, it will become progressive and worsen over the first few hours [26]. The primary mechanism, i.e., hypotension/hypoperfusion, embolism, will reach the plateau by 24 h; after that, the secondary mechanism will be more dominant [27], so we should highlight the importance of the treatment in the acute phase "the first 24 h" in reversing the primary mechanism and decrease the damage from the secondary mechanism.

In conclusion, early resuscitation and supportive measures will help us minimize spinal cord damage from secondary pathophysiological mechanisms and may improve quality of life in patients with long-term outcomes [28].

Ischemia Secondary to Embolism, Intravenous thrombolysis with recombinant tissue plasminogen activator was reported in many patients. One patient was quickly diagnosed, made a noticeable recovery, and was discharged with almost no deficits after 72 h [29]. Three other cases were reported; three injections of streptokinase and steroids were given over 1-week intervals. All three patients recovered with no or minimal neurological deficits [30]. The main barrier to such management is time, as there are

contraindications to using thrombolytic therapy [31], and excluding these, the time of diagnosis may also be beyond the optimal therapeutic windows.

Ischemia, Secondary to hypotension/hypoperfusion, can be a part of both primary mechanisms due to myocardial infarction and internal hemorrhage or part of the secondary mechanism of cord damage. To reverse the neurological deficits in spinal cord ischemia that happen after aortic surgery and thoracic endovascular aortic repair (TEVAR), specific management guidelines have been set [32]. If the patient awakes from anesthesia with a neurological deficit, the chance to reverse this pathology will be low, rather than the findings developing after a period of normal neurological function postoperatively [28].

The Role of High-Dose Steroids shows a benefit following acute spinal trauma in patients with complete and incomplete spinal cord injuries if it was administrated within 3 rather than 3–8-h window [28]. Microvascular perfusion and spinal cord blood flow may be improved by high-dose steroids [33, 34] and clinical neurologic recovery after experimental spinal cord injury [35].

Surgical Decompression, the timing, and the efficacy of early decompression (within 24 h) in improving neurologic recovery are still a matter of discussion [36,37]. Studies of early decompression from 1966 through 2000 [38] showed that surgery performed within 24 h will significantly improve neurologic recovery compared with late surgery, but the outcome shows that the evidence was not strong, and that early surgery could be considered only as a practice option.

Risk factors

We mentioned some of the risk factors in this article and to summarize them:

- Aortic surgery, surgical repair of thoracic and thoracoabdominal aortic aneurysms, and aortic dissections are the most common etiology for SCI [39, 40, 5].
- Atherosclerosis of segmental arteries.
- Abdominal/pelvic surgeries.
- Hypertension [7].
- Smoking, hyperlipidemia, and diabetes mellitus [8].
- Fibrocartilaginous embolism.
- Hypercoagulable conditions [41, 42].
- Spinal angiomas.
- Radiation injury [43, 44].
- Vasculitis [43, 44].
- Epidural anesthesia [39, 40, 45].
- Substance abuse (e.g., cocaine) [46].
- Drug-induced (e.g., sildenafil citrate) [47].

- Old age.

Prevention and Prognosis

As a preventive measurement, the key to spinal thrombolysis is early diagnosis. Early resuscitation measures to improve the local perfusion and decrease secondary cord damage may extend the current 3-h therapeutic window for intra-arterial thrombolysis [28]. The metabolism of the spinal cord, neurotoxic neurotransmitter level, and free radicals, along with inflammatory mediators, can be decreased by pharmacologic agents. However, in preventing spinal cord injury, there is no single technique that has proven consistently to be safe and effective. However, a combination of distal aortic perfusion and pharmacologic interventions that attenuate ischemic and reperfusion injury represent the most accepted methods in prevention [48]. The poor prognosis with permanent and disabling consequences is what the spinal cord infarction (SCI) carries. Therefore, the mortality rate of SCI based on published case series ranges from 9 % to 23 % [49, 5, 50, 51]. High-risk mortality rate associated with cardiac arrest, aortic rupture or dissection, and high cervical involvement [50]. Respiratory complications are the leading cause of death among acute phase survivors [52]. Secondary complications are typically chills, pressure sores, urinary sepsis, atelectasis, pneumonia, and deep vein thrombosis [53]. Joint contractures and heterotopic calcification may be present due to prolonged immobilization [52].

References

1. Oyinkan Marquis B, Capone PM. Myelopathy. *Handb Clin Neurol*. 2016; 136:1015-1026. doi:10.1016/B978-0-444-53486-6.00052-1
2. Finsterer J, Löscher W, Quasthoff S, et al. Hereditary spastic paraplegias with autosomal dominant, recessive, X-linked, or maternal trait of inheritance. J Neurol Sci 2012;318(1–2):1–18. doi: 10.1016/j.jns.2012.03.025.
3. Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. How common are the "common" neurologic disorders? Neurology 2007; 68:326.
4. Williams GR. Incidence and characteristics of total stroke in the United States. BMC Neurol 2001; 1:2.
5. Robertson CE, Brown RD Jr, Wijdicks EFM, Rabinstein AA (2012) Recovery after spinal cord infarcts: long-term outcome in 115 patients. Neurology 78(2):114–121. doi:10.1212/ WNL.0b013e31823efc93
6. Spencer SP, Brock TD, Matthews RR, Stevens WK. Three unique presentations of atraumatic spinal cord infarction in the pediatric emergency department. Pediatr Emerg Care 2014; 30:354.
7. Lynch DR, Dawson TM, Raps EC, Galetta SL. Risk factors for the neurologic complications associated with aortic aneurysms. Arch Neurol. 1992 Mar;49(3):284-8.
8. Zalewski NL, Rabinstein AA, Krecke KN, Brown RD, Wijdicks EFM, Weinshenker BG, Kaufmann TJ, Morris JM, Aksamit AJ, Bartleson JD, Lanzino G, Blessing MM, Flanagan EP. Characteristics of Spontaneous Spinal Cord Infarction and Proposed Diagnostic Criteria. JAMA Neurol. 2019 Jan 01;76(1):56-63
9. Kramer CL. Vascular Disorders of the Spinal Cord. *Continuum (Minneap Minn)*. 2018;24(2, Spinal Cord Disorders):407-426. doi:10.1212/CON.0000000000000595
10. Prasad S, Price RS, Kranick SM, et al. Clinical reasoning: a 59-year-old woman with acute paraplegia. Neurology 2007; 69: E41.
11. Hurst RW. Spinal vascular disorders. In: Resonance Imaging of the Brain and Spine, 2nd ed, Atlas SW (Ed), Lippincott, Philadelphia 2006. p.1387.
12. Romi F, Naess H: Characteristics of spinal cord stroke in clinical neurology. Eur Neurol 2011; 66:305-309.
13. Korse NS, Pijpers JA, van Zwet E, et al. Cauda equina syndrome: presentation, outcome, and predictors with focus onmicturition, defecation, and sexual dysfunction. Eur Spine J 2017;26(3): 894–904. doi:10.1007/s00586-017-4943-8.
14. Fairbank J, Hashimoto R, Dailey A, et al. Does patient history and physical examination predict MRI proven cauda equina syndrome? Evid Based SpineCare J 2011;2(4):27–33. doi:10.1055/s-0031-1274754.

15. Novy J, Carruzzo A, Maeder P, Bogousslavsky J. Spinal cord ischemia: clinical and imaging patterns, pathogenesis, and outcomes in 27 patients. Arch Neurol. 2006 Aug;63(8):1113-20.
16. Gleave JR,Macfalane R. Cauda equina syndrome: what is the relationship between timing of surgery and outcome? Br J Neurosurg 2002;16(4): 325–328. doi:10.1080/0268869021000032887.
17. Harringan M, Deveikis J: Handbook of Cerebrovascular Disease and Neurointerventional Technique, (ed 2), Springer Science, Business Media, New York: Humana Press, 2013
18. Vargas MI, Gariani J, Sztajzel R, et al. Spinal cord ischemia: practical imaging tips, pearls, and pitfalls. *AJNR Am J Neuroradiol*. 2015;36(5):825-830. doi:10.3174/ajnr. A4118
19. Berg D, Mulles W, Koltzenburg M, et al. Man-in-the-barrel syndrome caused by cervical spinal cord infarction. Acta Neurol Scand 1998; 97:417–19
20. Vargas MI, Gariani J, Sztajzel R, Barnaure-Nachbar I, Delattre BM, Lovblad KO, Dietemann JL. Spinal cord ischemia: practical imaging tips, pearls, and pitfalls. AJNR Am J Neuroradiol. 2015 May;36(5):825-30.
21. Weidauer S, Nichtweiß M, Hattingen E, Berkefeld J. Spinal cord ischemia: aetiology, clinical syndromes and imaging features. Neuroradiology. 2015 Mar;57(3):241-57.
22. Bosmia AN, Hogan E, Loukas M, et al: Blood supply to the human spinal cord: part I. Anatomy and hemodynamics. Clin Anat 28(1):52-64, 2015.
23. Ross Jeffrey S, Moore Kevin R: Diagnostic Imaging: Spine. Salt Lake City, UT: Amirsys Inc, 2004
24. Mawad ME, Rivera V, Crawford S, et al: Spinal cord ischemia after resection of thoracoabdominal aortic aneurysms. Am J Neuroradiol
25. Martínez Tébar MJ, Baeza Román A, Julia Mejia Olmos G. “Snake eye” and “pencil-like” signs together with diaphragmatic paralysis in a patient with anterior spinal cord ischemia. *Med Intensiva (English Ed*. 2019;43(7):452. doi: 10.1016/j.medine.2019.06.004
26. Fehlings MG, Tator CH, Linden RD (1989) The effect of nimodipine and dextran on axonal function and blood flow following experimental spinal cord injury. J Neurosurg 71(3):403–416. doi:10.3171/ jns.1989.71.3.0403
27. Tator CH (1991) Review of experimental spinal cord injury with emphasis on the local and systemic circulatory effects. Neurochirurgie 37(5):291–302
28. Boddu SR, Cianfoni A, Kim KW, et al. *Spinal Cord Infarction and Differential Diagnosis*.; 2016. doi:10.1007/978-1-4614-9029-6_30
29. Restrepo L, Wityk RJ, Grega MA et al (2002) Diffusion- and perfusion-weighted magnetic resonance imaging of the brain before and after coronary artery bypass grafting surgery. Stroke 33(12):2909–2915.
30. Baba H, Tomita K, Kawagishi T, Imura S (1993) Anterior spinal artery syndrome. Int Orthop 17(6):353–356
31. Jauch EC, Saver JL, Adams HP Jr et al (2013) Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 44(3):870–947. doi:10.1161/STR.0b013e318284056a
32. McGarvey ML, Cheung AT, Szeto W, Messe SR (2007) Management of neurologic complications of thoracic aortic surgery. J Clin Neurophysiol 24(4):336–343. doi:10.1097/ WNP.0b013e31811ec0b0
33. Young W, Flamm ES (1982) Effect of high-dose corticosteroid therapy on blood flow, evoked potentials, and extracellular calcium in experimental spinal injury. J Neurosurg 57(5):667–673. doi:10.3171/jns.1982.57.5.0667
34. Anderson DK, Means ED,Waters TR, Green ES (1982) Microvascular perfusion and metabolism in injured spinal cord after methylprednisolone treatment. J Neurosurg 56(1):106–113. doi:10.3171/ jns.1982.56.1.0106
35. Anderson DK, Saunders RD, Demediuk P et al (1985) Lipid hydrolysis and peroxidation in injured spinal cord: partial protection with methylprednisolone or vitamin E and selenium. Cent Nerv Syst Trauma 2(4):257–267
36. Fehlings MG, Tator CH (1999) An evidence-based review of decompressive surgery in acute spinal cord injury: rationale, indications, and timing based on experimental and clinical studies. J Neurosurg 91(1 Suppl):1–11
37. Fehlings MG, Perrin RG (2005) The role and timing of early decompression for cervical spinal cord injury: update with a review of recent clinical evidence. Injury 36(Suppl 2): B13–B26. doi:10.1016/ j. injury.2005.06.011
38. La Rosa G, Conti A, Cardali S, Cacciola F, Tomasello F (2004) Does early decompression improve neurological outcome of spinal cord injured patients? Appraisal of the literature using a metaanalytical approach. Spinal Cord 42(9):503–512. doi:10.1038/sj.sc.3101627
39. Sandson TA, Friedman JH (1989) Spinal cord infarction. Report of 8 cases and review of the literature. Medicine (Baltimore) 68(5):282–292
40. Cheshire WP, Santos CC, Massey EW, Howard JF Jr (1996) Spinal cord infarction: etiology and outcome. Neurology 47(2):321–330. doi:10.1212/WNL.47.2.321
41. Rothman SM, Nelson JS (1980) Spinal cord infarction in a patient with sickle cell anemia. Neurology 30(10):1072–1076
42. Von Pohle WR (1996) Disseminated mucormycosis presenting with lower extremity weakness. Eur Respir J 9(8):1751–1753
43. Whiteley AM, Hauw JJ, Escourolle R (1979) A pathological survey of 41 cases of acute intrinsic spinal cord disease. J Neurol Sci 42(2):229–242
44. Gibb WR, Urry PA, Lees AJ (1985) Giant cell arteritis with spinal cord infarction and basilar artery thrombosis. J Neurol Neurosurg Psychiatry 48(9):945–948
45. Sliwa JA, Maclean IC (1992) Ischemic myelopathy: a review of spinal vasculature and related clinical syndromes. Arch Phys Med Rehabil 73(4):365–372
46. Sawaya GR, Kaminski MJ (1990) Spinal cord infarction after cocaine use. South Med J 83(5):601–602
47. Walden JE, Castillo M (2012) Sildenafil-induced cervical spinal cord infarction. AJNR Am J Neuroradiol 33(3): E32–E33. doi:10.3174/ajnr. A2628

48. Mauney, M. C., Blackbourne, L. H., Langenburg, S. E., Buchanan, S. A., Kron, I. L., & Tribble, C. G. (1995). Prevention of spinal cord injury after repair of the thoracic or thoracoabdominal aorta. The Annals of Thoracic Surgery, 59(1), 245–252. https://doi.org/10.1016/0003-4975(94)00815-O
49. Nedeltchev K, Loher TJ, Stepper F et al (2004) Long-term outcome of acute spinal cord ischemia syndrome. Stroke 35(2):560–565. doi: 10.1161/01.STR.0000111598. 78198.EC
50. Salvador de la Barrera S, Barca-Buyo A, Montoto-Marqués A, Ferreiro-Velasco ME, Cidoncha- Dans M, Rodriguez-Sotillo A (2001) Spinal cord infarction: prognosis and recovery in a series of 36 patients. Spinal Cord 39(10):520–525. doi:10.1038/sj.sc.3101201
51. Masson C, Leys D, Meder JF, Dousset V, Pruvo JP (2004) Spinal cord ischemia. J Neuroradiol 31(1):35–46
52. DeVivo MJ, Kartus PL, Stover SL, Rutt RD, Fine PR (1989) Cause of death for patients with spinal cord injuries. Arch Intern Med 149(8):1761–1766
53. Aharon-Peretz J, Adir Y, Gordon CR, Kol S, Gal N, Melamed Y (1993) Spinal cord decompression sickness in sport diving. Arch Neurol 50(7):753–756

Article Topic: Meningitis.

Author: Hashem Mohammad Bani Ata.

Editors: Yaman Oudat, Aroob Awwad.

Reviewer: Ethar Hazaimeh

Keywords: meninges, meningismus, neuroinfectious disease.

Overview

Meningitis is defined as inflammation of the meninges, diagnosed by an abnormal number of white blood cells in the cerebrospinal fluid and certain clinical signs and symptoms.[1] The cause could be chemical or infectious; however, the most common micro-organisms are enteroviruses. Aseptic meningitis has a self-limiting course, but bacterial one has high morbidity and mortality rates, so immediate treatment and diagnosis should be done.[2] Patients with bacterial meningitis present with the abrupt onset of fever, headache, and meningismus.[3] Streptococcus pneumoniae and Neisseria meningitides are the primary bacterial causative pathogens outside the neonatal age.[4] Classical clinical signs used to diagnose meningitis are nuchal rigidity, Kernig's, and Brudzinski's sign[5].

Epidemiology[6] [7]

Globally, bacterial meningitis has a prevalence rate of more than one million cases and 135,000 deaths annually. Continuous neurological complications occur in 9-25% of cases. However, administering conjugate vaccines for Hemophilus influenzae type b, N. meningitidis, and S. pneumoniae decreases the incidence of bacterial meningitis.

Etiology[8] [9] [10]

The etiologies of meningitis range in severity of caused disease from benign and self-limited to life-threatening. **Bacterial meningitis requi**res fast recognition and treatment. Aseptic meningitis is the most common form, especially viral, requiring supportive treatment. **Enterovirus** accounts for the most common cases of meningitis.

Viral meningitis

- Enterovirus (most common cause)

- Herpes simplex virus
- Varicella zoster virus
- Arboviruses (e.g., West Nile virus)

Bacterial Meningitis

Depends on age, vaccination status, and recent trauma or instrumentation, as illustrated in Table 1.

Age /condition	**Probable Pathogen**
Infants within the first month	*Streptococcus agalactiae*, *Listeria monocytogenes, Escherichia coli*
Children 1 to 23 months of age	*Streptococcus pneumoniae*, *Neisseria meningitidis*, *S. agalactiae*, *haemophiles influenzae*, *E. coli*
Age (2 -50) year	*N. meningitidis*, *S. pneumoniae*
Age > 50 / immunocompromised / alcoholics	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*,
basilar skull fracture / cochlear implant	*S. pneumoniae*, *H. influenzae*
penetrating trauma/post-neurosurgery	*Staphylococcus aureus,* aerobic gram-negative bacilli (Pseudomonas *aeruginosa*), Coagulase-negative staphylococci
cerebrospinal fluid shunt	*Staphylococcus aureus,* aerobic gram-negative bacilli (*Pseudomonas. Aeruginosa*), *Propionibacterium acnes,* Coagulase-negative staphylococci

Table 1. Bacterial meningitis.

Fungal Meningitis

Fungal systemic infection can reach the subarachnoid space and cause meningitis, either **hematogenous or due to trauma or surgery**. Major fungal pathogens are:

1. **Neoformans, C. gattii, C. immitis**: cause infection in immunocompetent and immunocompromised individuals. Cryptococcal meningitis is the most common fungal meningitis, and **HIV is the largest risk factor** for it. **Other risk factors** are steroid therapy, chronic disease in kidney, liver, or lung disease, malignancy, and solid-organ transplants.
   Immunocompetent individuals with no chronic diseases commonly get infected by ***C. gattii,*** causing Cryptococcal meningitis.

2. **Histoplasma meningitis**: causes infection in immunocompetent and immunocompromised individuals mainly, these patients are AIDS patients, solid-organ transplant recipients, receiving corticosteroids or TNF-α antagonists.
3. **Coccidioides meningitis**: Although an ***immunosuppressed* state** increases the risk of Coccidioides meningitis, **genetics** play a major role in it because **Filipinos and African Americans** have the highest incidence.
4. **Candida meningitis** is an opportunistic fungus that can disseminate through the CNS in an immunocompromised state or disrupted protective structures. It is most common in infants with an immature BBB and patients with ventriculoperitoneal shunts or ventriculostomies.

Parasitic (Eosinophilic) meningitis

The presence of >10 eosinophils/μL in cerebrospinal fluid (CSF)**.** The most common causes are Angiostrongylus cantonensis and Gnathostoma spinigerum.

Noninfectious meningitis

- Drug-induced (e.g., non-steroidal anti-inflammatory drugs, trimethoprim/sulfamethoxazole)
- Neuro-sarcoidosis
- Neoplastic meningitis
- Leptomeningeal carcinomatosis
- Benign recurrent lymphocytic meningitis (Mollaret meningitis)

The least common causes are:

- Behçet syndrome
- Central nervous system abscess
- Ehrlichiosis
- Human immunodeficiency virus
- Lyme disease (neuroborreliosis)
- Neurosyphilis
- Systemic lupus erythematous
- Tuberculous meningitis
- Vasculitis

Pathogenesis[1]

There is no exact hypothesis that explains the pathogenesis of meningitis. One hypothesis depends on **Virchow-Robin space (VRS)** as the following:

1. Nasopharyngeal colonization.
2. Penetration into the bloodstream after crossing the mucosal membranes.
3. Proliferation of micro-organisms in the bloodstream.
4. Extravasations across the endothelium of the post-capillary venules to the perivascular VRS.
5. Passage from VRS to subpial space.
6. Moving through pia mater, infiltrating the CSF in subarachnoid space.
7. Invasion of the meninges.

Clinical features[12] [13] [8]

Presentation of meningitis has unique characteristics depending on the age group:

Neonate/ infant is non-specific in its clinical presentation as in older patients, so an infant will look ill with one or more of the following: loss of appetite, irritability, vomiting, hypotonia, apnea, grunting, bulging fontanelle, and seizure. Neck stiffness is uncommon.

Children: headache, fever, confusion, photophobia, nausea, vomiting, neck stiffness, irritability, and seizure.

Adults present with at least two of these four symptoms: headache, fever, neck stiffness, and altered mental status. Patients may have petechial rash from either pneumococcal or meningococcal meningitis.

Patients older than 65 may present with an atypical presentation like non-specific confusion. Fever, headache, and nuchal rigidity may not be present; moreover, the Listeria monocytogenes is common in elderly patients.

Additionally, a good history is essential to make a differential diagnosis[17]; that includes:

- Social history containing risk factors for sexually transmitted diseases.
- Immune status and vaccination history of all patients.
- Up to date medications are required because some medication groups (e.g., IV immunoglobulin [IVIg], non-steroidal anti-inflammatory medications) can lead to chronic meningitis.
- Travel history, vocational history.
- The presence of systemic symptoms or signs. Skin rash, joint pains, or mouth/genital ulcers might sometimes provide diagnostic clues.

Complications[14]

Complications may include seizures, Hydrocephalus, subdural collection, cerebral infarction, empyema, intracranial abscess, cranial nerve palsy, motor disability, intelligence quotient, sensorineural hearing loss, visual deficits, and venous sinus thrombosis.

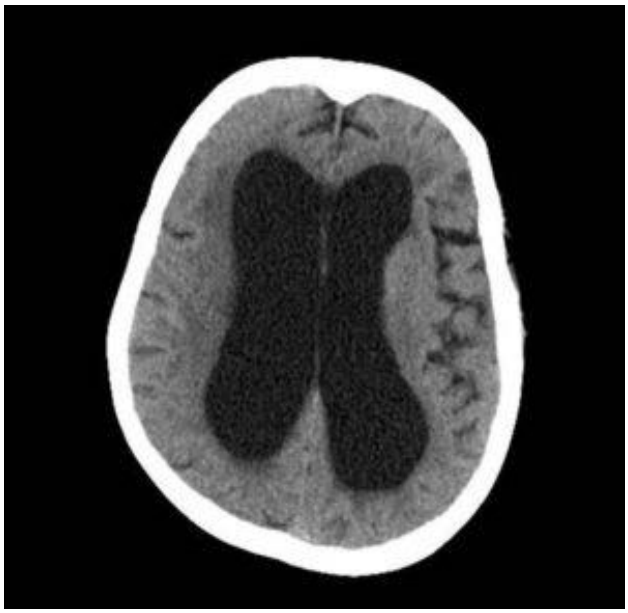


Figure 1: hydrocephalus: Case courtesy of Radswiki, Radiopaedia.org.[14]

Physical Examination

Classic physical examination maneuvers for evaluating meningitis that irritates the meningeal membrane are **nuchal rigidity, Kernig's sign,** and **Brudzinski's sign**.

Kernig's sign is performed with the patient supine in position, hips, and knees flexing, and the patient's knee extended. Pain involving the hamstring muscles as a result of stretching the inflamed sciatic nerve roots at angles less than 135° indicates a positive Kernig's sign .[20]

Brudzinski's sign is performed while the patient is in a supine position. With one hand behind the patient's head and the other on their chest, the examiner elevates the patient's head while the other prevents the patient from rising. If the patient has meningitis, passive neck flexion will pull the nerve roots through the meninges, both of which are inflamed, causing pain and involuntary movement of the lower extremities. Therefore, flexion of the patient's hips and knees after passive flexion of the neck indicates a positive Brudzinski sign .[20]

Figure 2: (a, b): Kernig's sign / (C): Brudzinski's sign [21]

Laboratory investigations[18, 19]

Blood culture

Blood samples should be drawn for **culture**, which is helpful before starting the antibiotics, because antibiotics influence the diagnosis. Blood cultures are positive in 50–80% of bacterial meningitis cases. To determine the exact pathogen, microscopic investigation is required with gram and acid-fast stains.

Blood PCR

Higher sensitivity rate compared to blood culture**.** It also has an important advantage: it detects bacteria after being administrated with an antibacterial agent**.**

Lumbar puncture (LP)[19]

Lumbar puncture is the **confirmatory test** for meningitis. Cell count in CSF indicates if there is inflammation, and the type of leukocytes helps determine the cause of meningitis. **Lymphocyte predominance** suggests viral, whereas Neutrophil predominance suggests bacterial infection, also observed in tuberculous meningitis.

In addition, the biochemistry of CSF is also helpful in diagnosis. **Cerebrospinal fluid glucose** is normally approximately two-thirds of the plasma concentration, but it is lower in bacterial and tuberculous meningitis, so we should consider plasma glucose when we approach lumbar puncture. Also, increased **protein levels in CSF** suggest inflammation. Finding the exact pathogen requires microscopic investigation with gram and acid-fast stains. However, one method with a higher sensitivity rate is CSF PCR, which is beneficial for patients who received antibiotics before LP.

Parameter	Normal	Bacterial	Viral	Tuberculous	Fungal

Opening pressure (cm CSF)	12–20	High	Normal or slightly raised	High	High
Appearance	Clear	Purulent	Clear	Clear /cloudy	Clear /cloudy
CSF WBC (cells/μL)	<5	>100	(5–1000)	(5–100)	(5–100)
Predominant cell		Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
CSF protein		High	Slightly raised	High	High
CSF Glucose level (mg/dL)	50 to 80	Usually, <40	Mostly normal	low **glucose level** (< 40 mg/dL)	normal or low
CSF to blood glucose ratio	>0.66	Very low	Normal or slightly low	Very low	low

TABLE 2. This table shows parameters change with different pathogens.[8, 15]

Lumbar puncture contraindications:[22]

Contraindications were identified in much clinical research. The most important contraindications are:

1. If the patient has low platelet levels >20,000/mm3 to 50,000/mm3 or an elevated international normalized ratio (INR) can be at risk of subarachnoid hemorrhage.
2. Presence of skin infection at the puncture site.
3. For congenital spine abnormalities (e.g., tethered cord), the LP procedure can be guided by fluoroscopy, ultrasound, or CT.
4. Possible high intracranial pressure with brain herniation. In this case, we should perform a fundoscopy and CT/MRI Brain before LP. Significant clinical symptoms and signs for possible high intracranial pressure with brain herniation when a patient has focal neurological deficits, recent generalized seizures, abnormal level of consciousness, respiratory abnormalities, decorticate or decerebrate posturing, dilated or fixed pupil or papilledema at fundoscopy.

It is also important to check medications before the procedure, like anticoagulant medications, and whether they can be temporarily discontinued.

Figure 3: Papilledema secondary to meningitis.[23]

Treatment[8, 18, 22, 24]

Patients with suspected **acute bacterial meningitis** need a **rapid diagnosis, empirical antimicrobial,** and early **adjunctive therapy (high dose dexamethasone);** a strong inflammatory response has its adverse sequelae, hearing loss and deafness, so the administration of dexamethasone reduces the rate of occurrence of these sequelae.

1. Consider a precaution droplet.
2. Stabilization of the patient if they have breathing or circulatory difficulties.
3. Intravenously dexamethasone with a dose of 2 x 0.4 mg/kg/24h or 4 x 8-12mg/24h (0.15 mg/kg every 6 h for infants and children): A high dose of dexamethasone is given to reduce the mortality and morbidity rate of acute bacterial meningitis. For maximum benefit, dexamethasone must be given early (the first dose should be administered shortly before or simultaneously with antibiotics).
4. Initiating empirical therapy: Therapy should begin as soon as possible; delay may increase morbidity and mortality, so such therapy should be initiated before brain CT if indicated. Recommended antibiotics are included in Table 3.
5. Once the causative pathogen is determined, the empirical therapy is stopped, and the patient is started on the specific antimicrobial agent. (Table 4)

Age and condition	**Recommended therapy**
Infant within 1st month	Ampicillin + cefotaxime
Age (2nd month – 50 years)	Vancomycin + ceftriaxone

Age > 50 years or immunocompromised or alcoholic patient	Vancomycin + ceftriaxone + ampicillin
basilar skull fracture / cochlear implant	Vancomycin/ceftriaxone
Penetrating trauma / post neurosurgery / Patients with cerebrospinal fluid shunt	Vancomycin + cefepime

Table 3. Recommended empirical antibiotics.

Pathogen	**Antibiotic**	**Duration of therapy (days)**
Streptococcus pneumonia	Vancomycin + 3rd generation cephalosporin	10 - 14
Neisseria meningitidis	3rd generation cephalosporin	7
Listeria monocytogenes	ampicillin or penicillin	>= 21
Streptococcus *agalactiae*	ampicillin or penicillin	14 - 21
Hemophilus influenza	3rd generation cephalosporin	7
Escherichia coli	3rd generation cephalosporin	21

Table 4. Pathogen-specific therapy.

Viral meningitis requires supportive treatment only; acyclovir is not necessary unless the patient has impairment of consciousness, focal neurological signs, and inflammation of the **temporal lobe** in imaging Figure (4); because **herpes encephalitis** is suspected in this case, it should be treated with a high-dose of acyclovir for no fewer than 14 days and still will have about a 50% chance of permanent neurologic sequelae.

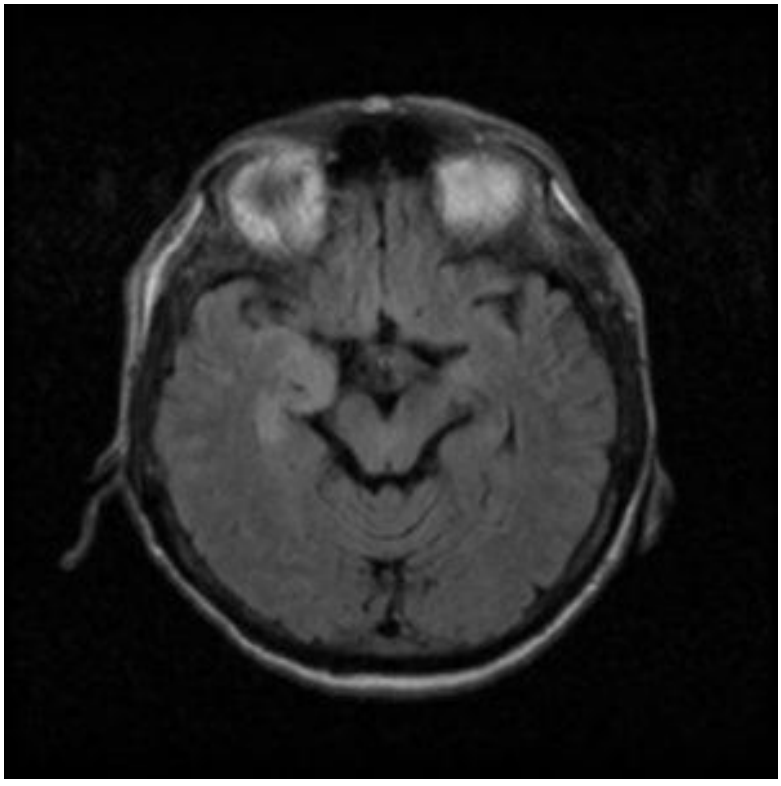


Figure 4: Herpes simplex encephalitis, Case courtesy of RMH Core Conditions, Radiopaedia.[25]

Prevention[26]

Meningococcal vaccination is recommended for these groups:

- Infants aged 2 through 18 months.
- Persons aged 9 months until 55 years of age.
- Persons aged ≥56 years.

High-risk patient populations that are recommended to get the meningococcal vaccine:

- Who suffer from Persistent Complement Component Deficiencies (C3, C5-9, Properdin, Factor D, and Factor H).
- Anatomic or Functional Asplenia.
- Human Immunodeficiency Virus.
- Traveling to an epidemic country.

Risk factor	**Most common causative organism**
Elderly > 65 years	S. pneumoniae, L. monocytogenes
Splenectomy / hyposplenic state	S. pneumoniae
Alcoholism	S. pneumoniae, L. monocytogenes
HIV/AIDS	S. pneumoniae, Salmonella spp
Diabetes mellitus	S. pneumoniae, L. monocytogenes
Cancer	S. pneumoniae, L. monocytogenes
Anatomical defect	S. pneumoniae
Organ transplant recipients	S. pneumonia, L. monocytogenes, Nocardia

Table 5. Risk factors and the most common causative organism[27]

Prognosis

Bacterial meningitis has a mortality rate of 14.8%**.**[28]

The mortality for each pathogen:

- *S. pneumoniae* is (16-37%).
- *N. meningitidis* is (5%).
- *Hemophilus influenzae* (3%).

And it is associated with bad outcomes as the following[18] [24].

- Focal neurological deficits occur in 50% of cases
- Hearing impairment (14%); most common outcome.
- Moderate to severe disability (14%).
- Cognitive impairments.

Viral meningitis is self-limiting; however, in rare cases, it is associated with long-term neuropsychiatric sequelae, particularly anxiety, depression, and neurocognitive dysfunction.[29]

References

1. Putz K, Hayani K, Zar FA. Meningitis. *Prim Care*. 2013;40(3):707-726. doi: 10.1016/j.pop.2013.06.001
2. Cordeiro AP, Silva Pereira RA, Chapeaurouge A, et al. Comparative proteomics of cerebrospinal fluid reveals a predictive model for differential diagnosis of pneumococcal, meningococcal, and enteroviral meningitis, and novel putative therapeutic targets. *BMC Genomics*. 2015;16 Suppl 5(Suppl 5): S11. doi:10.1186/1471-2164-16-S5-S11
3. Davis LE. Acute Bacterial Meningitis. *Continuum (Minneap Minn)*. 2018;24(5, Neuroinfectious Disease):1264-1283. doi:10.1212/CON.0000000000000660
4. Figueiredo AHA, Brouwer MC, van de Beek D. Acute Community-Acquired Bacterial Meningitis. *Neurol Clin*. 2018;36(4):809-820. doi: 10.1016/j.ncl.2018.06.007
5. Tracy A, Waterfield T. How to use clinical signs of meningitis. *Arch Dis Child - Educ & Pract Ed*. 2020;105(1):46 LP - 49. doi:10.1136/archdischild-2018-315428
6. McNeil HC, Jefferies JMC, Clarke SC. Vaccine preventable meningitis in Malaysia: epidemiology and management. *Expert Rev Anti Infect Ther*. 2015;13(6):705-714. doi:10.1586/14787210.2015.1033401
7. Hasbun R. Update and advances in community acquired bacterial meningitis. *Curr Opin Infect Dis*. 2019;32(3):233-238. doi:10.1097/QCO.0000000000000543
8. Mount HR, Boyle SD. Aseptic and Bacterial Meningitis: Evaluation, Treatment, and Prevention. *I am a Fam Physician*. 2017;96(5):314-322.
9. Charalambous LT, Premji A, Tybout C, et al. Prevalence, healthcare resource utilization and overall burden of fungal meningitis in the United States. *J Med Microbiol*. 2018;67(2):215-227. doi:10.1099/jmm.0.000656
10. Shah I, Barot S, Madvariya M. Eosinophilic meningitis: a case series and review of literature of Angiostrongylus cantonensis and Gnathostoma spinigerum. *Indian J Med Microbiol*. 2015;33(1):154-158. doi:10.4103/0255-0857.148430
11. Chan P, Meerdink DJ, Uchizono JA. Potential role of the Virchow Robin space in the pathogenesis of bacterial meningitis. *Med Hypotheses*. 2017; 109:114-118. doi: 10.1016/j.mehy.2017.09.014
12. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med*. 2004;351(18):1849-1859. doi:10.1056/NEJMoa040845
13. Goldacre MJ. Neonatal meningitis. *Postgrad Med J*. 1977;53(624):607-609. doi:10.1136/pgmj.53.624.607
14. Wu H-M, Huang W-Y, Lee M-L, Yang AD, Chaou K-P, Hsieh L-Y. Clinical features, acute complications, and outcome of Salmonella meningitis in children under one year of age in Taiwan. *BMC Infect Dis*. 2011; 11:30. doi:10.1186/1471-2334-11-30
15. radiopedia. hydrocephalus. https://radiopaedia.org/cases/meningitis-6?lang=us
16. radiopedia. hyrocephalus. https://radiopaedia.org/cases/hydrocephalus-1?lang=us
17. Thakur KT, Wilson MR. Chronic Meningitis. *Continuum (Minneap Minn)*. 2018;24(5, Neuroinfectious Disease):1298-1326. doi:10.1212/CON.0000000000000664
18. Griffiths MJ, McGill F, Solomon T. Management of acute meningitis. *Clin Med*. 2018;18(2):164-169. doi:10.7861/clinmedicine.18-2-164
19. Alamarat Z, Hasbun R. Management of Acute Bacterial Meningitis in Children. *Infect Drug Resist*. 2020; 13:4077-4089. doi:10.2147/IDR.S240162
20. Ward MA, Greenwood TM, Kumar DR, Mazza JJ, Yale SH. Josef Brudzinski and Vladimir Mikhailovich Kernig: signs for diagnosing meningitis. *Clin Med Res*. 2010;8(1):13-17. doi:10.3121/cmr.2010.862
21. kernigs and brudzisnki. https://annalsofian.org/article.asp?issn=0972-2327;year=2012;volume=15;issue=4;spage=287;epage=288;aulast=Mehndiratta;type=3
22. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39(9):1267-1284. doi:10.1086/425368

23. Papilledema secondary to meningitis. https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/papilledema-secondary-to-meningitis/index.htm
24. Barichello T, Generoso JS, Collodel A, Moreira AP, Almeida SM de. Pathophysiology of acute meningitis caused by Streptococcus pneumoniae and adjunctive therapy approaches. *Arq Neuropsiquiatr*. 2012;70(5):366-372. doi:10.1590/s0004-282x2012000500011
25. radiopedia. Herpes simplex encephalitis. https://radiopaedia.org/cases/herpes-simplex-encephalitis-2?lang=gb
26. Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm reports Morb Mortal Wkly report Recomm reports*. 2013;62(RR-2):1-28.
27. Adriani KS, Brouwer MC, van de Beek D. Risk factors for community-acquired bacterial meningitis in adults. *Neth J Med*. 2015;73(2):53-60.
28. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med*. 2011;364(21):2016-2025. doi:10.1056/NEJMoa1005384
29. McGill F, Griffiths MJ, Bonnett LJ, et al. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. *Lancet Infect Dis*. 2018;18(9):992-1003. doi:10.1016/S1473-3099(18)30245-7

Article Topic: Alzheimer's Disease.

Author: Leen Sawalha.

Editors: Yaman Oudat, Aroob Awwad.

Reviewer: Ethar Hazaimeh, Hassan Abushukair

KeyWords: Alzheimer's disease, AD, Dementia, Amyloid Beta, Tau, Neurodegenerative Diseases.

Overview and Epidemiology

Dementia is a cognitive degenerative disease that has affected 44 million people around the world, with predictions that this number will triple by the year 2050 (1). Out of all dementias, Alzheimer's is the most common. It affects the elderly, with the occurrence increasing by 15 times beyond the age of 65 (2).

Having Alzheimer's below the age of 65 is scarce. However, if it is present at those earlier ages, it is known as early-onset Alzheimer's disease (3). It has been estimated by the CDC (Centers for Disease Control and Prevention) that the number of those who surpass the age of 65 will rise from 420 million to 1 billion people between the years 2000 to 2030, hence, markedly increasing the susceptible target population of the disease (4).

Paradoxically, although it is believed that Alzheimer's will continue to increase in number, another study shows that the cases have decreased by 24% between 2000-2012 due to an increase in the levels of education seen in those years (5).

Pathogenesis and Etiology

It is hypothesized that cholinergic dysfunction could cause Alzheimer's (6). Patients with the disease have been reported to have a reduced level of activity in choline acetyltransferase compared to those who do not have Alzheimer's (7). A decrease in the number of nicotinic receptors along with muscarinic acetylcholine receptors in the presynaptic terminal contributes to a decrease in the individual's cognitive ability (8).

The most important genetic factor that plays a role in the pathogenesis of late-onset Alzheimer's is the presence of the APOE ε4 allele. This gene codes for apolipoprotein E, which is abundant in the brain and is thought to promote the accumulation of amyloid beta and tau proteins inside the brain (15).

Furthermore, inflammation in the brain, shown to have an initial protective function, will have deleterious effects on the progression of the disease when a chronic response is activated. This happens because microglial cells release many toxic products that harm the brain (16).

Clinical Presentation and Complications

10 early symptoms should be looked out. These include Significant memory loss, struggle in making plans, inability to use appliances and devices, forgetting locations, difficulty processing visuals, difficulty engaging in conversations, misplacing items, diminished ability to judge wisely, avoidance of social interactions, and lastly, anxiety and depression (18).

The later symptoms of Alzheimer's manifest both behaviorally and psychiatrically. Psychiatric symptoms include depression. A study suggests that the coexistence of Alzheimer's along with depression results in much worse clinical outcomes for patients (19). Apathy, which is defined as the loss of emotion and aimless cognition, is also a symptom of Alzheimer's. Its presence indicates swifter cognitive diminishment (20)(21). Agitation and aggression are also seen in patients (21). This poses a significant problem since this has been shown to correlate with an inability to be independent (22). Agitation is seen more commonly in male patients than in female patients (23). Furthermore, psychosis is also seen in those suffering from Alzheimer's and is considered to be the most profound yet least common complication in the early stages (24). As mentioned previously about depression, the presence of psychosis also contributes to an accelerated decrease in cognitive functional ability and an increase in mortality rate (25)(26)(27).

A study found that the most recurrent complications associated with Alzheimer's are patients going astray, stumbling, pneumonia, and fractured bones. The study also concluded that males are more likely to get lost and that a lower level of education was a risk factor for acquiring pneumonia (28). Another prominent complication of Alzheimer's is dysphagia, which subsequently leads to multiple problems such as malnutrition, dehydration, and loss of weight, all of which severely impact the quality of life of the individual and decrease it drastically (29).

Workup and Diagnosis

The preclinical stage of Alzheimer's is unnoticeable, with barely any symptoms. Hence, it is difficult to diagnose early on. However, for a diagnosis to be made, cognitive decline must be extremely evident and must reach a point where it interferes with daily activities (30).

The National Institute of Aging-Alzheimer's Association (NIA-AA) criteria is the currently used criteria for diagnosing the disease. These guidelines recognize that AD begins long before symptoms are evident.

There are 3 stages:

1. Preclinical AD, in which biomarkers of AD may be present but no symptoms.
2. MCI: Mild cognitive symptoms without significant functional impairment.
3. Dementia due to AD.

Mild cognitive impairment is a mental condition in which the symptoms observed are between those seen in normal aging and those seen in dementia. It can sometimes be a predecessor to probable AD. The cognitive state observed at this stage does not significantly impair day-to-day activities. Memory impediment is also observed (33). In some circumstances, mild cognitive impairment is caused by treatable precursors. Examples include MCI, which is acquired due to psychiatric diseases and concurrent illnesses. The cognitive diminishment seen here can be reversed. It should be noted that mild cognitive impairment is not necessarily indicative of Alzheimer's disease. Moreover, there are no treatments approved for MCI by the FDA (34)

Diagnosis

The NIA-AA divides Alzheimer's into possible and probable AD. To be diagnosed with probable AD:

1. The patient must meet the criteria for dementia, which include:

a. Inability to function in daily life.

b. A decrease in performance

c. Symptoms that are inexplicable by other psychiatric disorders like delirium,

d. Cognitive decline, which is diagnosed by taking history and cognitive assessment.

e. In addition to 2 of the following symptoms: inability to remember new information, hindered reasoning, diminished visuospatial skills, decrease in language skills and/or personality changes (35).

2. Affected by insidious onset, declining cognitive ability, and conspicuous cognitive deficits in tests done for one of the following amnestic symptoms: learning and recall deficits with impaired functioning ability in at least one other cognitive aspect. Additionally, they must have non-amnestic symptoms such as being

unable to recall and string together words, diminished visuospatial ability, and executive malfunction.

3. A diagnosis should not be made when these symptoms are accompanied by cerebrovascular disease, characteristics of dementia with Lewy bodies, behavioral characteristics of frontotemporal dementia, properties of semantic variant primary progressive aphasia or non-fluent or agrammatic variant primary progressive aphasia, the coexistence of another neurological/non-neurological disease or the use of drugs that affect cognitive functional ability (35).

Diagnosing possible dementia requires that the patient has an unusual course or an etiologically varied presentation (36).

Neuroimaging

Brain MRI

On MRI, cortical atrophy is apparent. This has been attributed to the presence of neurofibrillary tangles; thus, it is considered to be associated with Alzheimer's (38). Atrophy of structures found in the mesial temporal lobe, such as the hippocampus and entorhinal cortex, is also evident (39). Moreover, the presence of periventricular white matter hyperintensities is indicative of the development of mild cognitive impairment into AD (40). A substantial decrease in the size of the temporoparietal cortex is also seen on MRI and is a marker for the presence of the disease (41). Ventricular enlargement is also apparent on MRI and can be attributed to mild cognitive impairment and AD (42)(43)(44)(45)(46).

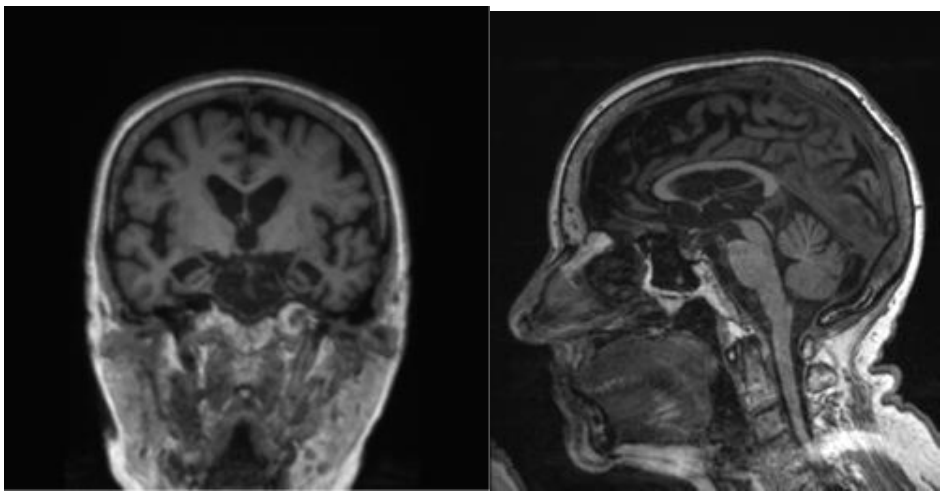


Figure 1: Alzheimer's Disease, Case courtesy of Dr Bruno Di Muzio (47)

Functional brain imaging (FDG-PET, SPECT)

The temporoparietal cortex and posterior cingulate/precuneus reveal distinct regions of hypometabolism (FDG-PET) or hypoperfusion (SPECT), useful for differentiating AD from FTD (predominant hypometabolism in frontal and anterior temporal regions).

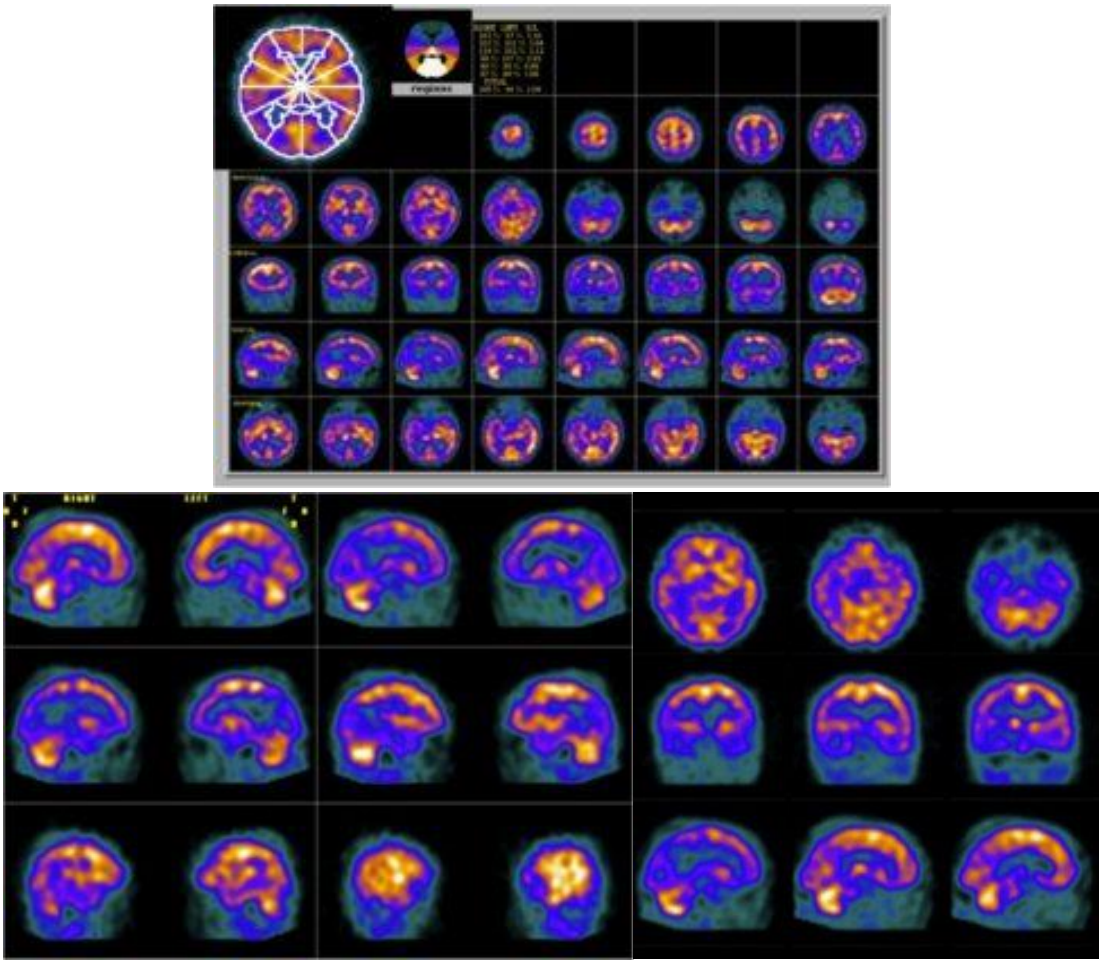


Figure 2: Brain perfusion with 99mTc-ECD shows bilateral temporoparietal hypoperfusion (48).

Neuropathology

On a neuropathological scale, AD is defined by the presence of two lesions:

1. Senile Amyloid plaques
2. Tau neurofibrillary tangles

Alzheimer's is caused by the accumulation of tau proteins forming neurofibrillary lesions (9)(10). Tau proteins are microtubule-associated proteins in the brain's neurons (11). Considering all this, the tau hypothesis states that abnormal phosphorylation of the protein leads to a change from normal tau into PHF tau (12).

Moreover, we have the amyloid cascade hypothesis. This hypothesis states that the accumulation of amyloid beta (Aβ) inside the brain can result in neurodegeneration, which can contribute to Alzheimer's (13)(14).

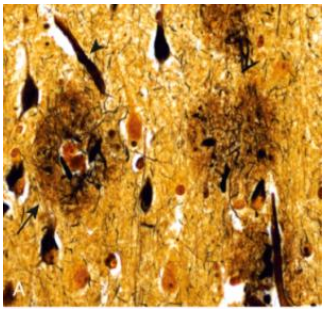


Figure 3: Plaques (arrow) contain a central core of amyloid and a surrounding region of dystrophic neurites (Bielschowsky stain) (17).

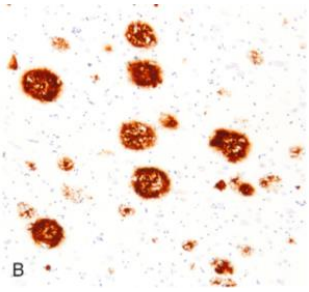


Figure 4: Immunohistochemical stain for Aβ. Peptide is present in the core of the plaques as well as in the surrounding region (17).

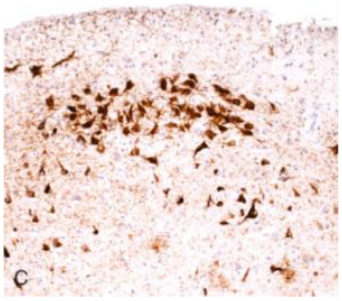


Figure 5: Neurons containing tangles stained with an antibody specific for tau (17).

Biomarkers

Biomarkers of amyloid, tau, and neurodegeneration proposed in the National Institute of Aging-Alzheimer's Association (NIA-AA) research framework for defining AD (TABLE 1):

TABLE 1. AT(N) biomarker grouping (49).

A: Aggregated Aβ or associated pathologic state • **CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio** • **Amyloid PET**
T: Aggregated tau (neurofibrillary tangles) or associated pathologic state • **CSF phosphorylated tau** • **Tau PET**
(N): Neurodegeneration or neuronal injury • **Anatomic MRI** • **FDG PET** • **CSF total tau**

Abbreviations: Aβ, β amyloid; CSF, cerebrospinal fluid.

A test called 'Mini Mental State Examination' is also used to screen for dementia. It tests various cognitive functions such as attention, memory, language, visuoconstruction, and orientation. The maximum score that could be obtained is 30. Scoring 23 or less is considered to signify impairment. Every year, those with Alzheimer's score 3 points less than they did the previous year. This is used as an adjunct diagnosis technique; it is never used by itself to make a diagnosis. It is very useful in determining the severity of dementia (37).

Treatment and Management

Psychosocial treatment options for Alzheimer's include changing the surrounding environment of the patient and aid from family members. Evidence suggests that this improves the well-being of those suffering from the disease (50)(51).

Many treatments nowadays only provide symptomatic relief rather than reverse the disease progression (52).

Pharmacological treatments

1. Acetylcholinesterase inhibitors such as donepezil, galantamine, and rivastigmine. They are all approved for the treatment of Alzheimer's and work by inhibiting the enzyme acetylcholinesterase (53)(54)(55). Acetylcholine is in charge of memory and learning, which would explain the therapeutic effect increasing its amount has on Alzheimer's (56).
2. Memantine, which is an N-methyl-D-aspartate receptor antagonist, is also used as a treatment option. Glutamate increases the amount of calcium inside the cells and leads to a malfunction in the mitochondria, resulting in an increased production of oxidants. Therefore, the destruction of neurons will occur. This

increase in stimulation can be counteracted by NMDA receptor antagonists (57)(58).

Some studies suggest that NSAIDs could help in the treatment of Alzheimer's, as transgenic animals that were given those drugs showed a reduction in the pathology of the disease (59). Unfortunately, when applied to humans, no evidence of efficacy has been observed in the trials conducted (60).

For behavioral disturbances, antipsychotics, anxiolytics, mood stabilizers, and hypnotics can be used to treat the associated symptoms (52).

To treat depression that accompanies Alzheimer's, tricyclic antidepressants like nortriptyline and desipramine can be used. They show less anticholinergic activity than their parent compounds (61). Additionally, reversible monoamine oxidase inhibitors, such as brofaromine and moclobemide, can be used in the treatment of depression related to Alzheimer's (62).

Furthermore, vitamin E, which is an antioxidant, has been suggested as a choice for prophylaxis against the disease. A study conducted showed that those who took vitamin E had decelerated progression to Alzheimer's. The same study indicated that the use of selegiline, which is a drug that increases the release of dopamine, is also beneficial in slowing down Alzheimer's (63)(64).

Risk Factors

1. The APOE gene presents a notable increase in the risk of the development of dementia. This was evident in a study conducted in 1993, which stated that as the amount of APOEe4 alleles escalates, the risk of early onset Alzheimer's grows from a mere 20% to a staggering 90% risk (65).
2. Gender has also been attributed as a risk factor for the development of Alzheimer's. A study has shown that females are more likely to suffer from Alzheimer's after 85 years of age (66).
3. A research paper suggests that being overweight can lead to Alzheimer's since obesity is also linked to diabetes and hyperinsulinemia, which are both risk factors for the development of the disease (67).
4. Age is also a risk factor. An increase in age increased the probability of Alzheimer's, as shown in studies conducted in many areas around the world and included nationalities such as European, Chinese, American, and Spanish (68)(69)(70)(71).
5. A study conducted on men 50 and older concluded that those who suffered from sleep disturbances had a 51% increased risk of developing Alzheimer's (72).

6. A French study concluded that there is a possible risk of users of benzodiazepines acquiring Alzheimer's. However, more research needs to be done in order for a solid correlation to be made (73).
7. Brain injury has also been suggested to increase the risk of acquiring the disease since the prevalence of brain injury and Alzheimer's has increased concurrently (74). It is thought that the link is due to the rise for amyloid beta within the brain a few weeks after head trauma. This can be attributed to a release of interleukin 1, which increases the deposition of amyloid-beta precursor protein (APP) and amyloid beta (75)(76).

Prevention

Multiple preventative measures could be taken.

A study found that those with higher blood pressure were more likely to develop Alzheimer's (77). In elderly patients suffering from hypertension, the intake of antihypertensives helped conserve cognitive functional ability and decreased the risk of dysfunction by 38% (78).

Elevated levels of cholesterol have also been associated with Alzheimer's (79). Hence, statins, which are drugs that reduce cholesterol levels, are used to defend against the disease (80).

Engaging in leisure activities that stimulate mental function, such as reading a newspaper, learning, playing card games, or arts and crafts, has also been shown to lower the risk of Alzheimer's (81)(82)(83). Additionally, physical exercise is suggested to have a preventative role against the development of the disease since it increases cognitive functional ability (84)(85).

Diet also plays a role in the risk of AD. An increase in ingestion of saturated and hydrogenated fats showed an association with a higher risk of Alzheimer's, while the consumption of monounsaturated and polyunsaturated fats has been shown to help prevent mental decline (86)(87)(88).

Prognosis

A study conducted to test the prognosis of Alzheimer's concluded that those suffering from AD had a high incidence of institutionalization and death. Additionally, they found that 11.84% of those with the disease experienced swift cognitive functional diminishment. Moreover, the cohort study showed that 2/3 of those participating had a notable evolution of Alzheimer's (89).

Another study showed that after a 5-year study period, those participating had an 80% dependence on others in their daily activities. 75% of those followed got institutionalized. Additionally, the percentage of incontinence among participants was 74%. After 4 years, most of the patients being studied showed incontinence or dependence on activities of daily living (90).

Furthermore, another study found that those suffering from probable AD had a 3.1-year median survival rate and 3.5 years for Alzheimer's (91).

Recent Updates

Stem cell therapy shows tremendous potential for the treatment of Alzheimer's. It is effective in the treatment of transgenic rodents. However, human trials have still not shown any evidence of efficacy. This may be due to the presence of many factors that govern the disease and the limitations of the studies conducted. Hence, more information and more studies are required to achieve substantial results (92).

Moreover, recent trials have shown a new monoclonal antibody, known as Aducanumab, to be promising. This drug targets amyloid beta and removes the accumulated cluster, thus decelerating the decline in mental capacity (93).

References

1. Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol. 2018 Jan;25(1):59–70.
2. Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, et al. Prevalence of Alzheimer's Disease in a Community Population of Older Persons: Higher Than Previously Reported. JAMA. 1989 Nov;262(18):2551–6.
3. Erkkinen MG, Kim M-O, Geschwind MD. Clinical Neurology and Epidemiology of Major Neurodegenerative Diseases. Cold Spring Harb Perspect Biol. 2018 Apr;10(4).
4. Public Health and Aging: Trends in Aging—United States and Worldwide. JAMA. 2003 Mar;289(11):1371–3.
5. Langa KM, Larson EB, Crimmins EM, Faul JD, Levine DA, Kabeto MU, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. JAMA Intern Med. 2017 Jan;177(1):51–8.
6. Contestabile A. The history of the cholinergic hypothesis. Vol. 221, Behavioral Brain Research. Elsevier; 2011. p. 334–40.
7. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. Vol. 2, Lancet (London, England). England; 1976. p. 1403.
8. Nordberg A, Alafuzoff I, Winblad B. Nicotinic and muscarinic subtypes in the human brain: Changes with aging and dementia. J Neurosci Res. 1992;31(1):103–11.
9. Forman MS, Trojanowski JQ, Lee VM-Y. Neurodegenerative diseases: a decade of discoveries paves the way for therapeutic breakthroughs. Nat Med. 2004;10(10):1055–63.
10. Trojanowski JQ, Mattson MP. Overview of protein aggregation in single, double, and triple neurodegenerative brain amyloidoses. NeuroMolecular Med. 2003;4(1):1–5.
11. Tucker RP. The roles of microtubule-associated proteins in brain morphogenesis: a review. Vol. 15, Brain Research Reviews. Elsevier; 1990. p. 101–20.
12. Mohandas E, Rajmohan V, Raghunath B. Neurobiology of Alzheimer's disease. Indian J Psychiatry. 2009 Jan;51(1):55–61.
13. Hardy JA, Higgins GA. Alzheimer's disease: The amyloid cascade hypothesis. Science (80-). 1992;256(5054):184–5.
14. Evin G, Weidemann A. Biogenesis and metabolism of Alzheimer's disease Aβ amyloid peptides. Peptides. 2002;23(7):1285–97.
15. Muñoz SS, Garner B, Ooi L. Understanding the Role of ApoE Fragments in Alzheimer's Disease. Neurochem Res. 2019 Jun;44(6):1297–305.

16. Kim YS, Joh TH. Microglia, a major player in the brain inflammation: their roles in the pathogenesis of Parkinson's disease. Exp Mol Med. 2006 Aug;38(4):333–47.
17. Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. Tenth Edit. Elsevier; 2018.
18. 2013 Alzheimer's disease facts and figures. Alzheimers Dement. 2013 Mar;9(2):208–45.
19. Zahodne LB, Ornstein K, Cosentino S, Devanand DP, Stern Y. Longitudinal relationships between Alzheimer disease progression and psychosis, depressed mood, and agitation/aggression. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry. 2015 Feb;23(2):130–40.
20. Ota M, Sato N, Nakata Y, Arima K, Uno M. Relationship between apathy and diffusion tensor imaging metrics of the brain in Alzheimer's disease. Int J Geriatr Psychiatry. 2012 Jul;27(7):722–6.
21. Li X-L, Hu N, Tan M-S, Yu J-T, Tan L. Behavioral and psychological symptoms in Alzheimer's disease. Biomed Res Int. 2014;2014:927804.
22. Bidzan L, Bidzan M, Pąchalska M. Aggressive and impulsive behavior in Alzheimer's disease and progression of dementia. Med Sci Monit Int Med J Exp Clin Res. 2012 Mar;18(3):CR182-9.
23. Kitamura T, Kitamura M, Hino S, Tanaka N, Kurata K. Gender differences in clinical manifestations and outcomes among hospitalized patients with behavioral and psychological symptoms of dementia. J Clin Psychiatry. 2012 Dec;73(12):1548–54.
24. Lanctôt KL, Herrmann N, Eryavec G, van Reekum R, Reed K, Naranjo CA. Central serotonergic activity is related to the aggressive behaviors of Alzheimer's disease. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2002 Oct;27(4):646–54.
25. Lee GJ, Lu PH, Hua X, Lee S, Wu S, Nguyen K, et al. Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. Biol Psychiatry. 2012 May;71(9):814–21.
26. Wilkosz PA, Seltman HJ, Devlin B, Weamer EA, Lopez OL, DeKosky ST, et al. Trajectories of cognitive decline in Alzheimer's disease. Int psychogeriatrics. 2010 Mar;22(2):281–90.
27. Gilley DW, Bienias JL, Wilson RS, Bennett DA, Beck TL, Evans DA. Influence of behavioral symptoms on rates of institutionalization for persons with Alzheimer's disease. Psychol Med. 2004 Aug;34(6):1129–35.
28. Alhazzani AA, Alqahtani M, Alshbriqe A, Awwadh A, Alyami T, Alshomrani M, et al. Prevalence of complications associated with Alzheimer disease. J Neurol Sci. 2017;381:315.
29. Boccardi V, Ruggiero C, Patriti A, Marano L. Diagnostic Assessment and Management of Dysphagia in Patients with Alzheimer's Disease. J Alzheimers Dis. 2016;50(4):947–55.
30. Förstl H, Kurz A. Clinical features of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci. 1999;249(6):288–90.
31. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984 Jul;34(7):939–44.
32. López OL, Dekosky ST. Clinical symptoms in Alzheimer's disease. Handb Clin Neurol. 2008; 89:207–16.
33. Petersen RC. Aging, mild cognitive impairment, and Alzheimer's disease. Neurol Clin. 2000 Nov;18(4):789–806.
34. Petersen RC. Mild Cognitive Impairment. Continuum (Minneap Minn). 2016 Apr;22(2 Dementia):404–18.
35. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CRJ, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):263–9.
36. Atri A. The Alzheimer's Disease Clinical Spectrum: Diagnosis and Management. Med Clin North Am. 2019;103(2):263–93.
37. Bernard BA, Goldman JG. MMSE - Mini-Mental State Examination. In: Kompoliti K, Metman LV, editors. Encyclopedia of Movement Disorders. Oxford: Academic Press; 2010. p. 187–9.
38. Whitwell JL, Josephs KA, Murray ME, Kantarci K, Przybelski SA, Weigand SD, et al. MRI correlates neurofibrillary tangle pathology at autopsy: a voxel-based morphometry study. Neurology. 2008 Sep;71(10):743–9.
39. Pennanen C, Kivipelto M, Tuomainen S, Hartikainen P, Hänninen T, Laakso MP, et al. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. Neurobiol Aging. 2004 Mar;25(3):303–10.
40. van Straaten ECW, Harvey D, Scheltens P, Barkhof F, Petersen RC, Thal LJ, et al. Periventricular white matter hyperintensities increase the likelihood of progression from amnestic mild cognitive impairment to dementia. J Neurol. 2008 Sep;255(9):1302–8.
41. Whitwell JL, Jack CRJ, Przybelski SA, Parisi JE, Senjem ML, Boeve BF, et al. Temporoparietal atrophy: a marker of AD pathology independent of clinical diagnosis. Neurobiol Aging. 2011 Sep;32(9):1531–41.
42. Jack CRJ, Shiung MM, Gunter JL, O'Brien PC, Weigand SD, Knopman DS, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology. 2004 Feb;62(4):591–600.
43. Wang D, Chalk JB, Rose SE, de Zubicaray G, Cowin G, Galloway GJ, et al. MR image-based measurement of rates of change in volumes of brain structures. Part II: application to a study of Alzheimer's disease and normal aging. Magn Reson Imaging. 2002 Jan;20(1):41–8.
44. Fox NC, Cousens S, Scahill R, Harvey RJ, Rossor MN. Using serial registered brain magnetic resonance imaging to measure disease progression in Alzheimer disease: power calculations and estimates of sample size to detect treatment effects. Arch Neurol. 2000 Mar;57(3):339–44.
45. Bradley KM, Bydder GM, Budge MM, Hajnal J V, White SJ, Ripley BD, et al. Serial brain MRI at 3–6-month intervals as a surrogate marker for Alzheimer's disease. Br J Radiol. 2002 Jun;75(894):506–13.

46. Schott JM, Price SL, Frost C, Whitwell JL, Rossor MN, Fox NC. Measuring atrophy in Alzheimer disease: a serial MRI study over 6 and 12 months. Neurology. 2005 Jul;65(1):119–24.
47. Radiopaedia. Alzheimer Disease.
48. Radiopaedia. FDG-PET, SPECT. In. Available from: https://radiopaedia.org/cases/alzheimer-disease-spect?lang=gb
49. Jack CRJ, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018 Apr;14(4):535–62.
50. Mittelman MS, Ferris SH, Shulman E, Steinberg G, Levin B. A family intervention to delay nursing home placement of patients with Alzheimer disease. A randomized controlled trial. JAMA. 1996 Dec;276(21):1725–31.
51. Stern Y, Tang MX, Albert MS, Brandt J, Jacobs DM, Bell K, et al. Predicting time to nursing home care and death in individuals with Alzheimer disease. JAMA. 1997 Mar;277(10):806–12.
52. Schachter AS, Davis KL. Alzheimer's disease. Dialogues Clin Neurosci. 2000 Jun;2(2):91–100.
53. Anand P, Singh B. A review on cholinesterase inhibitors for Alzheimer's disease. Arch Pharm Res. 2013 Apr;36(4):375–99.
54. Andrieu S, Coley N, Lovestone S, Aisen PS, Vellas B. Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions. Lancet Neurol. 2015 Sep;14(9):926–44.
55. Godyń J, Jończyk J, Panek D, Malawska B. Therapeutic strategies for Alzheimer's disease in clinical trials. Pharmacol Rep. 2016 Feb;68(1):127–38.
56. Mitsushima D, Sano A, Takahashi T. A cholinergic trigger drives learning-induced plasticity at hippocampal synapses. Nat Commun. 2013;4:2760.
57. Prentice H, Modi JP, Wu J-Y. Mechanisms of Neuronal Protection against Excitotoxicity, Endoplasmic Reticulum Stress, and Mitochondrial Dysfunction in Stroke and Neurodegenerative Diseases. Oxid Med Cell Longev. 2015;2015:964518.
58. Shi X, Lin X, Hu R, Sun N, Hao J, Gao C. Toxicological Differences Between NMDA Receptor Antagonists and Cholinesterase Inhibitors. Am J Alzheimers Dis Other Demen. 2016 Aug;31(5):405–12.
59. McGeer PL, McGeer EG. NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. Neurobiol Aging. 2007 May;28(5):639–47.
60. Miguel-Álvarez M, Santos-Lozano A, Sanchis-Gomar F, Fiuza-Luces C, Pareja-Galeano H, Garatachea N, et al. non-steroidal anti-inflammatory drugs as a treatment for Alzheimer's disease: a systematic review and meta-analysis of treatment effect. Drugs Aging. 2015 Feb;32(2):139–47.
61. Schweizer E, Rickels K, Hassman H, Garcia-España F. Buspirone and imipramine for the treatment of major depression in the elderly. J Clin Psychiatry. 1998 Apr;59(4):175–83.
62. Nair NP, Amin M, Holm P, Katona C, Klitgaard N, Ng Ying Kin NM, et al. Moclobemide and nortriptyline in elderly depressed patients. A randomized, multicentre trial against placebo. J Affect Disord. 1995 Jan;33(1):1–9.
63. Ebadi M, Sharma S, Shavali S, El Refaey H. Neuroprotective actions of selegiline. J Neurosci Res. 2002 Feb;67(3):285–9.
64. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med. 1997 Apr;336(17):1216–22.
65. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993 Aug;261(5123):921–3.
66. Andersen K, Launer LJ, Dewey ME, Letenneur L, Ott A, Copeland JR, et al. Gender differences in the incidence of AD and vascular dementia: The EURODEM Studies. EURODEM Incidence Research Group. Neurology. 1999 Dec;53(9):1992–7.
67. Luchsinger JA, Mayeux R. Adiposity and Alzheimer's disease. Curr Alzheimer Res. 2007 Apr;4(2):127–34.
68. Ganguli M, Dodge HH, Chen P, Belle S, DeKosky ST. Ten-year incidence of dementia in a rural elderly US community population: the MoVIES Project. Neurology. 2000 Mar;54(5):1109–16.
69. Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, et al. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology. 1999 Jan;52(1):78–84.
70. López-Pousa S, Vilalta-Franch J, Llinàs-Regla J, Garre-Olmo J, Román GC. Incidence of dementia in a rural community in Spain: the Girona cohort study. Neuroepidemiology. 2004;23(4):170–7.
71. Liu L, Guo X-E, Zhou Y-Q, Xia J-L. Prevalence of dementia in China. Dement Geriatr Cogn Disord. 2003;15(4):226–30.
72. Benedict C, Byberg L, Cedernaes J, Hogenkamp PS, Giedratis V, Kilander L, et al. Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. Alzheimers Dement. 2015 Sep;11(9):1090–7.
73. Lagnaoui R, Bégaud B, Moore N, Chaslerie A, Fourrier A, Letenneur L, et al. Benzodiazepine use and risk of dementia: a nested case-control study. J Clin Epidemiol. 2002 Mar;55(3):314–8.
74. Lye TC, Shores EA. Traumatic brain injury as a risk factor for Alzheimer's disease: a review. Neuropsychol Rev. 2000 Jun;10(2):115–29.
75. Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology. 2000 Oct;55(8):1158–66.

76. Goldgaber D, Harris HW, Hla T, Maciag T, Donnelly RJ, Jacobsen JS, et al. Interleukin 1 regulates synthesis of amyloid beta-protein precursor mRNA in human endothelial cells. Proc Natl Acad Sci U S A. 1989 Oct;86(19):7606–10.
77. Wu C, Zhou D, Wen C, Zhang L, Como P, Qiao Y. Relationship between blood pressure and Alzheimer's disease in Linxian County, China. Life Sci. 2003 Jan;72(10):1125–33.
78. Murray MD, Lane KA, Gao S, Evans RM, Unverzagt FW, Hall KS, et al. Preservation of cognitive function with antihypertensive medications: a longitudinal analysis of a community-based sample of African Americans. Arch Intern Med. 2002 Oct;162(18):2090–6.
79. Michikawa M. Cholesterol paradox: is high total or low HDL cholesterol level a risk for Alzheimer's disease? J Neurosci Res. 2003 Apr;72(2):141–6.
80. Burns M, Duff K. Use of in vivo models to study the role of cholesterol in the etiology of Alzheimer's disease. Neurochem Res. 2003 Jul;28(7):979–86.
81. Wilson RS, Bennett DA, Bienias JL, Aggarwal NT, Mendes De Leon CF, Morris MC, et al. Cognitive activity and incident AD in a population-based sample of older persons. Neurology. 2002 Dec;59(12):1910–4.
82. Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA. 2002 Feb;287(6):742–8.
83. Yates LA, Ziser S, Spector A, Orrell M. Cognitive leisure activities and future risk of cognitive impairment and dementia: systematic review and meta-analysis. Int psychogeriatrics. 2016 Nov;28(11):1791–806.
84. Lytle ME, Vander Bilt J, Pandav RS, Dodge HH, Ganguli M. Exercise level and cognitive decline: the MoVIES project. Alzheimer Dis Assoc Disord. 2004;18(2):57–64.
85. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly people with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil. 2004 Oct;85(10):1694–704.
86. Luchsinger JA, Mayeux R. Dietary factors and Alzheimer's disease. Lancet Neurol. 2004 Oct;3(10):579–87.
87. Solfrizzi V, Panza F, Capurso A. The role of diet in cognitive decline. J Neural Transm. 2003 Jan;110(1):95–110.
88. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, et al. Dietary fats and the risk of incident Alzheimer disease. Arch Neurol. 2003 Feb;60(2):194–200.
89. Cortes F, Nourhashémi F, Guérin O, Cantet C, Gillette-Guyonnet S, Andrieu S, et al. Prognosis of Alzheimer's disease today: a two-year prospective study in 686 patients from the REAL-FR Study. Alzheimers Dement. 2008 Jan;4(1):22–9.
90. Drachman DA, O'Donnell BF, Lew RA, Swearer JM. The prognosis in Alzheimer's disease. "How far" rather than "how fast" best predicts the course. Arch Neurol. 1990 Aug;47(8):851–6.
91. Wolfson C, Wolfson DB, Asgharian M, M'Lan CE, Ostbye T, Rockwood K, et al. A reevaluation of the duration of survival after the onset of dementia. N Engl J Med. 2001 Apr;344(15):1111–6.
92. Vasic V, Barth K, Schmidt MHH. Neurodegeneration and Neuro-Regeneration-Alzheimer's Disease and Stem Cell Therapy. Int J Mol Sci. 2019 Aug;20(17).
93. Malik GA, Robertson NP. Treatments in Alzheimer's disease. J Neurol. 2017 Feb;264(2):416–8.

Article Topic: Cerebral palsy.

Author: Maria A. AlShurman.

Editor: Aroob Awwad.

Reviwer: Ethar Hazaimeh, Hassan Abushukair.

***Keywords**: cerebral palsy, overview, epidemiology, causes, pathogenesis, outcomes, complications.*

An overview and epidemiology

The definition of Cerebral Palsy has been a dilemma in medical literature since it doesn't have a specific age limit of the time the brain insult occurred, nor the age of onset of motor disorder (1). However, the international panel agreed on a definition in 2006 : "cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation , that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain "(2).Although cerebral palsy is the most widespread and costly motor disability of children(3), the incidence and prevalence are not well established because of etiological and geographical variations(4). Nonetheless, the worldwide prevalence is 2 per 1000 live births (5).

Pathogenesis and etiology

The etiology of cerebral palsy is multifactorial. Although, there is still no complete understanding of the whole picture (2), but it is believed that there is always a cause of CP and every child with CP must undergo an evaluation and a complete investigation to establish a proper cause whether it is of prenatal, perinatal, or postnatal origin (6).

The type of injuries that could occur to the developing brain include hypoxia, infection, stroke, or hypotension with their subsequent inflammation that occurs after the original insult, can happen in utero, around the time of delivery, post-natal period or later in early childhood. As a result, they divided the causes of developing brain insults according to the time of occurrence: early brain injuries (usually before 20 weeks' gestation), injuries between 24-32 weeks of gestation, injuries around delivery and post-natal injuries (7).

Causes of early brain injuries (often before 20 weeks' gestation) that will lead to brain maldevelopment, figure (1), includes:

- Maternal infection—cytomegalovirus—polymicrogyria
- COL4A1 genetic mutations—porencephalic cysts, schizencephaly
- LIS1 genetic mutations—lissencephaly
- GPR56 gene—polymicrogyria

Insults that happen in early/mid-pregnancy (24–32 weeks' gestation) include:

- White matter disease of prematurity (periventricular leukomalacia), figure (2)
- Hypoxia, hypotension, sepsis
- Pressure from intraventricular hemorrhage (hemorrhagic parenchymal infarction)

Injuries that occur late in the developed brain include:

- Peripartum asphyxia
- Maternal infection
- Stroke

Lastly, post-neonatal brain injuries include:

- Meningitis/encephalitis
- Stroke
- Trauma—accidental/non-accidental
- Hypoxia—near drowning

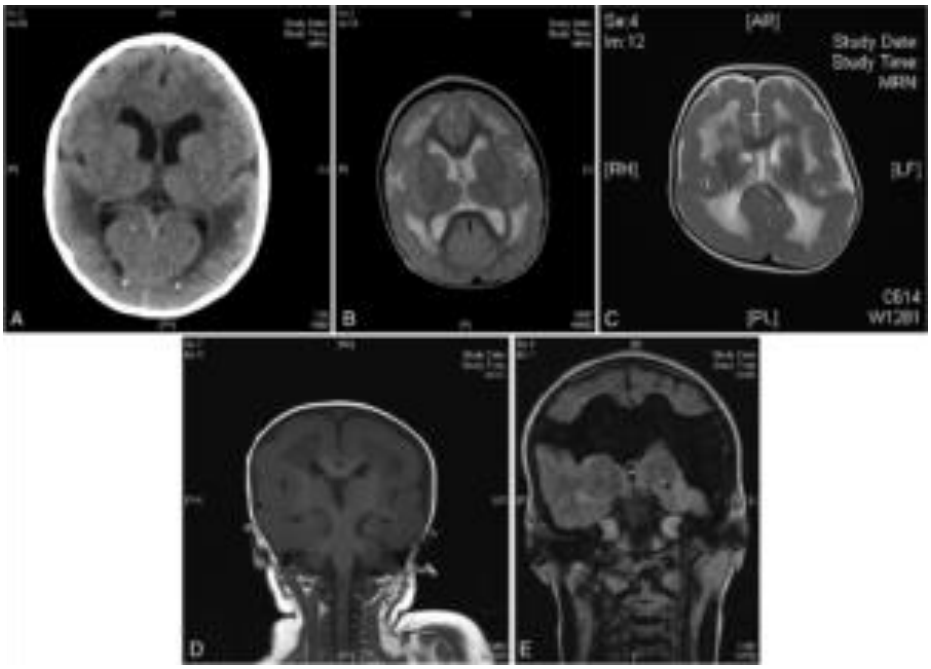


Figure 1: (A) CT scan of a head showing intracranial calcification associated with early cytomegalovirus infection. (B) MRI scan of brain (T2-weighted) showing extensive polymicrogyria typical of a congenital cytomegalovirus infection. (C) MRI scan of brain (T2-weighted) showing lissencephaly, a cerebral maldevelopment often associated with the LIS1 gene mutation. (D) MRI scan of brain (T1-weighted) showing lissencephaly. (E) MRI scan of brain (T1-weighted) showing bilateral open-lipped schizencephaly, which can be associated with COL4a1 genetic mutation predisposing to early infarcts.

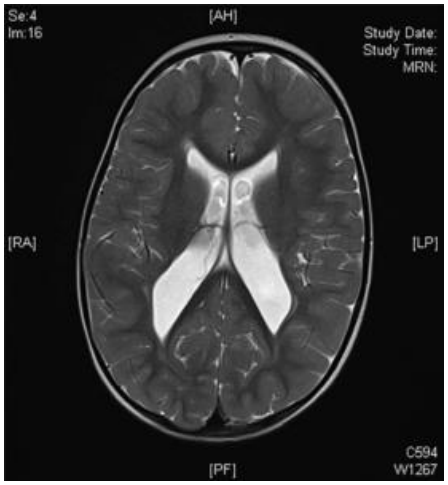


Figure 2: MRI scan of brain (T2-weighted) showing periventricular leukomalacia associated with preterm (24– 32 weeks' gestation) injury to the brain.

Clinical Presentation

Unusual restless movements or abnormalities of movement and tone, including hypotonia (floppiness),

spasticity (stiffness) or dystonia (fluctuating tone) are some of the motor features that appear early. There's also abnormal motor development, including late head control, rolling, and crawling and feeding difficulties can also be signs (8).

Early signs and symptoms

1. Neurobehavioral signs: Neurobehavioral signs unclear for CP are excessive irritability, tiredness, sleep disturbances, frequent vomiting, difficulty to handle and cuddle, and poor visual attention.
2. Developmental reflexes: procrastination in disappearance or exaggeration of a developmental reflex may be an early indicator of motor disability.
3. Motor tone and posture: Tone in extremities/ trunk might be normal, increased or decreased. Poor head control, persistent or asymmetric hand fisting, and

abnormal oral motor patterns (tongue thrusting/ grimacing) may be the early motor signs.

4. Motor milestones: a follow-up examination of motor milestones is an effective screening tool for detecting CP early. The American Academy of Pediatrics recommends complete developmental screening at 9-, 18-, 30-, and 48-months visit (5)

Classification

It is important to classify cerebral palsy in categories, as it has a very diverse spectrum of presentations, and the most appropriate classification is based on motor type, topography of motor impairment and the degree of functional impairment (2)(5)(7).

According to the motor type, it is subdivided into spastic, dyskinetic, hypotonic and ataxic. For the distribution, it is classified into hemiplegia, diplegia and quadriplegia. These two classifications do not give a clear idea about activity and participation. That's where the importance of the third classification (degree of functional impairment) was raised. The gross motor classification system GMCS is used to classify the patient's level of mobility according to age into 5 levels. Starting from level 1 where the patient has a slight disability to level 5 in which the patient is severely disabled where he can't maintain posture without the aid of a career or equipment, figure (3)(7).

Spastic CP

This type of cerebral palsy has signs consistent with upper motor neuron lesion, like spasticity, hyperreflexia (± clonus), extensor plantar response, mass movements (instead of fine and individual movements), and slow and effortful voluntary movements. Spastic type divided furtherly according to the distribution:

Diplegic

The problem here is particularly in lower limbs, with usually preserved fine motor functions in upper limbs. It is commonly associated with periventricular leukomalacia (PVL) and periventricular hemorrhagic infarction (PVHI). This type mainly affects preterm babies and the presentation in infants less than 6 months appears differently as the lower limbs are hypotonic. Infants older than 6 months have signs of Commando crawl, W-Sitting, and Tendo Achilles tightening. For older children when the spasticity starts to appear more after walking, toe walking could be a very suspicious sign.

Hemiplegic

In spastic hemiplegia, upper limbs are typically affected more than lower limbs, accompanied with sensory deficit reflected as poor muscle mass on the affected side.

They may also have cognitive, visual, and behavioral problems. Including anxiety, oppositional defiance, and specific phobias. The most common cause of hemiplegic CP is stroke, either prenatal or neonatal, in full term infants and appears as Asymmetry while natural hand movements/ bringing hands in midline or during neonatal reflexes like Moro's, Early hand dominance (before 12 months), and in sitting position, affected leg tends to extend.

Quadriplegic

This is the most severe type as all 4 limbs are affected nearly equally, and the majority have very little speech and language development, visual impairment, epilepsy, feeding difficulty, and chronic respiratory insufficiency. MRI in these children may show multi-cystic encephalomalacia. It affects both preterm and full-term infants and they have Severe motor and cognitive delay and Poor head control. Initially they may appear hypotonic in the first 4months which then turns to spasticity by 9–12 months, and by 12 months, infants when pulled to sitting are unable to flex their legs and have poor truncal balance (5)

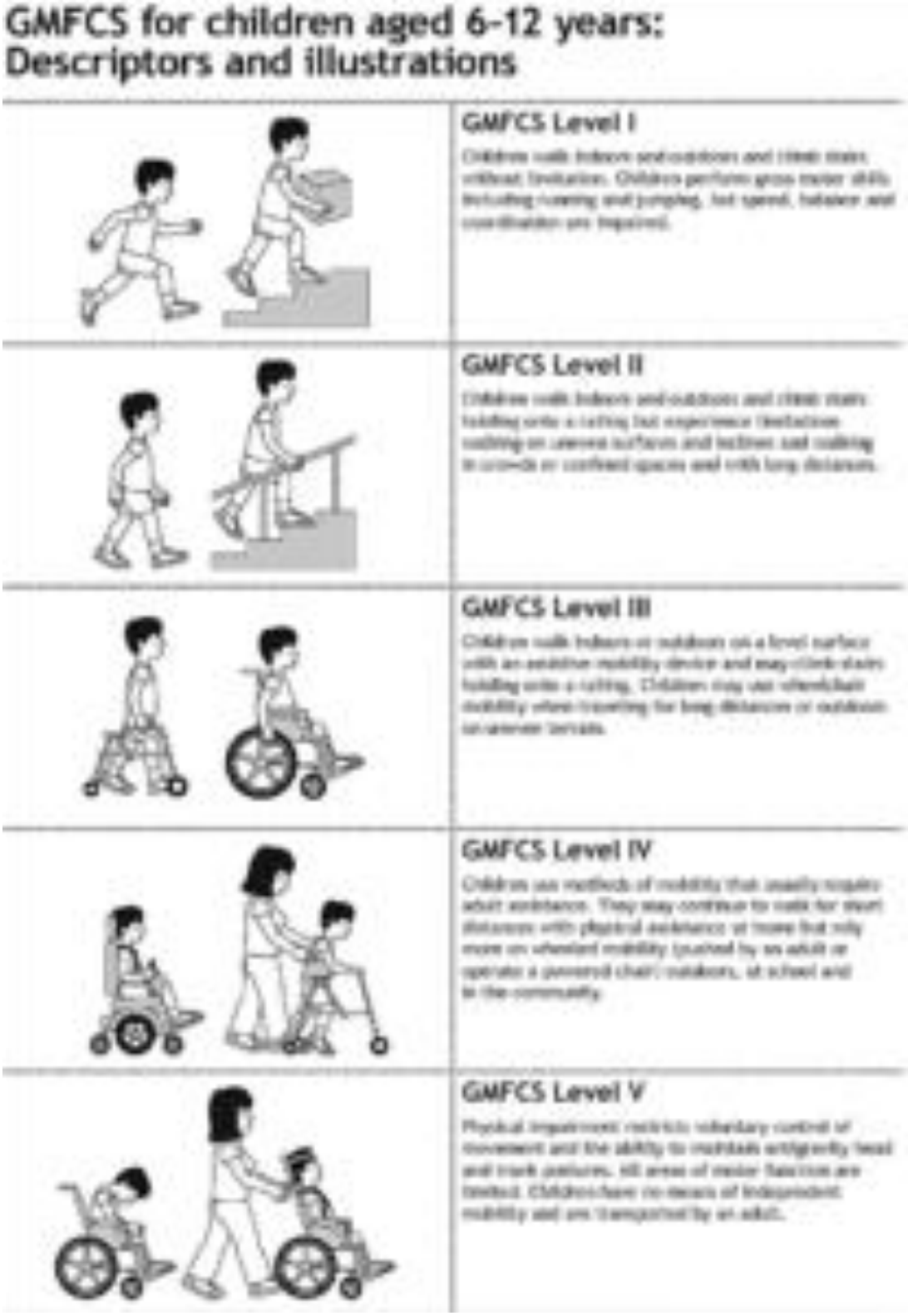


Figure 3: Gross motor function classification system to classify how a child with cerebral palsy mobilizes and is classified according to age.

Dyskinetic CP

This is characterized by having more than one form of involuntary movements. The limbs usually become stiff during attempted movement or when emotional. Tendon reflexes may be normal or may be difficult to evoke. Athetoid movements of toes especially the great toe (striatal toe) is a significant clue of extrapyramidal dysfunction. Dyskinesia can be seen in some spastic syndromes, but impurely dyskinetic syndromes contractures are less common. We can additionally sub-classify dyskinetic CP into:

Choreo-athetoid CP

Which is defined as rapid disorganized unpredictable contractions of individual muscles/ muscle groups involving face, bulbar muscles, proximal extremities and digits? They also have slow writhing movements involving distal muscles. Oropharyngeal difficulties may result from facial grimacing, and Primitive reflexes are persistent. Hyperbilirubinemia is a chief cause for this type as it occurs in infants who are born with (Rh/ ABO incompatibility/G6PD deficiency).

Dystonic CP

It is characterized by co-contraction of agonist and antagonist muscles. Simultaneously, they may have coexistent pyramidal signs and dysarthria. This mainly occurs as a consequence of birth asphyxia (5)

Ataxic CP

Ataxic CP is uncommon and should be differentiated from progressive neurodegenerative disorders. These patients have delayed development in motor and language milestones manifested ataxia and slow, jerky, explosive speech. Ataxia usually improves with time and have no apparent cause. (5)

Diagnosis

The diagnosis of CP depends on a multidisciplinary approach starting from recognition of clinical risk factors to neurological examination and ends up with neuroimaging. And because of its complexity, the diagnosis is often delayed and occurs between 1 to 2 years of age. Nowadays, early and precise diagnosis of CP is being achieved, as it's more favorable to initiate therapy as early as possible to improve long-term outcomes during the period of rapid brain growth and neuroplasticity.

For children who have identifiable risk factors, the best ways to detect CP before 5 months of age include: MRI, GMA and HINE which are extremely sensitive (90%) for CP. On the contrary, for those children that lack risk factors, the diagnosis is often delayed until they develop warning signs which indicate inability to achieve their expected milestones, such as: include the inability to sit independently by 9 months of

age, the presence of asymmetric movements or limb preference, or the inability of an infant to bear weight on the plantar surface of the feet.

Neuroimaging

MRI has been identified to have the highest sensitivity for the diagnosis of CP. There are some findings that increase the suspicion index for CP including: white matter injury (e.g.: cystic periventricular leukomalacia [CPVL], periventricular hemorrhagic infarction, progressive ventriculomegaly, neonatal stroke), injury to deep gray matter structures including basal ganglia, cerebellar hemorrhage, and developmental brain malformations (e.g.: lissencephaly, microgyria, cortical dysplasia).

Neuromotor assessment

In assessing the neuromotor function, 2 tools are considered the most sensitive and used ones.

GMA

A tool which uses the pattern of spontaneous movement of infants that are altered in predictable way during normal development. There are 2 specific movement patterns that are highly sensitive and specific for the diagnosis of CP: first, cramped synchronous general movements (70% sensitivity, 90% specificity), characterized by rigid contraction and relaxation of the infant's trunk and extremities; second, absent fidgety movements (97% sensitivity, 89% specificity) characterized by a lack of the normal small-amplitude fidgety movements that should be present in newborns 10 to 20 weeks of corrected age.

HINE

According to this tool, it is a standardized neurological examination for age ranges from 2 to 24 months, which contain 26 scored items that assess an infant's cranial nerve function, posture, movements, tone, and reflexes.

Complications

As cerebral palsy is mainly a motor disease resulting from insult to the developing brain, skeletal muscles are the most affected organs, and one of the most common complications is muscle contracture- limited joint movement that result from high passive muscle force- which leads to inability to walk and pain. In addition to this, there are non-motor complications which include: epilepsy, which happens in nearly 40% of patients with cerebral palsy, growth retardation and failure to thrive due to Oro-motor difficulties, gastroesophageal reflux disease, chronic lung disease, bladder control

problems, hip displacement, sleep disturbances, intellectual disability, deafness, blindness, and osteopenia. It's worth mentioning that respiratory complications, which are mainly due to aspiration and GERD, are responsible for the major morbidity and mortality rates (9).

Management

The mainstay in the management of CP is the early diagnosis and intervention as it improves the outcomes later on. Besides improving the motor function, enhancing the quality of life for these patients should be always a priority in management (2).

There is no definitive cure for CP, and its management requires a multidisciplinary approach concerned mainly with the symptoms (7).

Management of motor impairment

Physiotherapy and occupational therapy play an essential part in the management of CP, and the most evidence-based approaches include:

1. Bimanual training for hemiplegic CP in which the child is trained to use both hands at the same time to undergo repetitive tasks.
2. Constraint induced movement therapy includes restraint of the unaffected limb resulting in usage of affected limb during therapeutic tasks. Restraint may be achieved by the use of a cast or physical restraining by holding the normal limb.
3. Context focused therapy involves changing the environment rather than the child's approach.
4. Goal directed functional training lays emphasis on activities based on goals set by the child, using a motor learning approach. (5)

Management of spasticity

This includes oral medications like benzodiazepines, baclofen, and tizanidine; botulinum toxin A; intrathecal baclofen; alcohol and phenol in addition to surgical and orthopedic procedures (5)

Feeding and nutrition

If there are Oro-motor problems interfering with growth and gaining weight other feeding techniques should be considered like gastrostomy feeding. (5)

Drooling

Drooling (sialorrhea) is the uncontrolled spontaneous loss of saliva and oral content that occurs normally in infants until 24 months of age. After that the child should have the ability to do most activities without loss of saliva. It is considered pathological if it carries on after the age of 4 years. It is often seen with neurological disorders, including neuromuscular incoordination of swallowing and intellectual disabilities. (10)

Improving drooling is considered important as it interferes with social life, and different approaches could be recommended starting from behavioral therapy to pharmacotherapy (anticholinergic drugs (trihexyphenidyl or glycopyrrolate and BTX-A injection into salivary glands) and surgery (5).

Prevention

Magnesium sulfate

Various studies showed an increase in the risk of CP in infants who were born before 32 weeks of gestational age and received $MgSO_4$ during labor, as it is found to be a neuroprotective agent. (3)

Therapeutic hypothermia

Neonates born after the 35th week of gestation were exposed to a perinatal episode of hypoxia which may lead to perinatal hypoxic-ischemic encephalopathy, and hence causing CP, benefited from therapeutic hypothermia. Therapeutic hypothermia was found to improve the survival rate with normal neurological development and decrease the risk of death and major neurological disorders at the age of 18 months.

Therapeutic hypothermia must be implemented in the first 6 hours of postpartum.

Indications for hypothermia [35]:

- pH ≤ 7.0 and/or BE base deficiency of at least 16 mmol/l in a cord blood sample or a blood sample taken within 1 hour of life;
- 1 of the following:
    - Apgar score ≤ 5 in 1st, 3rd, 5th, 10th minute after birth;
    - Continuous resuscitation within 10 minutes after birth
- neurological symptoms indicative of moderate/severe encephalopathy on clinical examination (the Sarnat scale is used for qualification) (11)

Caffeine

Caffeine is one of the most commonly used therapies in neonatal intensive care units for apnea. There are some studies which are concerned in the use of caffeine in premature infants with apneic episodes resulted in a reduction in the risk of motor and cognitive impairment along with the treatment. The finding was statistically significant at 18 months but not at 5 years. (3)

Antenatal steroids

Studies are still debating about the relation between the use of antenatal steroids and the reduction of cerebral palsy risk. In spite of that, some observational studies indicate the clinical benefits of a single course of antenatal steroid therapy in reducing the risk of CP diagnosed in the first year of life or later, the percentage of CP diagnoses was 32% lower in patients whose mothers received a course of steroid therapy during pregnancy that was terminated prematurely. (11)

Prognosis

Most of the children diagnosed with CP survive to adulthood, and many factors play a role in the upcoming consequences like severity of impairment, birth weight, and socioeconomic status.

For children who cannot achieve their milestones (mainly head balance by 20 months of age, persistent primitive reflexes, or do not crawl by age of 5), the probability of being able to walk is very low. Whereas children who can sit by age of 2 years or crawl by age of 5, the prognosis for walking is good.

Besides the motor outcome, there is the functional outcome in CP which relies on multiple factors these include: intelligence, physical function, ability to communicate, and personality attributes. Social (e.g., family support) and environmental factors and the availability of specialist medical care have an essential impact. (5)

References

1. Robaina-Castellanos GR, Riesgo-Rodriguez S, Robaina-Castellanos MS. [Definition and classification of cerebral palsy: a problem that has already been solved?]. Rev Neurol. 2007 Jul;45(2):110–7.
2. Michael-Asalu A, Taylor G, Campbell H, Lelea LL, Kirby RS. Cerebral Palsy: Diagnosis, Epidemiology, Genetics, and Clinical Update. Adv Pediatr [Internet]. 2019;66:189–208. Available from: https://doi.org/10.1016/j.yapd.2019.04.002
3. Korzeniewski SJ, Slaughter J, Lenski M, Haak P, Paneth N. The complex aetiology of cerebral palsy. Nat Rev Neurol. 2018 Sep;14(9):528–43.
4. McIntyre S. The continually changing epidemiology of cerebral palsy. Acta Paediatr Int J Paediatr. 2018;107(3):374–5.
5. Gulati S, Sondhi V. Cerebral Palsy: An Overview. Indian J Pediatr. 2018;85(11):1006–16.
6. Appleton RE, Gupta R. Cerebral palsy: Not always what it seems. Arch Dis Child. 2019;104(8):809–14.
7. Wimalasundera N, Stevenson VL. Cerebral palsy. Pract Neurol. 2016;16(3):184–94.
8. Dean BE. news / clinical update. 2017;29(3):2017.
9. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin JP, Damiano DiL, et al. Cerebral palsy. Nat Rev Dis Prim. 2016;2.

10. Dias BLS, Fernandes AR, Maia Filho H de S. Sialorreia em crianças com paralisia cerebral. J Pediatr (Rio J) [Internet]. 2016;92(6):549–58. Available from: http://dx.doi.org/10.1016/j.jped.2016.03.006
11. Mlodawski J, Mlodawska M, Pazera G, Michalski W, Domanski T, Dolecka-Slusarczyk M, et al. Cerebral palsy and obstetric-neonatological interventions. Ginekol Pol. 2019;90(12):722–7.

Article topic: Guillain barre syndrome.

Author: Abdallah Said Al-hallaq.

Editor: Yaman Oudat.

Reviwer: Ethar Hazaimeh, Hassan Abushukair.

Keywords: GBS, Guillain Barré syndrome, Plasma exchange, SARS COV-2.

History of Guillain-Barré syndrome

The history of Guillain-Barré syndrome (GBS) is almost related to the discovery of the peripheral nervous system. Up to the second half of the 19th century, any injury to the peripheral nervous system had not yet emerged as a cause of palsy. In 1928, there was an epidemic occurring at an infirmary in Paris, manifestations included unpleasant tingling sensations associated with severe pain and weakness of the lower limbs. During the second half of the 19th century, many similar cases were reported. This epidemic was undoubtedly more related to a toxic phenomenon than to inflammation.

The final step in the description of GBS was the publication of an article in 1916 signed by Guillain-Barre and Strohl with the title of "Radiculo-neuritis syndrome with hyper-albuminosis of cerebrospinal fluid without a cellular reaction."[1]

The term GBS was introduced for the first time in Paris in 1927 by Draganescu and Claudian who had described that a radiculo-neuritis that occurs after staphylococcal osteomyelitis is GBS.

Overview and Epidemiology

Guillain-Barré syndrome (GBS) is a collection of acute autoimmune-related disorders of peripheral nerves with a monophasic course, and the progressive phase of GBS should be less than four weeks. There are many clinical variants of GBS that have been documented in medical literature [2], the most common variants are acute inflammatory polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN).

The disorder was first described as a benign form of limb weakness that is associated with full recovery, but now we recognize GBS as a prolonged, disabling neuromuscular disorder associated with respiratory difficulties in a third of patients[3].

Its incidence ranges between 0.40 and 3.25 cases per 100,000 persons, depending on geographic location. Despite the fact that its rare, Guillain-Barre syndrome (GBS) has a lot of major effects on the health care system[4], In different age groups, the annual

average rate of hospitalizations in the US related to GBS increases with age, being 1.5 cases per 100,000 population in persons younger than 15 years and peaking at 8.6 cases per 100,000 population in people aged 70-79 years[5].

Differences in the incidence of GBS in different populations could reflect variations in genetic susceptibility or in the exposure to causative pathogens like Campylobacter jejuni been the most widely reported infection: it has been found in 25–50% of adult patients and is more frequent in Asian countries[6].

GBS is slightly more frequent in males than in females, it has a male-to-female ratio of 1.5:1 and this male preponderance is seen in older patients especially. However, there is Swedish epidemiologic study has reported that GBS rates decrease during pregnancy and increase in the months immediately following delivery[7].

The syndrome can occur at any time between infancy and old age. It has been reported in the United States that the syndrome's age distribution seems to be bimodal which means that it comes with 2 peaks the first peak in young adulthood (ages 15-35 y) and a second higher one in middle-aged and elderly persons (ages 50-75 y)[8]. Infants have the lowest risk of developing GBS.

Guillain-Barré Syndrome and Criteria for Diagnosis

Diagnostic criteria for Guillain-Barré syndrome (GBS) took place in 1978 upon the request of the National Institute of Neurological and Communicative Disorders and Stroke NINCDS which now is called NIND, summarized in TABLE (1). This criterion is related to the swine of flu vaccine incident of 1976-1977[9].

Progressive motor muscle weakness for more than one limb and hypo/areflexia are the two clinical features required for the diagnosis of paralytic GBS.

In general, the diagnosis of GBS is typical and straight forward and the differentials are narrow but there are some patients with atypical presentation. Typically, the patient presents 2-4 weeks after a mild respiratory or gastrointestinal infection with progressive monophasic generalized and symmetric weakness, paresthesia, numbness these are the most common complaints.[10] The symptoms at the time of onset of classic GBS are pain, paresthesia, numbness, and rapidly progressive bilateral limb weakness[3,11].

Features Required for Diagnosis of Guillain barre syndrome.	Features Supportive of the Diagnosis	Features casting doubt on diagnosis.	Features that rule out the diagnosis.
Progressive motor muscle weakness for more than one limb, with or without mild ataxia. **Areflexia or hyporeflexia**	Progression of Symptoms and signs of motor weakness for 2-4 weeks. Relative symmetrical involvement. Mild sensory symptoms or signs. Cranial nerve involvement (Facial weakness occurs in approximately half of the patients and is frequently bilateral). Recovery begins 2-4 weeks after nadir. Autonomic dysfunction (Tachycardia and other arrhythmias, postural hypotension, hypertension, and vasomotor symptoms). Absence of fever. Elevated CSF protein.	Marked, persistent asymmetry of weakness. Persistent bladder or bowel dysfunction. Severe bladder or bowel dysfunction at onset. More than 50 mononuclear leukocytes/mmg in CSF. Presence of polymorphonuclear leukocytes in CSF. Sharp sensory level. Central nervous system signs except in MFS-Bickerstaff brainstem encephalitis spectrum disorders	History of hexacarbon abuse. Recent diphtheritic infection The occurrence of a purel sensory syndrome. Poliomyelitis, botulism, hysterical paralysis, or toxic neuropathy

TABLE (1): National Institute of Neurological Disorders and Stroke Diagnostic Criteria for Guillain-Barré Syndrome[12]

GBS variants

There are different clinical variants that are based on

- The types of nerve fibers involved (motor, sensory, sensory, and motor, cranial, or autonomic).
- The predominant mode of fiber injury (demyelinating versus axonal).
- The presence of an alteration in consciousness.

Acute inflammatory demyelinating polyneuropathy (AIDP) is the most frequent variant of GBS in developed countries, AIDP is also the predominant subtype around 60–80% of patients who are in North America and Europe[13], However, in Asia, Central and South America the axonal variants of GBS like acute motor axonopathy (AMAN) and acute motor-sensory axonopathy (AMSAN) represent 30% to 47% of cases.

The axonal motor variants of GBS termed acute motor axonal neuropathy (AMAN), is called Chinese paralytic illness because it was reported in 1993 from Northern China[14]. And not late later that an acute motor and sensory axonal neuropathy (AMSAN) was discovered[15]. Both AMAN and AMSAN are usually associated with clostridium Jejuni infection which is alone is considered a poor prognostic factor[16]. Patients with this AMAN variant present with symmetric proximal and distal weakness without

sensory abnormalities following C. jejuni enteritis and could have normal or brisk tendon reflexes. Moreover, patients with AMSAN have a poor prognosis because of severe involvement of sensory and motor nerve fibers and more likelihood of autonomic involvement.

There is another variant of GBS is Miller Fisher Syndrome (MFS) and it presents ophthalmoplegia (first presenting symptom) with ataxia and areflexia but without any weakness[17]. Miller fisher syndrome patients have at least 2 of these symptoms and have in support an elevated CSF protein and characteristic autoantibody.

MFS is more common in Eastern Asia accounting for up to 25% of Japanese cases, and it is thought to represent 5 to 10% of GBS cases In Western countries[18].

Bickerstaff's brain stem encephalitis (BBE) and is a variant of MFS characterized by alteration in consciousness, paradoxical hyperreflexia, ataxia, and ophthalmoparesis[19], it is a variant of that is with antecedent infection (92%), elevated CSF protein (59%), and anti-GQ1b antibody (66%)[20].

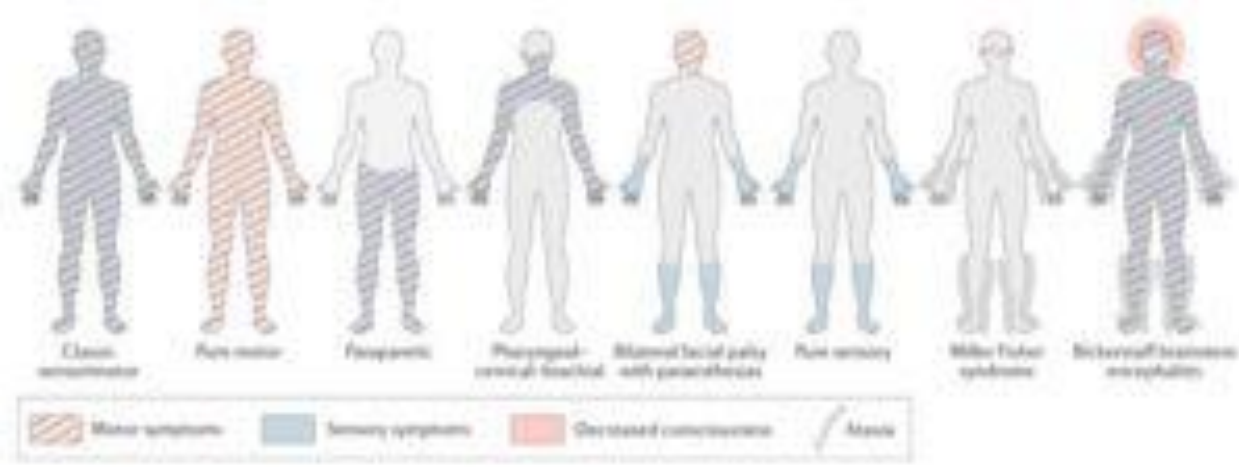


Figure (1) Pattern of symptoms invariants of Guillain–Barré syndrome[21]

Clinical presentation and complications

The features which allow a diagnosis for GBS include clinical, laboratory, and electrodiagnostic criteria. The presence of preceding events is frequent and could be seen, but they are not essential to the diagnosis, so the most commonly preceding events are usually viral infections but there are others like preceding surgery, inoculations, and Mycoplasma infections is also could be seen.

Muscle Weakness

In a typical presentation of Guillain-Barré syndrome, rapidly progressive bilateral weakness is usually the key symptom presenting in most patients, The weakness usually starts in the distal lower extremities and then progresses upwards over a period of hours to days (ascending symmetrical weakness), until the arms and facial muscles also are affected, which leads to bulbar weakness and respiratory difficulties[22].

The muscle weakness could start in the arms first (the descending type), or simultaneously in the arms and legs, and in some other forms of the disease, the weakness could only affect the cranial nerves, leading to facial, oculomotor, or bulbar weakness[23]. There is a small number of patients present with paraparesis, which unfortunately may remain during the course of disease[24].

The weakness reaches its peak after 2 to 4 weeks from symptom onset and should be symmetrical, if it is asymmetrical this calls the diagnosis of GBS into question.

Cranial nerve

Neurological examination is significant in those patients, as we could see cranial nerves signs like most frequently observed is Facial weakness (VII), followed by signs associated with cranial nerves VI, III, XII, V, IX, and X[25]. these patients could present with:

- Ptosis from cranial nerve III (oculomotor) palsy.
- Ophthalmoparesis may be observed in up to 25% of patients with GBS[26]
- Facial droop
- Dysphagia, dysarthria, and findings associated with disorders of the eye.
- In severe cases, tonic pupils have been observed.

Reflexes

Areflexia or hyporeflexia is one of the two clinical features required for the diagnosis of GBS and it is unusual to see normal reflexes or hyperreflexia throughout the course of GBS.[27]

Hyperreflexia could indicate that there is functional corticospinal tract involvement in patients with a GBS variant, and there is a study that showed 48% of Chinese and 33% of Japanese patients with AMAN showed hyperreflexia in the recovery phase[14]. Bickerstaff brainstem encephalitis might be present with hyperreflexia that is associated with external ophthalmoplegia and ataxia.

Reflexes typically are decreased or absent but initially might be close to normal in pure motor and axonal forms or sometimes even hyper-reflexes.

Sensory symptoms and pain

Most patients note paresthesia, numbness, or similar sensory changes, although prominent sensory signs are atypical (except in sensory variants).

The most common initial symptom is Acroparesthesia[28], progressing upward but generally not extending beyond the wrists or ankles and it could be accompanied by Loss of vibration, proprioception, touch, and pain distally may be present.

Moderate to severe neuropathic or radicular pain is a common that is seen in all variants of GBS including MFS[29], Persistent pain has been reported in the 2 weeks preceding weakness in 36% of patients while 66% of reported pain in the acute phase and 38% reported pain after 1 year[29].

Pain in Guillain-Barre´ syndrome (GBS) may be pronounced and is often overlooked. Muscle pain or radicular pain, often but not always in the spinal region, the pain is often described as aching or throbbing in nature.

Autonomic changes

In patients with GBS a dysfunction in the sympathetic and parasympathetic systems and could present with[30]:

- Most commonly of sinus tachycardia, but patients may experience bradycardia
- Facial flushing
- Cardiac arrhythmias
- Paroxysmal hypertension
- Orthostatic hypotension
- Anhidrosis and/or diaphoresis

5% of cases experience bladder (urinary retention) and gastrointestinal (constipation, ileus, gastric distension, diarrhea, fecal incontinence) dysfunction and these symptoms are unusual at the onset of the disease but commonly develop at the nadir of the disease[26].

Also, GBS patients can develop autonomic dysfunction, with usually GI manifestations diarrhea or constipation in 15% of patients also part of them develop hyponatremia (15%) with a smaller number of them develop a syndrome of inappropriate antidiuretic hormone secretion (5%), bradycardia (5%), and urinary retention (4%)[31].

As a result of autonomic nervous system involvement there could be on clinical exam[32]:

- Cardiac arrhythmias either tachycardia or bradycardia, and tachypnea could be a sign of ongoing dyspnea and progressive respiratory failure.
- absent bowel sounds indicate paralytic ileus.
- Variations of hypertension and hypotension also could be observed (Blood pressure lability).
- poor inspiratory effort or diminished breath sounds.
- Suprapubic tenderness or fullness may be suggestive of urinary retention.

Respiratory involvement

Given that up to 30% of GBS cases progress to respiratory failure[26], neuromuscular respiratory failure is the most thing that worries the clinicians, it could occur after the involvement of the lower cranial nerves (glossopharyngeal, vagus, and hypoglossal nerves) or after the involvement of the nerves of the muscles of respiration may lead to the need for artificial ventilation and it's a life-threatening complication[33]. The weakness of the diaphragm is thought to be caused by phrenic nerve demyelination[34]

They present with:

- Dyspnea on exertion
- Shortness of breath
- Difficulty swallowing
- Slurred speech

Approximately 25% of patients develop respiratory insufficiency requiring artificial ventilation[35], that is why good supportive care is the most important element of management.

Work up and diagnosis (Approach considerations)

In most cases, we consider Guillain-Barre syndrome (GBS) a clinical diagnosis because of that the diagnosis could be done at the bedside[12].

Peripheral Neuropathy Workup

These basic Peripheral Neuropathy Workup studies may include:

- Thyroid function test
- B12, Folate, Hba1c
- Rheumatology profiles
- Erythrocyte sedimentation rate (ESR)

- Check for SIADH: hypokalemia and hyponatremia.

Biochemical Screening

Biochemical screening includes Electrolyte levels, Liver function tests (LFTs), Creatine phosphokinase (CPK) levels. In a third of GBS patients, LFT results are elevated[36].

In some cases, we order a pregnancy test because in rare cases a high suspicion for an early diagnosis and prompt intensive supportive care in a GBS-complicated pregnancy will likely improve the prognosis for both mother and fetus[37].

Lumbar puncture

it is common to perform CSF analysis to support your diagnosis, Lumbar puncture and cerebrospinal fluid analysis show a classic pattern of albumino-cytologic dissociation which means that CSF typically reveals high protein levels with a normal white blood cell count but this pattern is present only in approximately 80% of patients after 2 weeks following the symptoms onset[1].

Nerve conduction studies

Nerve conduction studies and Electromyography are far more useful for diagnosis and helpful in diagnosing GBS and differentiating it from another disease that mimics it. Decreased conduction velocities or Conduction block are indicators of the demyelination process and there are specific tests for proximal nerve involvement that can be seen early in the disease including the recording of the F-waves and abnormalities like dispersion or dropout in F-wave signal[38], Prolongation or absence of the F-waves latencies is a common finding during the first week

Signs of demyelination on motor nerve conductions in AIDP:

- Prolongation or absence of the F-waves latencies
- Prolonged distal motor latencies
- Conduction blocks at non-compressible sites.

In an axonal variant of the disease there will be decreased compound muscle action potential (CMAP) amplitudes in AMAN and decreased CMAP and sensory nerve action potential (SNAP) amplitudes in AMSAN.

Serologic Studies

Check for antibodies to the following infectious agents should be considered:

- C jejuni
- Cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- Herpes simplex virus (HSV)
- HIV
- Mycoplasma pneumonia

The spectrum of GBS subtypes and serum antiganglioside antibodies

- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP): Unknown antibodies[39]
- Acute motor (and sensory) axonal neuropathy (AMAN or AMSAN): GM1, GM1b, GD1a, GalNAc-GD1a[40]
- MFS: GD3, GT1a, GQ1b[41].

Pulmonary function test (PFT):

Forced vital capacity (FVC) is very helpful in determining the best management of Guillain-Barre syndrome (GBS)[42], for those Patients who have FVC of < 15-20 mL/kg, maximum inspiratory pressure of < 30 cm water, or a maximum expiratory pressure < than 40 cm water progress to require prophylactic intubation and mechanical ventilation and need fast intervention. Respiratory assistance should also be considered when there is a decrease in oxygen saturation (arterial partial pressure of oxygen [PO_2] < 70 mm Hg)[42].

For difficult bedside patients, we perform Negative inspiratory force (NIF) which is a relatively easy bedside test to measure respiratory muscle function and can be performed easily every half hour to hour[43].

Magnetic resonance imaging

Brain or spine MRI could show enhancement of the spinal roots of cranial nerves in patients with GBS[44] and might be useful to rule out another differential diagnosis.

Pathogenesis and etiology

GBS tends to be a postinfectious and immune-mediated disease that targets peripheral nerves and about two-thirds of the patients had symptoms of an infection in the 3 weeks before the onset of weakness.

Previous infections are reported in up to 70% of patients with Guillain-Barre Syndrome so it is basically it is a postinfectious, immune-mediated disease so Cellular and humoral immune mechanisms probably play a role in its development[45].

Many patients report an infectious illness week prior to the onset of GBS, many of the identified infectious agents are thought to be inducing the production of antibodies that cross-react with specific gangliosides and glycolipids, such as GM1 and GD1b, that are distributed throughout the myelin sheath in the peripheral nervous system[11].

The fact that many cases of Guillain-Barré syndrome begin after a viral or bacterial infection suggests that there are certain characteristics of some viruses and bacteria that may activate the immune system inappropriately in one way or another.

Many infectious micro-organisms are linked to the onset of GBS, and Campylobacter jejuni is the most commonly associated specifically (serotype O:19), with the onset of axonal injury and Wallerian degeneration that leads to irreversible forms of GBS[46].

Research studies have also shown other triggers for GBS like Cytomegalovirus, Epstein Bar virus, Hemophilus influenza, and COVID-19.

In December 2019, the novel COVID-19 has been discovered in Wuhan (China), the pandemic disease had a number of neurological complications that have been reported. there was a confirmed GBS case however new studies show that Neuroscientists have found no significant association between COVID-19 and Guillain-Barré syndrome, their analysis shows that SARS-CoV-2 contains no additional immunogenic material known or proven to drive GBS[47].

There is a Concern that COVID-19 vaccination might cause GBS in any significant numbers are therefore almost certainly unfounded, so far there are no cases found related to the vaccine but with time we will be sure about it[47].

An epidemiological study in 1976, has shown a large increase in the incidence of GBS cases after influenza A vaccines in that year. However, recent studies have shown that the risk of acquiring GBS is only slightly higher after the vaccination and that there is a larger benefit in reducing the occurrence of GBS after vaccination[48].

There are other triggers such as Trauma, surgery, pregnancy these all could be possible triggers.

Treatment and therapeutic approach

GBS patients are at high risk of developing many complications, some of them may lead to death so because of that close monitoring is crucial to predict and prevent potential complications so the monitoring of respiratory, cardiac, and hemodynamic function is needed to prevent or manage complications.

The treatment of GBS needs a many-sided approach consisting of general medical care and immunological treatment.

General medical care

Good supportive care is crucial in the treatment of patients with GBS[49], As of monitoring the respiratory, cardiac and hemodynamic function because this is our main concern at the beginning, Prophylaxis for deep vein thrombosis is generally accepted, although it has never been subjected to controlled trial, we also check of the possible bladder and bowel dysfunction and we do Pain management using opioids or non-steroidal anti-inflammatory drugs[29], psychosocial care is also reported to be important.

Prehospital admission should be carefully done with (ABCs) airway, breathing, and circulation and should be immediately admitted to the hospital for close monitoring because the symptoms could progress rapidly[50]. Atropine is recommended for symptomatic bradycardia.

acute neuromuscular paralysis and its accompanying complications are what worry us, so patients need to be monitored closely in ICUs by physicians who are experienced and know how to deal with it.

In ICU we should focus on:

- Respiratory therapy with Cardiac monitoring
- Monitoring for infectious complications (e.g., pneumonia, urinary tract infections, septicemia.

There is a low threshold for intubation and if (FVC) falls to be below 1200 ml or 15 ml/kg and/or negative inspiratory force drops below 20 cm H2O, then intubation and respiratory support should be considered[51].

We should in ICU keep monitoring of respiratory function by frequent measurement of vital capacity and other clinical parameters, such as respiratory depth, respiratory frequency and cough strength[35]

Indications for ICU admission[52]:

- All patients come with labile dysautonomia.
- All patients with a forced vital capacity of less than 20 mL/kg.
- Patients with severe bulbar palsy.
- All patients show any clinical signs of respiratory compromise to any degree.
- Labile blood pressure.
- Cardiac arrhythmia.

Pain management

Medications for pain may be required in inpatient or outpatient settings. We start with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, with narcotic agents added if needed, it is usually recommended[50].

Opioids could be used for short-term treatment of pain but should be avoided for long-term pain management[53].

Immunological treatment

Immunomodulating therapy, intravenous immunoglobulin (IVIg) therapy and plasma exchange (PE), have been proved to be beneficial in improving outcome[54], either IVIg or Plasma Exchange should be started as soon as we can before any irreversible damage has taken place and make the situation even worse.

Immunotherapy is started usually for GBS patients if they are not able to walk 10 m unaided (GBS Disability Scale score ≥3)[55].

As IVIg is more widely available than plasma exchange because of its widespread availability and its good tolerability for the patients and is given at a dose of 0.4 g/kg daily for 5 consecutive days (or 2 g/kg over 3-5 days)[56], It is effective as a full course of five plasma exchange sessions applied over 2 weeks[57].

Plasma exchange helps in taking off autoantibodies, immune complexes, and cytotoxic constituents from serum and helps in decreasing the recovery time to half, A review of 6 randomized, controlled trials has been made involving 649 participants have found that PE helped speeding up the recovery time from GBS without causing any harm, apart from a slightly increased risk of relapse[58]. The standard dose of plasma exchange is to exchange 200 mL/kg to 250 mL/kg in four to five sessions over 7 to 14 days[59].

Combined Plasma Exchange and IVIg have been shown to be no better than Plasma Exchange or IVIg alone, studies of given plasma exchange followed by IVIg has been of no benefit[13].

Immunotherapy for pregnant women has not been studied well yet and safety for use during pregnancy has not been established and immunotherapy for children with GBS has not been studied yet with randomized, well-controlled studies that could be taken, but it is a standard aspect of treatment in this age group[13].

Prognosis and outcome

The outcomes of GBS are highly variable but their accurate prediction is critical to enable the clinicians to give supportive care and treatment to the patients' needs and to inform patients and their relatives about the exact clinical course of the disease to be well prepared for anything.

Predicators for the need for ventilation

There have been three studies that have been performed to predict the probability of respiratory insufficiency risk in GBS patients. The first one was a French study including 722 patients and found that time from onset to the admission of fewer than 7 days, inability to stand, inability to cough and the inability to lift the elbows or head from the bed, and increased liver enzyme levels were somehow predictors of an increased probability of the need for artificial ventilation for them[60].

A second study was a French study has found that if there were a peroneal nerve conduction block and low vital capacity it is mostly correlated with an elevated risk of respiratory failure[61].

The third study has taken place in the Netherlands, and they used data from a derivation cohort of 397 patients with GBS to identify clinical predictors of mechanical ventilation, which then were validated in an independent cohort of 191 patients with GBS[61]. The results of this study led to the development of what it called the Erasmus GBS Respiratory Insufficiency Score (EGRIS)[62]. The EGRIS is an accurate prediction model score that could be used in the emergency department to predict the probability of respiratory insufficiency during the first week after admission for GBS[62]. The score contains the following parameters: weakness severity (expressed as the MRC sum score), the number of days between the onset of weakness and admission, and facial and/or bulbar weakness. If the patient has a high probability of developing Respiratory insufficiency, we will rather admit the patient to the ICU rather than to a general neurology ward.

Predictors of poor long-term outcomes

Poor outcome is defined in all studies as a GBS Disability Scale score of 3 or more after either 6 months or 12 months[63], also diarrhea preceding GBS onset and advanced age all are predictors of poor outcome[64].

Guillain-Barré syndrome disability scale[65]

Score	Description
0	Healthy state
1	Minor symptoms and capable of running

2	Able to walk 10m or more without assistance but unable to run
3	Able to walk 10m across an open space with help
4	Bedridden or chair bound
5	Requiring assisted ventilation for at least part of the day
6	Dead

Erasmus GBS Outcome Score (EGOS) is one of the validated prognostic models that have been developed to be used in clinical practice for the prediction of long-term outcome in individual patients with GBS which is based on three clinical characteristics which are age, preceding diarrhea, and a GBS Disability Scale score at 2 weeks after hospital admission.

On the other hand, the modified EGOS can be used to predict the early outcomes in the course of GBS, before irreversible damage occurs, and this model can be used at admission and after admission by 1 week, and it is based on age, the severity of weakness (expressed as MRC sum score), and preceding diarrhea[66].

GBS mortality varies between 3% and 7%[67]. There are Predictors for an increased risk of death, and they are advanced age, having severe disease, increased comorbidity, respiratory and cardiac complications, mechanical ventilation, and systemic infection[68]. Death can occur in any phase of the disease but, there are two studies, that showed a large proportion of the deaths occurred >30 days from onset, and another study showed that the majority of patients who died were in the recovery phase[69].

Recent updates and Ongoing research

There was a new trial in 2014 of a randomized placebo-controlled trial of eculizumab in patients with an early course of GBS who are unable to walk is about to start[70], it is based on findings in an animal model of GBS which are mice, in which antiganglioside antibodies induce complement-dependent damage at the nodes of Ranvier, nerve terminals, and peri-synaptic Schwann cells[71 72].

These deleterious effects of complement on nerve terminals in mice could be blocked by the administration of (eculizumab), a humanized monoclonal antibody that binds with high affinity to complement factor C5 and prevents its cleavage to C5a and the pro-inflammatory, cytolytic C5b-9 complex.

There are many other studies, such as those investigating pain treatment, nerve regeneration, and other factors that may improve the outcomes of patients with GBS, which are awaited.

The most challenging needs we should work on is to develop improved diagnostic criteria for use in daily clinical practice, trials, and vaccine safety studies, and most importantly, is to develop a more effective and specific treatment also with protocols for supportive care[63].

References

1. Guillain G, Barré JA, Strohl A. [Radiculoneuritis syndrome with hyperalbuminosis of cerebrospinal fluid without cellular reaction. Notes on clinical features and graphs of tendon reflexes. 1916]. *Ann Med Interne (Paris)*. 1999;150(1):24-32.
2. Han ES, goleman, daniel; boyatzis, Richard; Mckee A. Gullian-barre syndrome. Journal of Chemical Information and Modeling. Published 2019. https://emedicine.medscape.com/article/315632-overview
3. Wijdicks EFM, Klein CJ. Guillain-Barré Syndrome. *Mayo Clin Proc*. 2017;92(3):467-479. doi:10.1016/j.mayocp.2016.12.002
4. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet (London, England)*. 2016;388(10045):717-727. doi:10.1016/S0140-6736(16)00339-1
5. Prevots DR, Sutter RW. Assessment of Guillain-Barré syndrome mortality and morbidity in the United States: implications for acute flaccid paralysis surveillance. *J Infect Dis*. 1997;175 Suppl: S151-5. doi:10.1093/infdis/175.supplement_1. s151
6. Esposito S, Longo MR. Guillain-Barré syndrome. *Autoimmun Rev*. 2017;16(1):96-101. doi: 10.1016/j.autrev.2016.09.022
7. Zochodne DW. Autonomic involvement in Guillain-Barré syndrome: a review. *Muscle Nerve*. 1994;17(10):1145-1155. doi:10.1002/mus.880171004
8. Maher J, Rutledge F, Remtulla H, Parkes A, Bernardi L, Bolton CF. Neuromuscular disorders associated with failure to wean from the ventilator. *Intensive Care Med*. 1995;21(9):737-743. doi:10.1007/BF01704741
9. Asbury AK. New concepts of Guillain-Barré syndrome. *J Child Neurol*. 2000;15(3):183-191. doi:10.1177/088307380001500308
10. Malek E, Salameh J. Guillain-Barre Syndrome. *Semin Neurol*. 2019;39(5):589-595. doi:10.1055/s-0039-1693005
11. Jacobs BC, Koga M, van Rijs W, et al. Subclass IgG to motor gangliosides related to infection and clinical course in Guillain-Barré syndrome. *J Neuroimmunol*. 2008;194(1-2):181-190. doi: 10.1016/j.jneuroim.2007.11.017
12. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. *Ann Neurol*. 1990;27 Suppl: S21-4. doi:10.1002/ana.410270707
13. Hughes RAC, Swan A V, Raphaël J-C, Annane D, van Koningsveld R, van Doorn PA. Immunotherapy for Guillain-Barré syndrome: a systematic review. *Brain*. 2007;130(Pt 9):2245-2257. doi:10.1093/brain/awm004
14. McKhann GM, Cornblath DR, Griffin JW, et al. Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. *Ann Neurol*. 1993;33(4):333-342. doi:10.1002/ana.410330402
15. Griffin JW, Li CY, Ho TW, et al. Pathology of the motor-sensory axonal Guillain-Barré syndrome. *Ann Neurol*. 1996;39(1):17-28. doi:10.1002/ana.410390105
16. Ho TW, Mishu B, Li CY, et al. Guillain-Barré syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies. *Brain*. 1995;118 (Pt 3:597-605. doi:10.1093/brain/118.3.597
17. FISHER M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). *N Engl J Med*. 1956;255(2):57-65. doi:10.1056/NEJM195607122550201
18. Overell JR, Hsieh ST, Odaka M, Yuki N, Willison HJ. Treatment for Fisher syndrome, Bickerstaff's brainstem encephalitis and related disorders. *Cochrane database Syst Rev*. 2007;(1):CD004761. doi: 10.1002/14651858.CD004761.pub2
19. Ito M, Kuwabara S, Odaka M, et al. Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum: clinical analysis of 581 cases. *J Neurol*. 2008;255(5):674-682. doi:10.1007/s00415-008-0775-0
20. Yuki N, Sato S, Tsuji S, Hozumi I, Miyatake T. An immunologic abnormality common to Bickerstaff's brain stem encephalitis and Fisher's syndrome. *J Neurol Sci*. 1993;118(1):83-87. doi:10.1016/0022-510x (93)90250-3
21. Department of Neurology, Erasmus University Medical Center, Rotterdam N. variants of GBS. 2019 Sep 20. Published 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6821638/figure/Fig2/
22. Pithadia AB, Kakadia N. Guillain-Barré syndrome (GBS). *Pharmacol Rep*. 2010;62(2):220-232. doi:10.1016/s1734-1140(10)70261-9
23. Hahn AF. Guillain-Barré syndrome. *Lancet (London, England)*. 1998;352(9128):635-641. doi:10.1016/S0140-6736(97)12308-X
24. van den Berg B, Fokke C, Drenthen J, van Doorn PA, Jacobs BC. Paraparetic Guillain-Barré syndrome. *Neurology*. 2014;82(22):1984-1989. doi:10.1212/WNL.0000000000000481
25. Michael T Andary, MD, MS Professor, Residency Program Director, Department of Physical Medicine and Rehabilitation MSUC of OM. Gullian barre syndrome clinical manifestations. https://emedicine.medscape.com/article/315632-clinical#b3
26. Dimachkie MM, Barohn RJ. Guillain-Barré syndrome and variants. *Neurol Clin*. 2013;31(2):491-510. doi: 10.1016/j.ncl.2013.01.005

27. Singhal V, Bhat KG. Guillain-Barre syndrome with hyperreflexia: A variant. *J Pediatr Neurosci*. 2011;6(2):144-145. doi:10.4103/1817-1745.92844
28. Barohn RJ, Saperstein DS. Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. *Semin Neurol*. 1998;18(1):49-61. doi:10.1055/s-2008-1040861
29. Ruts L, Drenthen J, Jongen JLM, et al. Pain in Guillain-Barre syndrome: a long-term follow-up study. *Neurology*. 2010;75(16):1439-1447. doi:10.1212/WNL.0b013e3181f88345
30. autonomic changes in GBS. https://emedicine.medscape.com/article/315632-clinical
31. Wang Y, Shang P, Xin M, Bai J, Zhou C, Zhang H-L. The usefulness of chief complaints to predict severity, ventilator dependence, treatment option, and short-term outcome of patients with Guillain-Barré syndrome: a retrospective study. *BMC Neurol*. 2017;17(1):200. doi:10.1186/s12883-017-0982-3
32. gbs physical examination. https://emedicine.medscape.com/article/315632-clinical#b3
33. Nguyen TP, Taylor RS. Guillain Barre Syndrome. In:; 2020.
34. Orlikowski D, Prigent H, Sharshar T, Lofaso F, Raphael JC. Respiratory dysfunction in Guillain-Barré Syndrome. *Neurocrit Care*. 2004;1(4):415-422. doi:10.1385/NCC:1:4:415
35. Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. *Brain*. 2014;137(Pt 1):33-43. doi:10.1093/brain/awt285
36. GBS workup. https://emedicine.medscape.com/article/315632-workup#c9
37. Zafar MSH, Naqash MM, Bhat TA, Malik GM. Guillain-barré syndrome in pregnancy: an unusual case. *J Fam Med Prim care*. 2013;2(1):90-91. doi:10.4103/2249-4863.109965
38. Brown WF, Feasby TE. Conduction block and denervation in Guillain-Barré polyneuropathy. *Brain*. 1984;107 (Pt 1:219-239. doi:10.1093/brain/107.1.219
39. Willison HJ, Yuki N. Peripheral neuropathies and anti-glycolipid antibodies. *Brain*. 2002;125(Pt 12):2591-2625. doi:10.1093/brain/awf272
40. Ang CW, Yuki N, Jacobs BC, et al. Rapidly progressive, predominantly motor Guillain-Barré syndrome with anti-GalNAc-GD1a antibodies. *Neurology*. 1999;53(9):2122-2127. doi:10.1212/wnl.53.9.2122
41. Chiba A, Kusunoki S, Shimizu T, Kanazawa I. Serum IgG antibody to ganglioside GQ1b is a possible marker of Miller Fisher syndrome. *Ann Neurol*. 1992;31(6):677-679. doi:10.1002/ana.410310619
42. Teitelbaum JS, Borel CO. Respiratory dysfunction in Guillain-Barré syndrome. *Clin Chest Med*. 1994;15(4):705-714.
43. PFT FOR GBS. https://emedicine.medscape.com/article/315632-workup#c12
44. Byun WM, Park WK, Park BH, Ahn SH, Hwang MS, Chang JC. Guillain-Barré syndrome: MR imaging findings of the spine in eight patients. *Radiology*. 1998;208(1):137-141. doi:10.1148/radiology.208.1.9646804
45. Jacobs BC, Rothbarth PH, van der Meché FG, et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. *Neurology*. 1998;51(4):1110-1115. doi:10.1212/wnl.51.4.1110
46. Mishu B, Ilyas AA, Koski CL, et al. Serologic evidence of previous Campylobacter jejuni infection in patients with the Guillain-Barré syndrome. *Ann Intern Med*. 1993;118(12):947-953. doi:10.7326/0003-4819-118-12-199306150-00006
47. Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. *Brain*. Published online December 2020. doi:10.1093/brain/awaa433
48. Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barré syndrome reported in association with the administration of swine influenza vaccines. *Am J Epidemiol*. 1984;119(6):841-879. doi: 10.1093/oxfordjournals.aje.a113809
49. de Vries JM, Hagemans MLC, Bussmann JBJ, van der Ploeg AT, van Doorn PA. Fatigue in neuromuscular disorders: focus on Guillain-Barré syndrome and Pompe disease. *Cell Mol Life Sci*. 2010;67(5):701-713. doi:10.1007/s00018-009-0184-2
50. Mx of GBS. https://emedicine.medscape.com/article/315632-treatment#d8
51. Arcila-Londono X, Lewis RA. Guillain-Barré syndrome. *Semin Neurol*. 2012;32(3):179-186. doi:10.1055/s-0032-1329196
52. Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barré syndrome. *J Infect Dis*. 1997;176 Suppl: S92-8. doi:10.1086/513793
53. Donofrio PD. Guillain-Barré Syndrome. *Continuum (Minneap Minn)*. 2017;23(5, Peripheral Nerve and Motor Neuron Disorders):1295-1309. doi:10.1212/CON.0000000000000513
54. Vitaliti G, Tabatabaie O, Matin N, et al. The usefulness of immunotherapy in pediatric neurodegenerative disorders: A systematic review of literature data. *Hum Vaccin Immunother*. 2015;11(12):2749-2763. doi:10.1080/21645515.2015.1061161
55. van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. *Lancet Neurol*. 2008;7(10):939-950. doi:10.1016/S1474-4422(08)70215-1
56. Madaan P, Jauhari P, Shruthi NM, Chakrabarty B, Gulati S. Intravenous Immunoglobulin for Severe Protracted Pediatric Guillain-Barre Syndrome: Is Single Dose Adequate? *Ann Indian Acad Neurol*. 2019;22(1):123-124. doi: 10.4103/aian.AIAN_100_18
57. van der Meché FG, Schmitz PI. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. Dutch Guillain-Barré Study Group. *N Engl J Med*. 1992;326(17):1123-1129. doi:10.1056/NEJM199204233261705
58. Raphaël JC, Chevret S, Hughes RAC, Annane D. Plasma exchange for Guillain-Barré syndrome. *Cochrane database Syst Rev*. 2012;(7):CD001798. doi: 10.1002/14651858.CD001798.pub2
59. Ortiz-Salas P, Velez-Van-Meerbeke A, Galvis-Gomez CA, Rodriguez Q JH. Human Immunoglobulin Versus Plasmapheresis in Guillain-Barre Syndrome and Myasthenia Gravis: A Meta-Analysis. *J Clin Neuromuscul Dis*. 2016;18(1):1-11. doi:10.1097/CND.0000000000000119

60. Sharshar T, Chevret S, Bourdain F, Raphaël J-C. Early predictors of mechanical ventilation in Guillain-Barré syndrome. *Crit Care Med*. 2003;31(1):278-283. doi:10.1097/00003246-200301000-00044
61. Durand M-C, Porcher R, Orlikowski D, et al. Clinical and electrophysiological predictors of respiratory failure in Guillain-Barré syndrome: a prospective study. *Lancet Neurol*. 2006;5(12):1021-1028. doi:10.1016/S1474-4422(06)70603-2
62. Walgaard C, Lingsma HF, Ruts L, et al. Prediction of respiratory insufficiency in Guillain-Barré syndrome. *Ann Neurol*. 2010;67(6):781-787. doi:10.1002/ana.21976
63. Cheng B-C, Chang W-N, Chen J-B, et al. Long-term prognosis for Guillain-Barré syndrome: evaluation of prognostic factors and clinical experience of automated double filtration plasmapheresis. *J Clin Apher*. 2003;18(4):175-180. doi:10.1002/jca.10066
64. Rees JH, Soudain SE, Gregson NA, Hughes RA. Campylobacter jejuni infection and Guillain-Barré syndrome. *N Engl J Med*. 1995;333(21):1374-1379. doi:10.1056/NEJM199511233332102
65. van Koningsveld R, Steyerberg EW, Hughes RAC, Swan A V, van Doorn PA, Jacobs BC. A clinical prognostic scoring system for Guillain-Barré syndrome. *Lancet Neurol*. 2007;6(7):589-594. doi:10.1016/S1474-4422(07)70130-8
66. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barre syndrome. *Neurology*. 2011;76(11):968-975. doi:10.1212/WNL.0b013e3182104407
67. Alshekhlee A, Hussain Z, Sultan B, Katirji B. Guillain-Barré syndrome: incidence and mortality rates in US hospitals. *Neurology*. 2008;70(18):1608-1613. doi: 10.1212/01.wnl.0000310983. 38724.d4
68. Lawn ND, Wijdicks EF. Fatal Guillain-Barré syndrome. *Neurology*. 1999;52(3):635-638. doi:10.1212/wnl.52.3.635
69. van den Berg B, Bunschoten C, van Doorn PA, Jacobs BC. Mortality in Guillain-Barre syndrome. *Neurology*. 2013;80(18):1650-1654. doi: 10.1212/WNL.0b013e3182904fcc
70. NHS Greater Glasgow and Clyde. Inhibition of Complement Activation (Eculizumab) in Guillain-Barre Syndrome Study (ICA-GBS). Published online 2014. https://www.clinicaltrials.gov/ct2/show/NCT02029378
71. Susuki K, Rasband MN, Tohyama K, et al. Anti-GM1 antibodies cause complement-mediated disruption of sodium channel clusters in peripheral motor nerve fibers. *J Neurosci*. 2007;27(15):3956-3967. doi:10.1523/JNEUROSCI.4401-06.2007
72. Plomp JJ, Willison HJ. Pathophysiological actions of neuropathy-related anti-ganglioside antibodies at the neuromuscular junction. *J Physiol*. 2009;587(Pt 16):3979-3999. doi:10.1113/jphysiol.2009.171702

Article topic: Migraine.

Author: Yara Shatnawi.

Editor: Aroob Awwad.

Reviewer: Ethar Hazaimeh, Hassan Abushukair

Keyword: chronic disease, pathophysiology, episodic migraine.

Overview

Migraine is a chronic neurological disorder characterized by attacks of mild or severe headache and reversible neurological and systemic symptoms;[1] some attacks preceded by aura and some without. The pathogenesis of migraines is not completely understood; it is thought to involve the trigeminal nerves and its additional axonal projections with the intracranial vascular system.[2] Those with migraines may not receive the correct diagnosis, adequate treatment, or proper support.[3] The economic and societal effect of migraine is substantial, it affects patients' quality of life and reduces work efficiency, social activities, and family life.

Epidemiology

Migraine is classified as the second most common neurological disorder; to which tension-type headache comes first, a female to male ratio of 3:1 and an estimated one year prevalence of 15% in the general population.[5] the disease shows a peak prevalence in ages that range between 35-39 years with 75% of the general population suffering from a migraine attack before the age of 35 years.[5,6] School-aged children on the other hand, show a one-year disease prevalence of 7%. [7] the disease leans towards remission in people aged 50 and above, an onset of a migraine attack among this age group usually leads to the suspension of secondary headache causes.[5,8]

Pathogenesis And Etiology

A migraine attack is divided into three phases:

- Premonitory
- Aura phase
- Headache phase.

Premonitory phase

Migraine is accompanied by a non-painful symptomatology also known as the premonitory phase; this can also include aura; the symptoms can start hours to days prior to the attack and it can be recognized as a marker for an impending headache. The premonitory mostly included symptoms like, fatigue, yawning, changes in cognitive abilities, fluctuation in homeostasis, increased thirst, frequency of micturition and photophobia.[8–19]

Functional neuroimaging studies brought forth evidence regarding the association of the hypothalamus in the premonitory phase[20], in a positron emission tomography study using the cerebral blood flow as a marker for patients with trinitrate-induced migraine attacks; it has been found that the activations were in:

- Posterolateral hypothalamus
- Midbrain tegmental area
- Dorsal pons
- Periaqueductal gray and multiple other cortical areas.

Functional magnetic resonance imaging was done during the interictal phase; defined as the time between migraine attacks. The results showed a strong association between the hypothalamus and areas related to pain transmission and autonomic function. This explains the autonomic symptoms experienced during the interictal and premonitory phase.[21]

There are two main theories that raised to explain the mechanism of action:

- There's an increase in parasympathetic tone that led to the activation of meningeal nociceptors and then subsequent vasodilation and release of local inflammatory mediators (Figure 1).
- The regulation of nociceptive signals by neuropeptides from trigeminal nucleus caudalis to supratentorial structures required in processing pain.[22,23]

The parasympathetic system is enhanced and involved in the activation of meningeal nociceptors as evidenced by lacrimation, teary eyes, nasal congestion[22]

To elaborate more; multiple migraine triggers (e.g. stress, sleep deprivation, food and etc.) are involved in networks which project to preganglionic parasympathetic neurons located in the Superior Salivatory Nucleus (SSN) this in turn leads to the release of neuropeptides in the postganglionic neurons located in the Sphenopalatine ganglion (SPN) that innervates the blood vessels in the meninges.[22]

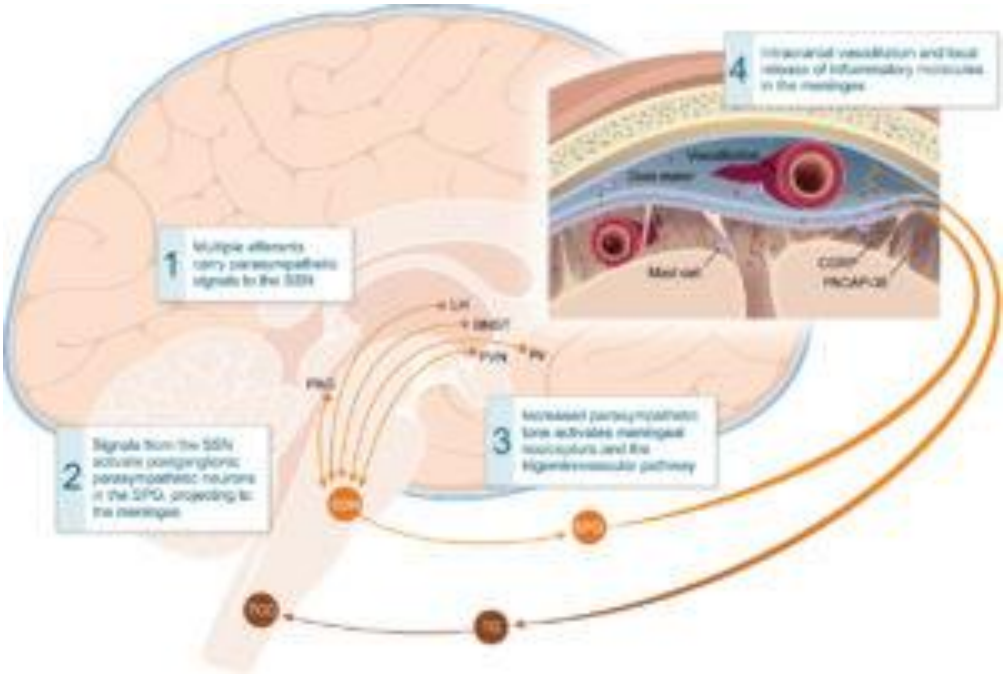


Figure 1: Activation of meningeal nociceptors by increased parasympathetic tone. BNST = bed nucleus of stria terminalis; LH = lateral hypothalamus; PAG = periaqueductal gray; Pir = piriform cortex; PVN = paraventricular hypothalamic nucleus; SPG = sphenopalatine ganglion; SSN = superior salivatory nucleus; TCC = trigeminal cervical complex; TG = trigeminal ganglion.[24]

Migraine Aura

The changes that follow the onset of aura is thought to be explained by the cortical spreading depression which is a self-propagating wave of depolarization across the cerebral cortex, this causes cerebral hypoperfusion and ionic imbalance,[25] those hemodynamic changes following cortical depression have been confirmed by neuroimaging techniques where patients who have migraine with aura showed changes that weren't seen on images of patients who have migraine without aura.[26] to elaborate more, the transient cortical depression (Figure 2) is thought to result in the onset of aura by:

- Opening neuronal pannexin-1 channels,[27]
- Release of inflammatory mediators (e.g., nitric oxides and prostanoids) which are known for their vasodilatory effect[28]
- Vasodilatation of the intracranial arteries results in the stimulation and activation of trigeminal primary afferents that terminates in the perivascular space of intracranial arteries[2] and function as transmitters of nociceptive impulses, the impulses are then relayed and processed into the cortical areas finally yielding a migraine attack.[29,30]

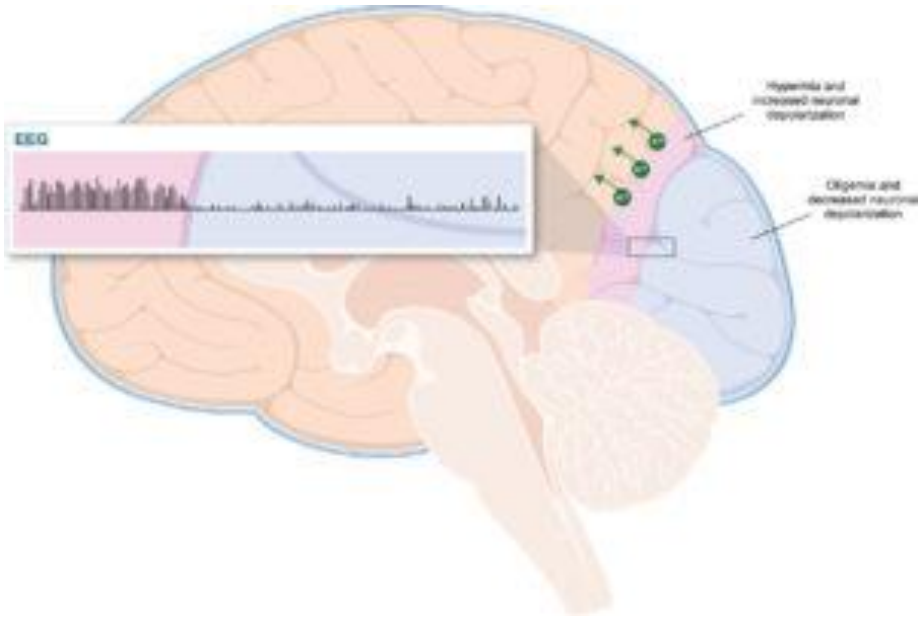


Figure 2: Cortical spreading depression. EEG = electroencephalogram; K^+ = potassium.[2]

Headache phase

The trigemino-vascular system is believed to act as a substrate that will eventually yield a migraine attack by nociceptive transmission.[32] The trigeminal afferent fibers innervates the meninges and its respective blood vessels, in order for a migraine attack to initiate; first-order trigeminal neurons need to be sensitized and activated, as a consequence of activation, the neurons secretes vasoactive peptides (e.g., substance P, calcitonin gene-related peptide) and stimulates local inflammatory reactions[33] this whole process results in neurogenic inflammation of the meningeal vessels and propagation of trigeminal sensory fibers[2] which in turn initiates the stimulation and activation of secondary and third-order neurons located in the brain stem and the thalamus respectively. Finally somatosensory and other cortical areas associated with pain sensation receive impulses from the nociceptors in order to manifest the migraine attack.[2]

Diagnosis and work up

The International Classification of Headache Disorders, 3rd edition (ICDH-3) provides a diagnostic criterion for migraine disorders, it mainly divides migraines into three subtypes:

- Migraine without aura.
- Migraine with aura.

- Chronic migraine.[42]

At least five attacks fulfilling criteria 1, 2 and 3:

1. Headache lasting 4-72 hours (when left untreated or unsuccessfully treated).
2. Headache with at least two of the following characteristics:
   - Unilateral location.
   - Pulsating quality.
   - Moderate or severe pain intensity.
   - Aggravation by or causing avoidance of routine.
   - physical activity (e.g., walking or climbing stairs).
3. Headache associated with at least one of the following symptoms.
   - Nausea, vomiting or both.
   - Photophobia and phonophobia.
4. Not better accounted by another ICDH-3 diagnosis.[7]

Table 1. ICHD-3 Diagnostic Criteria for Migraine without Aura

At least two attacks fulfilling criteria 1 and 2:

1. One or more of the following reversible auras
   - Visual.
   - Sensory.
   - Speech, language, or both.
   - Motor
   - Brain.
   - Retinal.
2. At least three of the following six characteristics:
   - At least one aura symptom spreading gradually over a period ≥5 minutes.
   - Two or more aura symptoms occurring in succession Each aura symptom lasting 5–60 minutes.
   - At least one unilateral aura symptom.
   - At least one positive aura symptom.
   - Headache accompanying the aura or following the aura within 60 minutes.
3. Not better accounted by an ICDH3 diagnosis.[7]

Table 2. ICHD-3 Diagnostic Criteria for Migraine with Aura

Visual auras account as the most common type of auras in migraine with aura subtype; it most often presents as scintillations and scotoma; a less frequent form of auras are

sensory disturbances followed by speech disturbances or aphasia. Sensory disturbances include the sensation of pins and needles affecting a significant or a minor area of the body like the tongue or face.

Aura symptoms can be single or multiple and usually follow the same order i.e., visual, sensory then aphasia. The duration of most auras until the onset of headache is one hour (60 minutes), this may also occur in the absence of a following headache.[7]

Headaches (suggestive of migraine or tension headaches) for on ≥15 days/month for >3 months that fulfil the following criteria:
1. Occurring in a patient who has had at least five at- tacks meeting the criteria for migraine without aura or the criteria for migraine with aura or both. 2. On ≥8 days/month for >3 months, features of migraine without aura or of migraine with aura or believed by the patient to be migraine at onset that is relieved by a triptan or ergot derivative. 3. Not better accounted for by another ICHD-3 diagnosis.[7]

Table 3. ICHD-3 Diagnostic Criteria for Chronic migraine

Differential diagnoses:

The differential diagnosis of headache includes other primary causes and secondary causes. Primary causes include tension-type headache. Secondary causes include subarachnoid hemorrhage, meningitis, encephalitis, carbon monoxide poising, etc.[42]

Treatment and Management

The clinical management of patients with migraine is ideally managed and maintained by practitioners, if the patient's diagnosis is challenging or the patient did not respond to any kind of treatment then referral to a specialist must be considered.[7,43]

1. Acute and preventative methods with the use of non-pharmacological therapy as an adjunct to the already given medications.[44–46]
2. Benefits were found in noninvasive neuromodulator devices, acupuncture and biobehavioral therapies.[47–49]
3. Dietary approaches and physical therapy have shown no to little evidence regarding its benefits to therapy.[7]

There are acute and preventive pharmacological treatments for migraine, acute treatment is either specific (triptans and ergots) or non-specific (analgesics). Preventive treatment reduces the frequency of attacks and improves quality of life. The plan to choose medications should be individualized that are specific to each patient, including the presence of associated symptoms like nausea or vomiting and the time to peak severity.

Acute treatment

Generally, headache phase especially early, is the best time to administer medications when trying to alleviate or remove the pain as a consequence of the attack.[49]

1. Triptans, All triptans and triptan combination medications have a good evidence for effectiveness for acute treatment of migraine, in cases where oral triptans didn't show any effect, other drugs of the same family can also provide pain relief .[7] Currently there are seven oral triptans present (almotriptan, frovatriptan, sumatriptan, naratriptan, rizatriptan, zolmitriptan, and eletriptan), patients are advised to switch the type of oral Triptan when three attacks of migraines are treated with no success.[50]
2. Analgesia including acetaminophen and certain nonsteroidal anti-inflammatory drugs (NSAIDs) include ibuprofen, diclofenac, naproxen and acetyl-salicylic acid.[51] Non-steroidal Anti-inflammatory Drugs (NSAIDS) are most used [52–54], this drug family has advantages over other drugs as it is of low cost and over-the-counter drug so easier accessibility.

When the treatment is only partially effective, clinicians can recommend a combination therapy including NSAIDs (e.g., naproxen sodium) with triptans.[55] Subcutaneous triptans have shown better efficacy when compared with other triptans on the basis of patients who noted relief from pain after 2 hours from treatment. Thus, when presented with a patient who complains of inadequate treatment, subcutaneous triptans is the first choice.[42,56] Triptans can cause vasoconstriction of arteries of coronary and limb arteries, therefore Triptans are contraindicated in patients with a history of stroke, myocardial infarction, coronary artery disease, hemiplegic migraine, uncontrolled hypertension, migraine with brainstem aura, and peripheral vascular disease.

Clinicians must be alert to the risk of medication overuse headache, which is a state where the patient expresses continuous headache or increase in the frequency of headache; a contribution of continuous medication overuse for migraines by patients who complain of headaches for 15 days per month.[56] In such instances, medication withdrawal and initiation of preventative treatment is necessary.[57–60]

Recently, there has been enthusiasm regarding the small molecule calcitonin gene-related peptide CGRP receptor antagonists called gepants and 5-Hydorxytryptamine

type 1-F (5-HT_{1F}) receptor agonists called ditans, primarily used in the management of acute migraine.[61] The Food and Drug Administration (FDA) has approved the use of the following oral ditans and geptans in the treatment of acute migraines: Ubrogepant, Lasmiditan and Rimegepant. However, due to its high costs and reduced availability, patients who are contraindicated or have shown ineffectiveness in the treatment modality with the use of NSAIDs or triptans are limited to the use of oral ditans and geptans. Moreover, Lismitdan have shown regression in driving and an insufficiency to assess ones driving expertise.[61] As a consequence patient are recommended to avoid driving for at least 8 hours after ingestion.[7,62] Thus, the broad use of Lismitdan can been limited by clinicians. Finally, guidelines are against the use of opioids and barbiturates due to its risk of dependency and its side effects.[7]

Preventive therapy of Migraine

Migraine prevention requires a comprehensive approach that includes lifestyle modifications and trigger avoidance. Further interventions can include medications, nutraceuticals, behavioral therapies, and neurostimulation, where the aim is to reduce frequency of attacks and severity and duration.[7]
Generally, treatment is recommended for patients who have three headache per month that are ineffective to treatment and affect their societal life.[63] unresponsive to acute therapy, accompanied by particularly bothersome symptoms (e.g., brainstem aura, intractable vomiting), or when a patient is at risk of developing overuse of acute migraine medications.
The decision of which therapy to recommend is based on multiple factors include:

- The level of evidence that a specific therapy is effective.
- Its safety profile and cost.
- Patient comorbidities.
- Potential interactions with other therapies and if the patient is tolerating the therapy or not.

Clinicians may use such information and advise the patients in order to reach a mutual agreement about a realistic treatment plan. due to the restricted number of approved preventive medications, off-label use of medications is becoming more common.[49]

The most used preventive medications and nutraceuticals are topiramate, propranolol, nadolol, metoprolol, timolol, amitriptyline, gabapentin, candesartan, divalproex sodium, sodium valproate, flunarizine, pizotifen, venlafaxine, verapamil, lisinopril, coenzyme Q10, magnesium citrate, riboflavin, and feverfew. Chronic migraines have shown effectiveness with the use of topiramate and on a botulinum toxin A (Botox).[64–73]

In addition, New preventative therapies have been introduced including monoclonal antibodies, they work by:

- Targeting a calcitonin gene-related peptide (CGRP) or its receptor (e.g., Erenumab, Galcanezumab, Fremanezumab, and Eptinezumab).
- As a prevention treatment of both episodic and chronic migraine attacks.[64]
- The drugs have rapid onset and few side effects, a common side effect include pain and erythema at the injection site.[65]

A 5-year open-lab extension study was done to study the long-term effect of Erenumab, results showed that it continued to be safe in patients with diagnosed episodic migraines.[74] The agents have not been compared to the above mentioned less expensive, more common, and more accessible oral preventative medications. As a result, its recommended that the estimation and substitution of another medication can be considered after:

1. Two to three months when treated with oral preventative therapy.
2. Three to six months when treated with monoclonal antibodies that target CGRP or its receptors.
3. Six to nine months when treated with Botox.[75]

Risk Factors

Several studies show that genetics play an essential role in the development of migraines where if one parent has migraine, chances of a child having migraine can rise up to 40%, if however, two parents have migraine chances increase to 75%.[76] Other studies report an estimated 2.5% to 3% of people diagnosed with episodic migraines transitioned to chronic migraines each year.[77] Risk factors for the development of chronic migraines include:

1. Socioeconomic status, lifestyle factors and habits- obesity, low family socioeconomic status, female sex, daily caffeine intake and major life events.[77]
2. Headache features and symptoms- increase in headache frequency, followed by headache persistent or frequent headaches associated with nausea and cutaneous allodynia.[77]
3. Comorbid and concomitant diseases or conditions like depression, asthma, non cephalic pain, head, and neck injury, snoring and insomnia.
4. Pharmacological- acute medication overuse and acute migraine treatment efficacy.[77]

A few studies tested the outcomes of patients with chronic migraine when an intervention on modifiable risk factors was done, results showed a decrease in headache frequency and severity with some patients reporting remission from chronic migraine to episodic migraines.[78]

Prognosis

The prognosis of migraine is poorly studied and as result research regarding this topic is still in its easy beginnings.[79] Generally prognosis is divided into short term and long term. A study was done on 16,2576 individuals to assess the prevalence and prognosis by following up with the patients over the years, the results of the first wave (1-year) of follow up showed that:

- 84% of the individuals still had migraines.
- 10% showed 1-year clinical remission.
- 3% reported partial remission.
- 3% developed chronic migraines, the long-term outcomes weren't reported.[80]

Few studies were done to assess the long-term outcomes in patients with migraines; a long duration follow up study was done in Sweden in 1955 to assess migraines in 9000 schoolchildren, a subgroup of those children [76 people] diagnosed with migraines were followed up after 40 years, around the age of 50, more than fifty percent of them still had migraine attacks.[81]

Another study was done on schoolchildren aged 7 years in Finish and were followed up 7 years later, of those children:

- 22% showed complete remission.
- 37% showed partial remission.
- 41% showed progression or persistence.[82]

Recent updates

A clinical trial was done on 1,072 chronic migraineurs with a mean monthly migraine of 16.1 to assess the effect of Epitnezumab. Adults were randomly divided and given IV Epitnezumab 100 mg, Epitnezumab 300 mg and placebo, this was done on day 1 and week 12. Results on week 12 showed significant decrease in mean monthly migraines in patients who took 100mg and 300 mg Epitnezumab in comparison to placebo effects from day 1 through week 12.[83]

Another clinical trial was done to assess the effect of fremanezumab among people with episodic or chronic migraines by administering fremanezumab quarterly, or monthly over a period 12 weeks, responders to treatment were defined as those with reduction in monthly migraine days by at least 2 monthly migraine days in patients with episodic migraines and 4 monthly migraine days in patients with chronic migraines. Responders were identified and the results showed significant reduction in the monthly average number of migraine days by more than 50% in episodic migraines (EM: quarterly,

59,8%; monthly 63.7%) and chronic migraines (CM: quarterly, 52.8%; monthly, 59%). This can provide further understanding of the treatment gains in patients who responded to fremanezumab in clinical practice.[83]

References

1. Dodick DW. Migraine. *The Lancet*. 2018;391(10127):1315-1330. doi:10.1016/S0140-6736(18)30478-1
2. Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R, Moskowitz MA. Migraine and the trigeminovascular system—40 years and counting. *The Lancet Neurology*. 2019;18(8):795-804. doi:10.1016/S1474-4422(19)30185-1
3. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends from Government Health Studies. *Headache*. 2018;58(4):496-505. doi:10.1111/head.13281
4. Stovner LJ, Nichols E, Steiner TJ, et al. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2018;17(11):954-976. doi:10.1016/S1474-4422(18)30322-3
5. Stewart WF, Wood C, Reed ML, Roy J, Lipton RB. Cumulative lifetime migraine incidence in women and men. *Cephalalgia*. 2008;28(11):1170-1178. doi:10.1111/j.1468-2982.2008. 01666.x
6. Wöber C, Wöber-Bingöl Ç, Uluduz D, et al. Undifferentiated headache: broadening the approach to headache in children and adolescents, with supporting evidence from a nationwide school-based cross-sectional survey in Turkey. *Journal of Headache and Pain*. 2018;19(1). doi:10.1186/s10194-018-0847-1
7. Steiner TJ, Jensen R, Katsarava Z, et al. Aids to management of headache disorders in primary care (2nd edition): On behalf of the European Headache Federation and Lifting the Burden: The Global Campaign against Headache. *Journal of Headache and Pain*. 2019;20(1). doi:10.1186/s10194-018-0899-2
8. Giffin NJ, Ruggiero; L, Lipton; R B, et al. *Premonitory Symptoms in Migraine an Electronic Diary Study*.; 2003.
9. Kelman L. *The Premonitory Symptoms (Prodrome): A Tertiary Care Study of 893 Migraineurs*.
10. Schoonman GG, Evers DJ, Terwindt GM, van Dijk JG, Ferrari MD. The prevalence of premonitory symptoms in migraine: A questionnaire study in 461 patients. *Cephalalgia*. 2006;26(10):1209-1213. doi:10.1111/j.1468-2982.2006. 01195.x
11. Quintela E, Castillo J, Muñoz P, Pascual J. Premonitory and resolution symptoms in migraine: A prospective study in 100 unselected patients. *Cephalalgia*. 2006;26(9):1051-1060. doi:10.1111/j.1468-2982.2006. 01157.x
12. Karsan N, Prabhakar P, Goadsby PJ. Characterising the premonitory stage of migraine in children: a clinic-based study of 100 patients in a specialist headache service. *Journal of Headache and Pain*. 2016;17(1). doi:10.1186/s10194-016-0689-7
13. Cuvellier JC, Mars A, Vallée L. The prevalence of premonitory symptoms in paediatric migraine: A questionnaire study in 103 children and adolescents. *Cephalalgia*. 2009;29(11):1197-1201. doi:10.1111/j.1468-2982.2009. 01854.x
14. Amery WK, Waelkens J, Vandenbergh V. *Original Articles Migraine Warnings*. Vol 26.; 1986.
15. Waelkens J. Warning symptoms in migraine: characteristics and therapeutic implications.
16. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. *Cephalalgia*. 1992; 12:221-229.
17. Laurell K, Artto V, Bendtsen L, et al. Premonitory symptoms in migraine: A cross-sectional study in 2714 persons. *Cephalalgia*. 2016;36(10):951-959. doi:10.1177/0333102415620251
18. Rusinkiewicz WI, Phillips A. *10 Card WI. Rational Justification for Therapeutic Decisions*. Vol 281. Oxford University Press; 1980.
19. *Russell MB, Rasmussen BK, Fenger K, Olesen J. Migraine without Aura and Migraine with Aura Are Distinct Clinical Entities: A Study of Four Hundred and Eighty-Four Male and Female Migraineurs from the General Population. Cephalalgia 1996;16(4): 239–245. Doi:10.1046/j.1468-2982.1996.1604239. x.*.
20. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain*. 2014;137(1):232-241. doi:10.1093/brain/awt320
21. Moulton EA, Becerra L, Johnson A, Burstein R, Borsook D. Altered hypothalamic functional connectivity with autonomic circuits and the locus coeruleus in migraine. *PLoS ONE*. 2014;9(4). doi: 10.1371/journal.pone.0095508
22. Burstein R, Jakubowski M. Unitary hypothesis for multiple triggers of the pain and strain of migraine. In: *Journal of Comparative Neurology*. Vol 493.; 2005:9-14. doi:10.1002/cne.20688
23. Noseda R, Kainz V, Borsook D, Burstein R. Neurochemical pathways that converge on thalamic trigeminovascular neurons: Potential substrate for modulation of migraine by sleep, food intake, stress and anxiety. *PLoS ONE*. 2014;9(8). doi: 10.1371/journal.pone.0103929
24. Dodick DW. A Phase-by-Phase Review of Migraine Pathophysiology. Published online 2018. https://headachejournal.onlinelibrary.wiley.com/cms/asset/d1f9782e-19ea-4187-8f93-1d4ca8f1c27f/head13300-fig-0001-m.jpg
25. Sanchez de M. *Perfusion Weighted Imaging during Migraine: Spontaneous Visual Aura and Headache*.

26. Karatas H, Erdener SE, Gursoy-Ozdemir Y, et al. Spreading depression triggers headache by activating neuronal Panx1 channels. *Science*. 2013;339(6123). doi:10.1126/science.1231897
27. Ashina M, Hansen JM, Á Dunga BO, Olesen J. Human models of migraine-short-Term pain for long-Term gain. *Nature Reviews Neurology*. 2017;13(12):713-724. doi:10.1038/nrneurol.2017.137
28. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Published online 2002. doi:10.1038/nm0202-136
29. Dodick DW. A Phase-by-Phase Review of Migraine Pathophysiology. *Headache: The Journal of Head and Face Pain*. 2018; 58:4-16. doi:10.1111/HEAD.13300
30. Dodick DW. a phase-by-phase review of migraine pathophysiology. Published online 2018. https://headachejournal.onlinelibrary.wiley.com/cms/asset/d1f9782e-19ea-4187-8f93-1d4ca8f1c27f/head13300-fig-0001-m.jpg
31. Moskowitz MA. *The Neurobiology of Vascular Head Pain*. Vol 16.; 1984.
32. Brust JCM (John CM). *Current Diagnosis & Treatment. Neurology*.
33. Al-Karagholi MAM, Hansen JM, Guo S, Olesen J, Ashina M. Opening of ATP-sensitive potassium channels causes migraine attacks: A new target for the treatment of migraine. *Brain*. 2019;142(9):2644-2654. doi:10.1093/brain/awz199
34. Negro A, Delaruelle Z, Ivanova TA, et al. Headache and pregnancy: a systematic review. *Journal of Headache and Pain*. 2017;18(1). doi:10.1186/s10194-017-0816-0
35. Reuter U, McClure C, Liebler E, Pozo-Rosich P. Non-invasive neuromodulation for migraine and cluster headache: A systematic review of clinical trials. *Journal of Neurology, Neurosurgery and Psychiatry*. 2019;90(7):796-804. doi:10.1136/jnnp-2018-320113
36. Sharpe L, Dudeney J, Williams AC de C, et al. psychological therapies for the prevention of migraine in adults. *Cochrane Database of Systematic Reviews*. 2019;2019(7). doi: 10.1002/14651858.CD012295.pub2
37. Linde K, Allais G, Brinkhaus B, et al. Acupuncture for the prevention of episodic migraine. *Cochrane Database of Systematic Reviews*. 2016;2016(6). doi: 10.1002/14651858.CD001218.pub3
38. Luedtke K, Allers A, Schulte LH, May A. Efficacy of interventions used by physiotherapists for patients with headache and migraine - Systematic review and meta-analysis. *Cephalalgia*. 2015;36(5):474-492. doi:10.1177/0333102415597889
39. Chaibi A, Benth J, Tuchin PJ, Russell MB. Chiropractic spinal manipulative therapy for migraine: a three-armed, single-blinded, placebo, randomized controlled trial. *European Journal of Neurology*. 2017;24(1):143-153. doi:10.1111/ene.13166
40. *AtlAs of Headache Disorders and Resources in the World 2011*.; 2011. www.who.int
41. Law S, Derry S, Moore RA. Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults. *Cochrane Database of Systematic Reviews*. 2016;2016(4). doi: 10.1002/14651858.CD008541.pub3
42. Dahlöf CGH. Infrequent or non-response to oral sumatriptan does not predict response to other triptans - Review of four trials. *Cephalalgia*. 2006;26(2):98-106. doi:10.1111/j.1468-2982.2005. 01010.x
43. Rabbie R, Derry S, Moore RA, McQuay HJ. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. In: Moore M, ed. *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2010. doi: 10.1002/14651858.CD008039.pub2
44. Saguil A, Herness J. Aspirin with or without an antiemetic for acute migraine headaches in adults. *American Family Physician*. 2014;89(3):176-177. doi: 10.1002/14651858.cd008041.pub2
45. Derry S, Rabbie R, Moore RA. Diclofenac with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews*. 2013;2017(9). doi: 10.1002/14651858.CD008783.pub3
46. Derry CJ, Derry S, Moore RA. Sumatriptan (all routes of administration) for acute migraine attacks in adults - overview of Cochrane reviews. *Cochrane Database of Systematic Reviews*. 2014;2014(5). doi: 10.1002/14651858.CD009108.pub2
47. Diener HC, Dodick D, Evers S, et al. Pathophysiology, prevention, and treatment of medication overuse headache. *The Lancet Neurology*. 2019;18(9):891-902. doi:10.1016/S1474-4422(19)30146-2
48. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the Treatment of Migraine. *New England Journal of Medicine*. 2019;381(23):2230-2241. doi:10.1056/nejmoa1813049
49. Lipton RB, Dodick DW, Ailani J, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: The achieve ii randomized clinical trial. *JAMA - Journal of the American Medical Association*. 2019;322(19):1887-1898. doi:10.1001/jama.2019.16711
50. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *The Lancet*. 2019;394(10200):737-745. doi:10.1016/S0140-6736(19)31606-X
51. Goadsby PJ, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain*. 2019;142(7):1894-1904. doi:10.1093/brain/awz134
52. Pearlman EM, Wilbraham D, Dennehy EB, et al. Effects of lasmiditan on simulated driving performance: Results of two randomized, blinded, crossover studies with placebo and active controls. *Human Psychopharmacology*. 2020;35(5). doi:10.1002/hup.2732
53. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The American headache society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20. doi:10.1111/head.12499
54. The American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice. *Headache*. 2019;59(1):1-18. doi:10.1111/head.13456
55. Charles A, Pozo-Rosich P. Targeting calcitonin gene-related peptide: a new era in migraine therapy. *The Lancet*. 2019;394(10210):1765-1774. doi:10.1016/S0140-6736(19)32504-8

56. Ashina M, Goadsby PJ, Reuter U, et al. Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine. *Cephalalgia*. 2019;39(11):1455-1464. doi:10.1177/0333102419854082
57. Goadsby PJ, Reuter U, Hallström Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. *New England Journal of Medicine*. 2017;377(22):2123-2132. doi:10.1056/nejmoa1705848
58. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *The Lancet Neurology*. 2017;16(6):425-434. doi:10.1016/S1474-4422(17)30083-2
59. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of Fremanezumab compared with placebo for prevention of episodic migraine a randomized clinical trial. *JAMA - Journal of the American Medical Association*. 2018;319(19):1999-2008. doi:10.1001/jama.2018.4853
60. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. *New England Journal of Medicine*. 2017;377(22):2113-2122. doi:10.1056/nejmoa1709038
61. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo controlled REGAIN study. *Neurology*. 2018;91(24): E2211-E2221. doi:10.1212/WNL.0000000000006640
62. Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia*. 2020;40(3):241-254. doi:10.1177/0333102420905132
63. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology*. 2020;94(13): E1365-E1377. doi:10.1212/WNL.0000000000009169
64. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: The EVOLVE-1 randomized clinical trial. *JAMA Neurology*. 2018;75(9):1080-1088. doi:10.1001/jamaneurol.2018.1212
65. Ashina M. Migraine. Ropper AH, ed. *New England Journal of Medicine*. 2020;383(19):1866-1876. doi:10.1056/NEJMra1915327
66. MacGregor EA. Migraine. *Annals of internal medicine*. 2017;166(7): ITC49-ITC64. doi:10.7326/AITC201704040
67. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: A longitudinal population-based study. *Headache*. 2008;48(8):1157-1168. doi:10.1111/j.1526-4610.2008. 01217.x
68. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. *Neurologic Clinics*. 2019;37(4):631-649. doi: 10.1016/j.ncl.2019.06.001
69. Bigal ME, Lipton RB. *The Prognosis of Migraine*.
70. Lipton RB, Bigal ; M E, Diamond; M, Freitag; F, Reed ML, Stewart WF. *Migraine Prevalence, Disease Burden, and the Need for Preventive Therapy*.; 2007.
71. bille1997.
72. Sillanpää M, Anttila P. *Original Articles Increasing Prevalence of Headache in 7-Year-Old Schoolchildren*.
73. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology*. 2020;94(13): E1365-E1377. doi:10.1212/WNL.0000000000009169
74. Silberstein SD, Cohen JM, Yang R, et al. Treatment benefit among migraine patients taking fremanezumab: results from a post hoc responder analysis of two placebo-controlled trials. *Journal of Headache and Pain*. 2021;22(1). doi:10.1186/s10194-020-01212-4

Article Topic: Trigeminal Autonomic Cephalalgias (TACs).

Author: Sara Shatnawi.

Editor: Yman Oudat.

Reviewer: Ethar Hazaimeh, Hassan Abushukair.

Keywords: cluster headache, hemicrania continua, paroxysmal hemicrania, nVNS, SUNCT.

Overview

Trigeminal autonomic cephalalgias (TACs) are a group of primary headache disorders which include cluster headache, paroxysmal hemicrania (PH), hemicrania continua, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), and short-lasting unilateral headache with cranial autonomic symptom (SUNA). All TACs share common features of recurrent unilateral pain and are often accompanied by ipsilateral cranial autonomic features such as ptosis, conjunctival injection, lacrimation, nasal congestion, or rhinorrhea. The duration of the attacks, their frequency, and the way the headache responds to treatment differentiate between each type. SUNCT and SUNA are the most frequent, but their attacks lie for a short duration of time, inversely, cluster headache has the lowest attack frequency, but often the longest duration. Paroxysmal hemicrania lies at the midpoint of the spectrum; it occurs more frequently than cluster headache but significantly less than SUNCT/SUNA, with a duration between the two. (1)

Figure 1. Typical durations and frequencies of individual attacks of Trigeminal autonomic cephalalgias per day.

Pathogenesis and Etiology

The three brain systems involved in TACs are the trigeminovascular system, the autonomic system, and the hypothalamus (2).

1. **The trigeminovascular system: facial pain system.**

The ophthalmic branch of the trigeminal nerve receives input information from the forehead, eyes, dura and large cranial nerves. The trigeminal nerve connects to several nociceptive nuclei in the brainstem and upper cervical cord also called trigeminocervical complex, which then reaches the thalamus, and finally the pain NeuroMetrix (a collection of areas in the brain that processes many types of pain) (3). During a cluster attack, the trigeminovascular system elevates several signaling molecules including calcitonin gene-related peptide (CGRP) (3, 4).

2. **The autonomic system**

It handles cranial autonomic features (lacrimation, conjunctival injection) which is a series of parasympathetic over-activation and sympathetic inactivation. The superior salivary nucleus provides parasympathetic input to the sphenopalatine ganglion, which in turn supplies the face, specifically the lacrimal gland and paranasal sinuses. The most direct evidence of autonomic nervous system involvement is achieved by placing an electrode over the sphenopalatine ganglion in patients with cluster headaches, the attack can be exaggerated or relieved by changing the stimulation parameters (5). Vasoactive intestinal peptide is a signaling molecule in the autonomic nervous system that is elevated during a cluster attack (3, 4).

3. **The hypothalamus**

It includes the circadian system and aggression areas, which may explain the predictable daily rhythmicity of the cluster headache and restlessness seen in patients with TACs. Furthermore, molecules regulated by the hypothalamus, such as melanin, are altered in patients with cluster headaches (6). The hypothalamus appears to be the first area activated during a cluster attack, followed by trigeminovascular and autonomic activation. Genetics may play a role in the occurrence of all types of TACs (3).

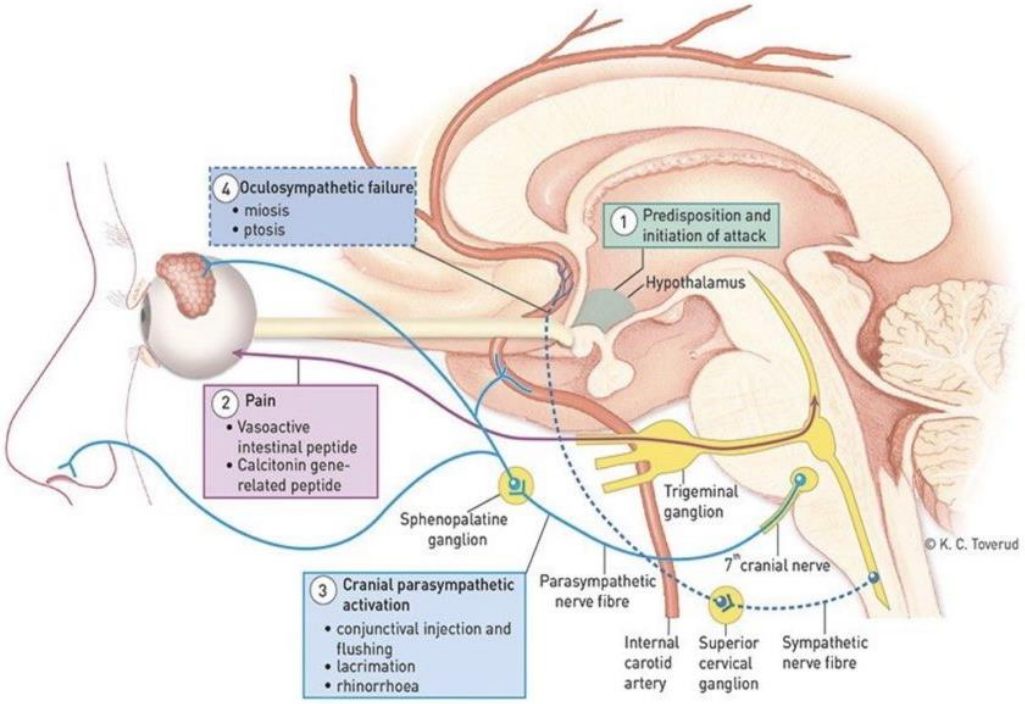


Figure 2: Pathophysiology of cluster headache initiation. (38).

Cluster Headache

Cluster headaches have a male predominance of approximately 72% (7), with an age of onset between 20 and 40 years (8). In addition, its prevalence is 0.1% of the general population (9).

Figure 3: Patient with cluster headache during a right-sided painful attack. note the ipsilateral ptosis, miosis, lacrimation and rhinorrhea. (36).

Clinical presentation

Table 1. ICHD-3 Diagnostic Criteria for Cluster Headache*

1. At least five attacks fulfilling criteria 2-4
2. Severe or extremely severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 minutes (when untreated)
3. Either or both of the following:
    - At least one of the following symptoms or signs, ipsilateral to the headache:
        - Conjunctival injection and/or lacrimation
        - Nasal congestion and/or rhinorrhea
        - Eyelid edema
        - Forehead and facial sweating
        - Miosis and/or ptosis
    - A sense of restlessness or agitation
4. Occurring with a frequency between one every other day and eight per day
5. Not better accounted for by another ICHD-3 diagnosis.

* International Classification of Headache Disorders, Third Edition.

The criteria for cluster headache are shown in Table 1. (37)

There are two types of cluster headache based on (ICHD-3) Diagnostic Criteria for Cluster Headache:

1. Episodic cluster headache: Attacks fulfilling criteria for cluster headache and occurring in cluster periods with at least two lasting from 7 days to 1 year when untreated, separated by pain-free periods that last for more than 3 months.
2. Chronic cluster headache: Attacks fulfilling criteria for cluster headache and occurring without a remission period, or with pain-free periods lasting less than 3 months for at least 1 year. (2, 3)

Cluster headaches are diagnosed according to the patient's description of pain. Patients complain of unilateral orbital or temporal pain, the onset and cessation of the attack is sudden (11). In addition, the pain reaches its maximum intensity over 5 to 15 minutes (3). The most distinctive feature of this type of headache is its clocklike regularity reported in 82% of the patients. Moreover, it can be triggered by many factors including alcohol, nitroglycerin, heat, high altitude, exercise, and strong scents such as solvents and cigarettes.

Management

Treatment of cluster headaches includes a combination of acute, transitional, and preventative medications. Additionally, lifestyle modifications can be encouraged to avoid any triggering factors such as alcohol (3).

Acute treatment

Patients with an acute attack can be treated by high-flow oxygen and triptans. Oxygen should be administered at 100% via a nonrebreather mask at a rate of 12-15 L/min for at least 20 minutes. Triptans have several routes of administration including subcutaneous, oral, and nasal, with subcutaneous being the most effective, followed by nasal and oral. However, for patients who encounter multiple attacks per day or who are unable to take the full dose of Triptan each month, the safest treatment is oxygen and noninvasive vagus nerve stimulation. Nasal lidocaine and oxygen can be given to pregnant and breastfeeding women (15).

Transitional medications

The mainstay of short-term prophylaxis is greater occipital nerve block with local anesthetic and steroids, or a course of oral steroids. Oral steroids are then tapered over three weeks to avoid potential side effects such as osteonecrosis of the hip, especially when used for a prolonged period. The use should be limited to 2 to 3 courses per year.

Preventative medications

Cluster headache can be prevented using verapamil. A typical daily maintenance dose is 480 mg to 720 mg, divided into 3 doses. High doses of verapamil should be avoided because of its ability to cause cardiac conduction abnormalities, specifically elongation of the PR interval. Therefore, ECG monitoring is required as a baseline investigation (before initiating the first dose), 10 to 14 days after each dose, and every 6 months whilst on medication. (3,11)

Other medications that have been shown to be helpful for cluster headache are topiramate, lithium, Melatonin, baclofen and valproic acid.

Refractory cases

A sleep study and pituitary laboratory studies should be considered, as well as invasive approaches. Neuromodulation is preferredpreferred because it is minimally destructive. Sphenopalatine ganglion stimulation, occipital nerve stimulation, and deep brain stimulation of the hypothalamus are invasive neuromodulation treatments for cluster headache. (3)

Patients with cluster headaches will acquire substantial but short-lasting relaxation from subcutaneous sumatriptan and high-flow oxygen, if it is not potent then indomethacin is used to rule out other TACs. In addition, brain MRI with pituitary and cavernous sinus view is the workup required for patients diagnosed with cluster headache according to European Headache Federation consensus (12). A magnetic resonance angiogram (MRA) of the head and neck can be done for patients who don't respond to verapamil. In some patient's erythrocytes sedimentation rate may be required to rule our temporal arteritis or referral to ophthalmology, dentistry, or otolaryngology may be appropriate. (3, 13, 14)

Paroxysmal Hemicrania

Paroxysmal hemicrania is less common compared to cluster headaches, and more prevalent in women. Its overall rate is 0.5 per 1000 or less, with an age of onset between 30 and 40 years. Patients with paroxysmal hemicrania are present with a severe unilateral headache. The pain is often described as throbbing, sharp, or stabbing pain localized around or behind the eye, with a similar intensity to cluster headache. It usually occurs more than 5 times a day. Furthermore, the pain is associated with ipsilateral cranial autonomic features and/or restlessness. Lacrimation is the most common autonomic symptom, as well as restlessness (16). It may be associated with migraine-like symptoms including photophobia ipsilateral to the pain and vomiting (2).

Clinical presentation

Table 2. ICHD-3 Diagnostic Criteria for Paroxysmal Hemicrania*

1. At least 20 attacks fulfilling criteria 2-5
2. Severe unilateral orbital, supraorbital, and/or temporal pain lasting 2–30 minutes.
3. Either or both of the following:
   a. At least one of the following symptoms or signs, ipsilateral to the headache:
      - Conjunctival injection and/or lacrimation
      - Nasal congestion and/or rhinorrhea
      - Eyelid edema
      - Forehead and facial sweating
      - Miosis and/or ptosis
   b. A sense of restlessness or agitation
4. Occurring with a frequency of ≥5 per day
5. Prevented absolutely by therapeutic doses of indomethacin.
6. Not better accounted for by another ICHD-3 diagnosis

* International Classification of Headache Disorders, Third Edition.

The criteria for paroxysmal hemicrania are shown in Table 1 (37)

The patient complains of pain usually located in the orbital, supraorbital and temporal areas described as throbbing or stabbing pain. Furthermore, the attack must last for a duration of 2 to 30 minutes, and pain peaks in less than 10 minutes. The pain is often accompanied by cranial autonomic features, most commonly, lacrimation. It can be triggered by alcohol, neck movements and pressure against the occiput or cervical transverse process, stress, or exercise. Patients are followed up with brain MRI and arterial imaging of the head and neck. (3, 12).

Management

Paroxysmal hemicrania attacks are too short for acute medications, thus management is focused on prevention.

The treatment begins with indomethacin, starting with a dose of 25mg taken 3 times a day over 1 to 2 weeks. The dose is then stepped up to 75mg, 3 times a day for 1 to 2 weeks (17). NSAIDS like Indomethacin have a high risk of causing gastrointestinal ulcers, so it is given along with proton pump inhibitors or histamine receptor 2 antagonist (h2 blockers). Indomethacin can also increase the risk of cardiovascular events, kidney toxicity and bleeding. Usually, patients report a new type of headache after starting the treatment (18). Once the headache improves, women of childbearing

age should stop indomethacin before pregnancy. If indomethacin is not effective other causes should be ruled out. For patients who can't tolerate indomethacin, cyclooxygenase type 2 inhibitors, verapamil, and topiramate can be used. Sphenopalatine ganglion and greater occipital nerve blocks have also been useful in treating paroxysmal Hemicrania (3, 19)

SUNCT and SUNA

SUNCT and SUNA are somewhat more common in men and have a prevalence of 0.05 to 1 in 1000, the age of onset is older in comparison with other TACs, and thus it is found in people aged between 40 to 70 years.

Patients with SUNCT and SUNA typically present with unilateral headache with orbital, supraorbital, temporal, and/or other trigeminal distribution of moderate to severe intensity. Attacks typically last from 1 to 600 seconds, occurring as single stabs, series of stabs, or in a saw-tooth pattern at least once a day and associated with ipsilateral cranial autonomic features.

The SUNCT and SUNA have similar clinical features. To differentiate between them, patients with SUNCT present with both lacrimation and conjunctival injection, while patients with SUNA may present with one or neither. Triggers are touching the area of pain, chewing, or brushing the teeth (2, 20). Work up includes brain MRI and arterial imaging of the head and neck (12). Trigeminal nerve view can also be evaluated (3).

There are two different types of SUNCT and SUNA:

1. The episodic type: patients have 2 episodes often lasting from 7 days to 1 year if left untreated, and pain remission periods of more than 3 months.
2. The chronic type: occurs with no remission periods or with remission periods lasting less than 3 months in 1 year.

Management

SUNCT and SUNA are mainly treated with Lamotrigine, taken daily with a dose ranging between 100 mg to 200 mg. The second line treatment is topiramate or gabapentin. Patients who require short-term relief can be given steroids. However, the most effective treatment is IV lidocaine given at a rate of 1 to 3.5 mg/kg/h, but IV lidocaine should be avoided in patients with cardiac conduction abnormalities. The typical protocol involves 1 week admission with continuous monitoring of the vital signs. (3)

Hemicrania continua

Hemicrania continua true prevalence is unknown, since only few cases have been reported, but it is more common in women and is found in 0.8% of the patients who complain of day-to-day headaches.3

Hemicrania continua is characterized by unilateral frontal or temporal pain that is throbbing in nature. Patients often describe the pain as a foreign body or itchy sensation of the eye. The intensity of the pain is mild or moderate. Moreover, Headache exacerbation often lasts minutes to days and is accompanied by ipsilateral cranial autonomic features as well as nausea, vomiting and photophobia (3). Triggers are alcohol, stress, and irregular sleep (11).

Hemicrania continua is divided into two types, remitting and unremitting (7):

1. Remitting: the headache is not daily or continuous and has remission periods of more than 24 hours (without treatment).
2. Unremitting: headache is daily, ongoing, and has no remission periods more than 24 hours.

Patients with hemicrania continua are followed up with brain MRI and arterial imaging of the head and neck using MRA to evaluate structural causes of chronic daily headache (12). Moreover, venous imaging using magnetic resonance venogram (MRV) is done to rule out venous sinus thrombosis, and erythrocytes sedimentation rate (ESR) is measured to exclude temporal arteritis (3).

Management

The first-line treatment of hemicrania continua is indomethacin, the starting dose is 225 mg/d for 2 weeks followed by down-titration to find the smallest effective dose for the patient. Gastro-protective agents should be prescribed as well. For patients whom indomethacin is contraindicated, other medications such as celecoxib, topiramate, gabapentin, and melatonin have been suggested as second or third-line treatment (21). Melatonin can be used as an adjunct to decrease the dosage of indomethacin (22). Effective treatment with occipital nerve blocks and botulinum, toxin have also been reported. For refractory patients, occipital nerve stimulation as well as radiofrequency of the sphenopalatine ganglion may be helpful (2).

Recent updates

In a recent placebo-controlled trial, the calcium gene-related peptide (CGRP) monoclonal antibody galacanezumab has shown effectiveness in the prevention of cluster headaches. (23) The study involved 106 participants, 49 of them received galacanezumab and 57 of them received a placebo. During the study the patients' vital signs, electrocardiograms and laboratory measures were monitored to avoid any potential side effect. Galacanezumab recipients experienced a significant reduction in the weekly frequency of attacks from week 1 to week 3 compared with placebo. 71% and 53% in the galcanezumab and placebo groups, achieved 50% reduction in headache frequency respectively. (24)

Sodium oxybate has been evaluated for the prophylaxis of cluster headaches in a small open labeled study involving four patients (25). The results proved a long-lasting improvement in frequency and intensity of both nocturnal and daytime headaches. Additionally, the treatment is dose dependent. (26)

The effectiveness of Psilocybin and Lysergic Acid Diethylamide (LSD) for the treatment of cluster headache is not well known. 53 patients were enrolled in a case study that showed promising results, 25 for LSD as a prophylactic treatment and psilocybin as both a prophylactic and acute treatment. (27)

Deep brain stimulation of the posterior hypothalamus was recently practiced treating the chronic cases of cluster headaches (28). It was also found to be effective in three cases diagnosed with SUNCT (29, 30). The surgery showed an evident and absolute decrease in attack frequency. However, the useful outcome of the surgery is not immediate and requires a variable period of 1 to 4 months to be apparent. The post-operative side effects included diplopia (31), vertigo (32), and a rarely intracerebral hemorrhage which can subsequently result in death (33, 34).

Other new surgical methods have been identified for the treatment of SUNCT and SUNA including microvascular decompression of the trigeminal nerve (9). Cases diagnosed with SUNCT and SUNA unresponsive to medical therapy, agreed on following surgical treatment, MRI imaging of their brain revealed an abnormal arterial loop compressing the trigeminal nerve. The end result of surgery was 67% of the patients were completely relieved during the follow up period of 9 to 32 months and 33% of the cases didn't improve. This concludes that patients with chronic SUNCT and SUNA with an abnormal vascular loop may benefit from surgery. (34)

A study in the UK was done to evaluate the effectiveness of noninvasive vagal nerve stimulation (nVNS) in the treatment of cluster headache for patients who are unresponsive or cannot tolerate multiple preventative medications or acute treatments. 30 patients participated in the study, out of which 29 had chronic CH and 1 patient had

episodic CH. The results have shown a notable decrease in the attack frequency, duration and severity, and no serious side effects, thus demonstrating the efficacy and safety of nVNS in CH. (35)

References

1. Newman LC. Trigeminal Autonomic Cephalalgias. www.ContinuumJournal.com
2. Burish MJ, Rozen TD. Trigeminal Autonomic Cephalalgias. Neurologic Clinics. 2019;37(4):847-869. doi: 10.1016/j.ncl.2019.07.001
3. Burish M. Cluster Headache and Other Trigeminal Autonomic Cephalalgias. 2018. http://journals.lww.com/continuum
4. Goadsby PJ, Edvinsson L. Human in Vivo Evidence for Trigeminovascular Activation in Cluster Headache Neuropeptide Changes and Effects of Acute Attacks Therapies. 1994;117. http://brain.oxfordjournals.org/
5. Schytz HW, Barløse M, Guo S, et al. Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. Cephalalgia. 2013;33(10):831-841. doi:10.1177/0333102413476370
6. Waldenlind E, Ekbom K, Wetterberg L, et al. Lowered circannual urinary melatonin concentrations in episodic cluster headache. Cephalalgia. 1994; 14:199-204.
7. Rozen TD, Fishman RS. Cluster Headache in the United States of America: Demographics, Clinical Characteristics, Triggers, Suicidality, and Personal Burden. Headache. 2012;52(1):99-113. doi:10.1111/j.1526-4610.2011. 02028.x
8. Manzoni GC, Taga A, Russo M, Torelli P. Age of onset of episodic and chronic cluster headache – a review of a large case series from a single headache centre. Journal of Headache and Pain. 2016;17(1). doi:10.1186/s10194-016-0626-9
9. Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: A meta-analysis of population-based studies. Cephalalgia. 2008;28(6):614-618. doi:10.1111/j.1468-2982.2008. 01592.x
10. Olesen J. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. doi:10.1177/0333102417738202
11. Goadsby PJ, Cohen AS, Matharu MS. Trigeminal autonomic cephalalgias: Diagnosis and treatment. Curr Neurol Neurosci Rep. 2007;7(2):117-125. doi:10.1007/s11910-007-0006-6
12. Mitsikostas DD, Ashina M, Craven A, et al. European headache federation consensus on technical investigation for primary headache disorders. Journal of Headache and Pain. 2015;17(1):1-8. doi:10.1186/s10194-016-0596-y
13. de Coo IF, Wilbrink LA, Haan J. Symptomatic Trigeminal Autonomic Cephalalgias. Current Pain and Headache Reports. 2015;19(8). doi:10.1007/s11916-015-0514-z
14. Cittadini E, Matharu MS. Symptomatic trigeminal autonomic cephalalgias. Neurologist. 2009;15(6):305-312. doi:10.1097/NRL.0b013e3181ad8d67
15. VanderPluym J. Cluster Headache: Special Considerations for Treatment of Female Patients of Reproductive Age and Pediatric Patients. Current Neurology and Neuroscience Reports. 2016;16(1):1-10. doi:10.1007/s11910-015-0610-9
16. Cittadini E, Matharu MS, Goadsby PJ. Paroxysmal hemicrania: A prospective clinical study of 31 cases. Brain. 2008;131(4):1142-1155. doi:10.1093/brain/awn010
17. Marmura MJ, Silberstein SD, Gupta M. Hemicrania continua: Who responds to indomethacin?. Cephalalgia. 2009;29(3):300-307. doi:10.1111/j.1468-2982.2008. 01719.x
18. Jürgens TP, Schulte LH, May A. Indomethacin-induced de novo headache in hemicrania continua-fighting fire with fire. Cephalalgia. 2013;33(14):1203-1205. doi:10.1177/0333102413490345
19. Zhu S, McGeeney B. When Indomethacin Fails: Additional Treatment Options for "Indomethacin Responsive Headaches." Current Pain and Headache Reports. 2015;19(4). doi:10.1007/s11916-015-0475-2
20. Benoliel R, Sharav Y, Haviv Y, Almoznino G. Tic, Triggering, and Tearing: From CTN to SUNHA. Headache. 2017;57(6):997-1009. doi:10.1111/head.13040
21. Rossi P, Tassorelli C, Allena M, Ferrante E, Lisotto C, Nappi G. Focus on therapy: hemicrania continua and new daily persistent headache. The journal of headache and pain. 2010;11(3):259-265. doi:10.1007/s10194-010-0194-3
22. Rozen TD. How effective is melatonin as a preventive treatment for hemicrania continua? A clinic-based study. Headache. 2015;55(3):430-436. doi:10.1111/head.12489
23. Belin AC, Ran C, Edvinsson L. Calcitonin gene-related peptide (CGRP) and cluster headache. Brain Sciences. 2020;10(1). doi:10.3390/brainsci10010030
24. Khatami R, Tartarotti S, Siccoli MM, Bassetti CL, Sándor PS. Long-Term Efficacy of Sodium Oxybate in 4 Patients with Chronic Cluster Headache. 2011.
25. Brandt RB, Doesborg PGG, Haan J, Ferrari MD, Fronczek R. Pharmacotherapy for Cluster Headache. CNS Drugs. 2020;34(2):171-184. doi:10.1007/s40263-019-00696-2
26. Sewell RA, Halpern JH, Pope HG. Response of cluster headache to psilocybin and LSD. Neurology. 2006;66(12):1920-1922. doi: 10.1212/01.wnl.0000219761.05466.43
27. Am S, Onta TD. The New Eng Land Jour Nal of Medicine Treatment of Patients with Persistent Symptoms and a History of Lyme Disease. 2001;345. www.nejm.org
28. Bartsch T, Falk D, Knudsen K, et al. Deep brain stimulation of the posterior hypothalamic area in intractable short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). Cephalalgia. 2011;31(13):1405-1408. doi:10.1177/0333102411409070

29. Lyons MK, Dodick DW, Evidente VGH. Responsiveness of short-lasting unilateral neuralgiform headache with conjunctival injection and tearing to hypothalamic deep brain stimulation: Case report. Journal of Neurosurgery. 2009;110(2):279-281. doi:10.3171/2008.4.17493
30. Leone M, Franzini A, Proietti Cecchini A, Mea E, Broggi G, Bussone G. Deep Brain Stimulation in Trigeminal Autonomic Cephalalgias. Neurotherapeutics. 2010;7(2):220-228. doi: 10.1016/j.nurt.2010.02.001
31. Bartsch T, Paemeleire K, Goadsby PJ. Neurostimulation approaches to primary headache disorders. Current Opinion in Neurology. 2009;22(3):262-268. doi:10.1097/WCO.0b013e32832ae61e
32. Schoenen J, di Clemente L, Vandenheede M, et al. Hypothalamic stimulation in chronic cluster headache: A pilot study of efficacy and mode of action. Brain. 2005;128(4):940-947. doi:10.1093/brain/awh411
33. Sebastian S, Schweitzer D, Tan L, Broadley SA. Role of trigeminal microvascular decompression in the treatment of SUNCT and SUNA. Current Pain and Headache Reports. 2013;17(5). doi:10.1007/s11916-013-0332-0
34. Williams M, Bazina R, Tan L, Rice H, Broadley SA. Microvascular decompression of the trigeminal nerve in the treatment of SUNCT and SUNA. Journal of Neurology, Neurosurgery and Psychiatry. 2010;81(9):992-996. doi:10.1136/jnnp.2009.182824
35. Marin J, Giffin N, Consiglio E, McClure C, Liebler E, Davies B. Non-invasive vagus nerve stimulation for treatment of cluster headache: Early UK clinical experience 11 Medical and Health Sciences 1103 Clinical Sciences. Journal of Headache and Pain. 2018;19(1). doi:10.1186/s10194-018-0936-1
36. Matharu MS, Goadsby PJ. Trigeminal autonomic cephalgias. Neurology in Practice. 2002;72(2). doi:10.1177/2049463712456355
37. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013 Jul;33(9):629-808. doi: 10.1177/0333102413485658. PMID: 23771276.
38. Alstadhaug KB, Ofte HK. Cluster headache. Tidsskr Nor Laegeforen. 2015 Aug 25;135(15):1361-4. English, Norwegian. doi: 10.4045/tidsskr.14.0824. PMID: 26315237.

Article topic: Ischemic Stroke.

Author: Zain Sarhan Alsaddi.

Editor: Yaman Oudat.

Reviewer: Ethar Hazaimeh.

Keywords: Ischemic Stroke, Neurology, Neuro-medicine, Cerebrovascular Diseases

Overview

A stroke results from a sudden cessation of sufficient blood supply to the brain. The disruption of blood supply is either due to a blockage of a main cerebral artery or a rupture in one causing it to bleed. This subsequently deprives the brain tissue of oxygen and nutrients and eventually leads to cell death within few minutes. [1]

There are three main types of strokes. The most common type is the Ischemic stroke, which accounts for 87% of all strokes. It is the consequence of an occluded cerebral artery that is clogged up by either a thrombus or an embolism. The second, less common yet more severe type is the hemorrhagic stroke, and this happens as a leaking or burst of a blood vessel. It is further subdivided into types which are intracerebral hemorrhage as well as subarachnoid hemorrhage. [7]

The third type, sometimes called a “mini stroke”, or what is more commonly known as the transient ischemic attack (TIA), the definition of a TIA has changed from time-based to tissue based. It is defined as a transient episode of neurologic dysfunction due to the focal brain, spinal cord or retinal ischemia without acute infarction. A TIA is a temporary disruption of blood flow that typically lasts a few minutes and does not cause lasting symptoms. It is important to know that a TIA is a warning sign of a future stroke and just like the other two major types of strokes, it requires emergency care. [8]

Stroke is considered the third leading cause of death in the world and tends to lead to a long-term disability and cognitive impairment. Immediate or delayed vascular cognitive impairment (VCI) or vascular dementia (VaD) was detected in about 25–30% of ischemic stroke survivors. [1, 9]

Pathogenesis And Etiology

The exact mechanism for stroke injury is not fully understood despite considerable research efforts. However, it is established that cerebral ischemia induces a cascade of inflammatory and immune reactions that encircle molecular, cellular as well as genomic events. Furthermore, the body's Immune response has been shown to play a major role in ischemic stroke progression. Neuronal damage's extent seems to correlate with the degree of innate immune activity.

After the ischemic stroke event occurrence, Pathophysiological changes take place like ionic imbalance, neuro-inflammation, excitotoxicity, and activation of microglia which contribute to neuronal death. Moreover, Ischemia induces a significant increase in microvascular density, a sign of angiogenesis and its degree is positively correlated with the survival rate of stroke patients. In addition to that, an improvement in functional outcome after ischemic stroke was found to be associated with increased angiogenesis. However, in a clinical setting, neither neuroprotection nor angiogenesis strategies showed any therapeutic benefit.

Marcet et al. discussed the impacts of inflammation in ischemic stroke and traumatic brain injury indicating that although the initial trauma that led to brain damage is most likely unsalvageable, the secondary immunologic deterioration of neural tissue gives many opportunities for therapeutic strategists. [9, 10]

Risk Factors

The risk factors for ischemic stroke mirror the risk factors of atherosclerosis and primary prevention of stroke focuses on the identification and modification of risk factors. They are divided into non-modifiable and modifiable risk factors. [2, 11, 12]

Non-modifiable risk factors

Age: In general, stroke is known to be a disease of aging. Its incidence increases as the person grows older, with the incidence doubling after age 55 for each decade. [34]

Gender: The relationship of sex to stroke risk mainly depends on age. Previously the risk of stroke was thought to be higher in men, however recent studies and research suggest otherwise indicating that, at younger ages, women have a higher risk of stroke, and this is related to pregnancy and the postpartum state that follows it as well as hormonal factors like the use of contraception. Furthermore, it is believed to be higher in women due to their longer lifespan when compared to men. [34] A study that was performed in 8 different European countries discovered that the risk of stroke increased in men and women yearly by 9% and 10% respectively. [35]

Race: when compared to their white counterparts, African Americans showed that they are at twice the risk of stroke incidence, and have a higher mortality associated with stroke.[36]

Family history

Genetic risk factors [33]

1. Single gene disorders that primarily cause stroke
2. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
3. Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL)
4. Familial amyloid angiopathy
5. Collagen 4 (COL4A1) mutations
6. Ehlers-Danlos Type 4
7. Fabry Disease
8. Marfan syndrome
9. Mitochondrial encephalopathy with lactic acid and stroke- like episodes (MELAS)
10. Sickle cell disease
11. Smooth Muscle Alpha-Actin (ACTA2) mutation associated disorders

Modifiable risk factors

Hypertension

It is the most important modifiable risk factor for stroke. With the increasing age, the risk of developing hypertension also increases regardless of the hypertension status. Alongside medical hypertension control, the hypertensive patients are also encouraged to engage in lifestyle behavioral modifications, such as dieting and increase physical activity. These two methods of hypertension remain the most effective strategies in reducing stroke risk. [37]

Diabetes mellitus is an independent risk factor that increases the risk for stroke by 2 folds. [38]

Dyslipidemia

Stroke incidence also increases with an increase in total cholesterol level and low LDL. It causes thick and hard plaque to build up in your arteries and thus clog them. Subsequently reducing the flow of blood and leading to an infarct.

Cardiovascular diseases

Cardiovascular issues like Atrial fibrillation (AF) for the longest, the relation between AF and stroke has been initially assumed to be due to blood stasis in the fibrillating left atrium that causes a thrombus to form and embolize to the brain. However, recent data challenged this assumption stating that, First, around one-third of patients do not show evidence of AF until after a stroke despite being preceded by months of continuous monitoring of the heart-rhythm.[39] Second, other types of arrhythmias like PSVT have also been linked to stroke risk. Finally, those with a genetic mutation that is associated with AF like the gene for Natriuretic Peptide Precursor A, can have a stroke even before the onset of AF.[40]

Kidney Disease

The risk of stroke is high in patients with chronic kidney disease, especially in patients on dialysis

Diet and Exercise

Low Physical inactivity is linked with many health issues, stroke included. In those who are physically active, their risk of stroke is lesser than those who are not active. The relationship is explained by the fact that exercising decreases blood pressure, reduces excess body fat and subsequently diabetes. [41]

Smoking

It is also considered a major risk factor for stroke, which nearly doubles the stroke risk. [42]

Alcohol

Heavy drinking associated with an increased risk of ischemic stroke. [43]

Substance abuse

Like cocaine, heroin, amphetamines, and ecstasy have been shown to increase the risk of both ischemic and hemorrhagic stroke. [44]

A continuously updated well known and widely used score that is used to estimate a 10-year stroke risk stratified by the gender is the Framingham Stroke Risk Profile (FSRP). It combines the various predictors of stroke like age, systolic blood pressure, anti-hypertensive therapy, diabetes, cigarette smoking, left ventricular hypertrophy by electrocardiogram, and the presence of cardiovascular disease (coronary heart disease,

peripheral vascular disease, congestive heart failure). [45] There are other scores, which were developed from different population samples, that determine the risk of stroke and include additional metrics like physical disabilities, depression, and marital status. [46]

Clinical Presentation and Complications

Stroke typically presents a sudden rapid onset of neurological deficits. The signs and symptoms that the patient presents vary depending on the area of the brain is involved and whether a main artery or its branches are affected. Thus, the clinical presentation is influenced by the size of the infarct.

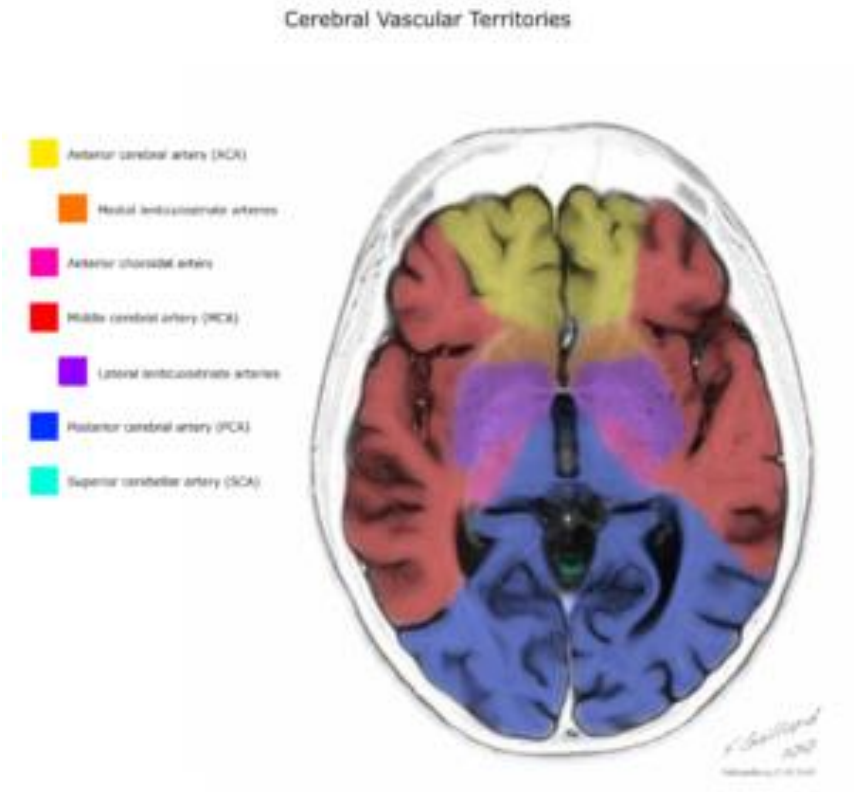


Figure 1. Case courtesy of Assoc Prof Frank Gaillard.

Focal weakness and speech disturbance are the two most common physical findings of ischemic stroke. Other signs and symptoms of ischemic stroke that are also considered as most common are listed below: [13, 14, 15]

Symptoms

- Subjective arm weakness
- Subjective leg weakness

- Self-reported speech disturbance
- Subjective facial weakness
- Arm paresthesia
- Leg paresthesia
- Headache
- Non-orthostatic dizziness
- Seizure

Signs

- Arm and/or leg paresis
- Aphasia
- Dysphasia or dysarthria
- Hemiparetic or ataxic gait
- Facial paresis
- Eye movement abnormality or diplopia
- Visual field defect

The person might be present with speech problems and will have difficulty understanding what others are saying and may be confused. Face droopiness, which is the weakness of one side of the face, is another visible clinical finding. It is usually accompanied by vision problems in either one or both eyes. The person may have blurred, blackened or double vision. Moreover, he may develop a sudden weakness or feeling of numbness or the arm or leg. This often affects just one side of the body. To test this, ask the person to raise both arms over the head at the same time. If one arm begins to fall, it may be a sign that they are having a stroke. They may also have a problem with maintaining balance, so they will present with troubled walking. Furthermore, a sudden, severe headache that is accompanied by vomiting, dizziness or altered consciousness, may indicate that they are having a stroke.

Workup and Diagnosis

History and physical examination are the initial steps to diagnosing stroke. The most vital component to obtain from history is when was the person last seen normal and with no symptoms. Stroke treatment is most effective when given as soon as possible as it has a narrow time window of effectiveness. Quick assessment of the person with suspected acute ischemic stroke is made to determine the most suitable intervention among the available options as well as further assess the eligibility for thrombolysis.[16]

Usually, The National Institutes of Health Stroke Scale (NIHSS) provides a quantitative measure of stroke-related neurologic deficit, its widely used as a clinical assessment tool to evaluate acuity of stroke patients, determine proper treatment, and predict patient

outcome. The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the patent's ability to answer questions and perform activities. Ratings for each item are scored on a 3- to 5-point scale, with 0 as normal, and there is an allowance for untestable items. Scores range from 0 to 42, with higher scores indicating greater severity.

Immediate Diagnostic Studies:

1. Non contrast brain CT or brain MRI
2. Blood glucose
3. Serum electrolytes and renal function tests
4. Electrocardiograph
5. Markers of cardiac ischemia
6. Complete blood count, including platelet count
7. Prothrombin time/international normalized ratio
8. Activated partial thromboplastin time
9. Oxygen saturation

For Selected patients, the following can be done:

1. Hepatic function tests.
2. Chest radiography if a lung disease is suspected.
3. Lumbar puncture (if subarachnoid hemorrhage suspected and head CT negative for blood).
4. Electroencephalogram, if seizure is suspected.

Despite the desire to know the results of these tests before giving the recombinant tissue plasminogen activator, thrombolytic therapy should not be delayed while awaiting the results unless a bleeding abnormality or thrombocytopenia is clinically suspected, or the patient has received heparin or warfarin used unknown anticoagulants.

In order to be able to distinguish between ischemic stroke and hemorrhagic stroke as well as rule out other types of central nervous system lesions, neuro-images must be done. However, the choice of neuroimaging depends on its availability at the hospital, eligibility to be used for acute stroke intervention and if there are any patient contraindications present.

Clinically, the diagnosis of stroke is usually accurate but determining the pathological type of stroke is best achieved by conducting an early brain computed tomography (CT) scan or by performing an autopsy, for confirmation. A CT scan is not only needed to rule in the diagnosis of ischemic stroke, but also to exclude the presence of certain

stroke mimics and detect hemorrhage. In other words, a normal CT scan does not rule out the diagnosis of ischemic stroke. [16]

Although MRI scans have better resolution when compared to CT scans, they are less available and more expensive than CT scanners. Also, MRI scans cannot be performed on people who have certain types of implanted devices (e.g., pacemakers) or in those who are claustrophobic. In addition, CT scans have a 95- 100% sensitivity of detecting subarachnoid blood in the first 12 hours; however, over time as the subarachnoid blood is cleared, its sensitivity greatly decreases to about 50% after one week and is not detectable by CT after a period of about two to three weeks, unlike ischemic stroke. [24, 27, 28]

According to the guidelines, it is recommended that an MRI scan is ordered if it can be obtained as quickly as a CT scan and more importantly if the patient is presented within the time window of acute stroke intervention. If not, then CT is the go-to test because when the history and physical is consistent for acute, its treatments should not wait for detailed imaging. [26]

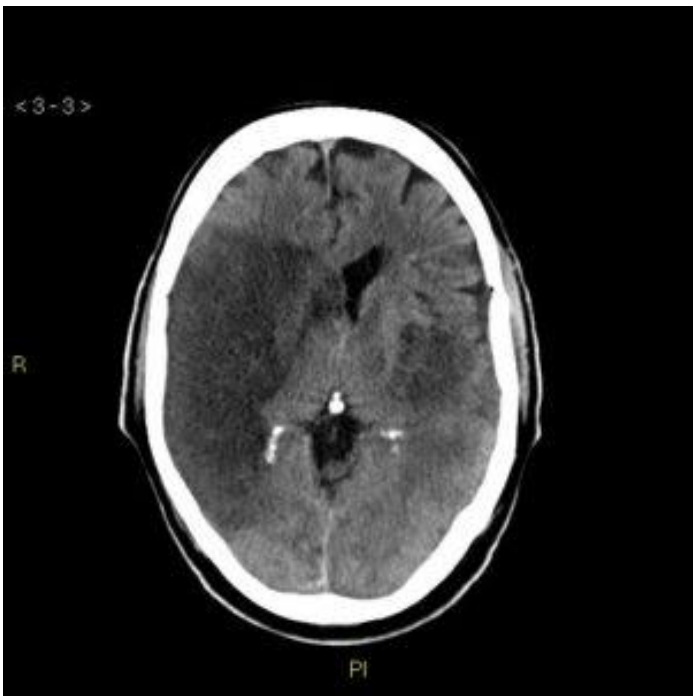


Figure 3. Middle Cerebral Artery (MCA) infarct 29 Case courtesy of Dr. Sajoscha Sorrentino.

Factors such as poor public awareness of symptoms, lack of quick detection by emergency medical services (EMS), poor coordination between EMS and the hospital emergency department or delay of diagnosis upon arrival at the emergency department are considered factors that contribute in the failure to provide prompt diagnosis and treatment of acute ischemic stroke.

Stroke Mimics and Differential Diagnosis

When evaluating a patient presenting with a suspected stroke, other possible conditions associated with the central nervous system must be ruled out as there is a large number of stroke- mimickers [18,20-23]

- Seizures, status epilepticus in particular, can mimic a stroke
- Subdural hematomas (SDH), intracranial hemorrhages (ICH), or masses
- Demyelinating disorders like multiple sclerosis
- Toxic and metabolic differentials like Sepsis, uremia, hypo and hyperglycemia, hyponatremia, and hyperkalemia can all cause symptoms that resemble a stroke
- Complex migraines
- Systemic infections, the most common source is the chest.
- Dementia.
- Psychiatric disorders are like panic disorders.
- Could be associated with alcohol intoxication, an adverse effect to a secondhand medication or other encephalopathy

References

- Gibson CL. Cerebral ischemic stroke: Is gender important? J Cereb Blood Flow Metab. 2013; 33:1355–61.
- Tsivgoulis, Georgios et al. “Recent Advances in Primary and Secondary Prevention of Atherosclerotic Stroke.” Journal of stroke vol. 20,2 (2018): 145-166. doi:10.5853/jos.2018.00773
- Nogles TE, Galuska MA. Middle Cerebral Artery Stroke. [Updated 2020 Aug 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556132/
- Matos Casano HA, Tadi P, Ciofoaia GA. Anterior Cerebral Artery Stroke. [Updated 2020 Jul 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537333/
- Toyoda K. Anterior cerebral artery and Heubner's artery territory infarction. Front Neurol Neurosci. 2012; 30:120-2.
- . Case courtesy of Dr Henry Knipe, <ahref="https://radiopaedia.org/">Radiopaedia.org. From the case rID: 39328
- Mozzafarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al., on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation 2016;133(4): e38–360.
- American Heart Association/American Stroke Association. TIA (Transient Ischemic Attack)external icon. Accessed October 6, 2016.
- Kalaria RN, Akinyemi R, Ihara M. Stroke injury, cognitive impairment and vascular dementia. Biochim Biophys Acta. 2016;1862(5):915-925. doi: 10.1016/j.bbadis.2016.01.015
- Su H. Inflammation and genetic factors in stroke pathogenesis. Neuroimmunol Neuroinflamm. 2017; 4:260-262. doi:10.20517/2347-8659.2017.22
- Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, Mensah GA, Norrving B, Shiue I, Ng M, Estep K, Cercy K, Murray CJL, Forouzanfar MH., Global Burden of Diseases, Injuries and Risk Factors Study 2013 and Stroke Experts Writing Group. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 2016 Aug;15(9):913-924.

- O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, Lopez-Jaramillo P, Damasceno A, Langhorne P, McQueen MJ, Rosengren A, Dehghan M, Hankey GJ, Dans AL, Elsayed A, Avezum A, Mondo C, Diener HC, Ryglewicz D, Czlonkowska A, Pogosova N, Weimar C, Iqbal R, Diaz R, Yusoff K, Yusufali A, Oguz A, Wang X, Penaherrera E, Lanas F, Ogah OS, Ogunniyi A, Iversen HK, Malaga G, Rumboldt Z, Oveisgharan S, Al Hussain F, Magazi D, Nilanont Y, Ferguson J, Pare G, Yusuf S., INTERSTROKE investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016 Aug 20;388(10046):761-75.
- Interobserver agreement for the bedside clinical assessment of suspected stroke.Hand PJ, Haisma JA, Kwan J, Lindley RI, Lamont B, Dennis MS, Wardlaw JM Stroke. 2006 Mar; 37(3):776-80
- The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument. Nor AM, Davis J, Sen B, Shipsey D, Louw SJ, Dyker AG, Davis M, Ford GA Lancet Neurol. 2005 Nov; 4(11):727-34.
- Is this patient having a stroke? Goldstein LB, Simel DL JAMA. 2005 May 18; 293(19):2391-402.
- Yew, Kenneth S, and Eric Cheng. "Acute stroke diagnosis." American family physician vol. 80,1 (2009): 33-40.
- Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. N Engl J Med. 2006;354(4):387–396. Medline.
- Hand PJ, Kwan J, Lindley RI, Dennis MS, Wardlaw JM. Distinguishing between stroke and mimic at the bedside: the brain attack study. Stroke. 2006;37(3):769–775. Medline.
- Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack–proposal for a new definition. N Engl J Med. 2002;347(21):1713–1716. Medline.
- Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. Arch Neurol. 1995;52(11):1119–1122. Medline
- Hemmen TM, Meyer BC, McClean TL, Lyden PD. Identification of nonischemic stroke mimics among 411 code strokes at the University of California, San Diego, Stroke Center. J Stroke Cerebrovasc Dis. 2008;17(1):23–25. Medline.
- Hosseininezhad M, Sohrabnejad R. Stroke mimics in patients with clinical signs of stroke. Caspian J Intern Med. 2017 Summer;8(3):213-216.
- Vilela P. Acute stroke differential diagnosis: Stroke mimics. Eur J Radiol. 2017 Nov; 96:133-144. doi: 10.1016/j.ejrad.2017.05.008. Epub 2017 May 5. PMID: 28551302.
- Kidwell CS, Chalela JA, Saver JL, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA. 2004;292(15):1823–1830. Medline.
- Fiebach JB, Schellinger PD, Gass A, et al. Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. Stroke. 2004;35(2):502–506. Medline. [PubMed] [Google Scholar]
- Adams HP, Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists [published corrections appear in Stroke. 2007;38(6): e38, and Stroke. 2007;38(9): e96] Stroke. 2007;38(5):1655–1711. Medline.
- Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. N Engl J Med. 2006;354(4):387–396. Medline.
- Masdeu JC, Irimia P, Asenbaum S, et al. EFNS guideline on neuroimaging in acute stroke. Report on an EFNS task force. Eur J Neurol. 2006;13(12):1271–1283. Medline.
- Case courtesy of Dr Sajoscha Sorrentino, Radiopaedia.org. From the case rID: 14777
- Merwick Á, Werring D. Posterior circulation ischaemic stroke. BMJ. 2014;348 (may19 33): g3175. doi:10.1136/bmj.g3175
- Searls DE, Pazdera L, Korbel E et-al. Symptoms and signs of posterior circulation ischemia in the new England medical center posterior circulation registry. (2012) Archives of neurology. 69 (3): 346-51. doi:10.1001/archneurol.2011.2083
- Navarro-Orozco D, Sánchez-Manso JC. Neuroanatomy, Middle Cerebral Artery. [Updated 2020 Aug 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526002/
- Boehme AK, Esenwa C, Elkind MS. Stroke Risk Factors, Genetics, and Prevention. Circ Res. 2017;120(3):472-495. doi:10.1161/CIRCRESAHA.116.308398
- Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: Heart disease and stroke statistics--2012 update: A report from the American heart association. Circulation. 2012; 125:188–197
- Asplund K, Karvanen J, Giampaoli S, Jousilahti P, Niemela M, Broda G, et al. Relative risks for stroke by age, sex, and population based on follow-up of 18 european populations in the morgam project. Stroke. 2009; 40:2319–2326.
- Cruz-Flores S, Rabinstein A, Biller J, Elkind MS, Griffith P, Gorelick PB, et al. Racial-ethnic disparities in stroke care: The American experience: A statement for healthcare professionals from the American heart association/American stroke association. Stroke. 2011; 42:2091–2116.

- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The jnc 7 report. JAMA. 2003; 289:2560–2572.
- Banerjee C, Moon YP, Paik MC, Rundek T, Mora-McLaughlin C, Vieira JR, et al. Duration of diabetes and risk of ischemic stroke: The northern manhattan study. Stroke; a journal of cerebral circulation. 2012; 43:1212–1217.
- Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation. 2014; 129:2094–2099.
- Disertori M, Quintarelli S, Grasso M, Pilotto A, Narula N, Favalli V, et al. Autosomal recessive atrial dilated cardiomyopathy with standstill evolution associated with mutation of natriuretic peptide precursor a. Circulation. Cardiovascular genetics. 2013; 6:27–36.
- . Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med. 1991; 151:1141–1147.
- Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, et al. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. Stroke. 2008; 39:2439–2443.
- Hillbom M, Numminen H, Juvela S. Recent heavy drinking of alcohol and embolic stroke. Stroke. 1999; 30:2307–2312.
- Brust JC. Neurological aspects of substance abuse. Butterworth-Heinemann; Philadelphia, Pa: 2004.
- Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: A risk profile from the framingham study. Stroke. 1991; 22:312–318.
- Boehme AK, Esenwa C, Elkid MS. Stroke Risk Factors, Genetics, and Prevention. Circ Res. 2017;120(3):472-495. doi:10.1161/CIRCRESAHA.116.308398

Article topic: Multiple Sclerosis.

Author: Najla O. Khalil.

Editor: Aroob Awwad.

Reviewer: Ethar Hazaimeh.

Keywords: Multiple sclerosis, MS, RRMS, SPMS, McDonald criteria, Demyelinating disorders.

Overview and Epidemiology

Multiple sclerosis (MS) is a chronic disabling inflammatory disease that leads to demyelination and neurodegeneration in the central nervous system (1). MS causes different signs and symptoms depending on the amount and type of nerves involved. Some people may experience symptom-free periods between attacks whilst others might lose their ability to walk altogether, as it can reach sensory, motor, visual, and autonomic systems (2). The course of multiple sclerosis is quite unpredictable, as physicians can never accurately predict who will be spared from the devastating and disabling outcomes of the disease or who will have benign symptoms. The true cause of this altered connection between the brain and the rest of the body is still not fully understood, but it has been hypothesized that environmental factors and genetic susceptibility could be related to the pathogenesis of multiple sclerosis (3). MS is currently incurable but the ongoing search for a cure will always be underway.

MS mostly manifests in young adults; affecting 2.3 million people worldwide (as of 2013), with a female: male ratio of 2:1. It is most common in North America (140 cases per 100,000) followed by Europe (108 cases per 100,000), East Asia (2.2 cases per 100,000), and finally, sub-Saharan Africa (2.1 cases per 100,000). It is also the leading cause of non-traumatic disability in young adults (4). This high prevalence seen in North America and Europe could be related to the higher income, thus, the availability of neurologists and the ease of accessing imaging modalities leads to an easier and more accurate diagnosis.

Classification and Diagnostic Criteria

As of 2021, the 2017 McDonald criteria is being used for diagnosing multiple sclerosis with high accuracy. It is described in more detail below.

The 2017 revisions to the McDonald Criteria:

There is no specific test to diagnose MS so a complete neurological exam and medical history must be obtained from the patient, as it mainly relies on ruling out other diseases. The more unusual the symptoms are the more difficult it is to accurately diagnose the patient with multiple sclerosis. The most recent tool for the diagnosis of MS is the 2017 McDonald criteria and is described in (Table 1) and continues to be revised and updated. High-income countries use the 2017 McDonald criteria to diagnose MS, which relies on clinical presentations and MRI findings. It facilitates earlier diagnosis compared to other diagnostic criteria which mostly rely on clinical findings. This is especially helpful for those with clinically isolated syndrome (CIS). In lower- and middle-income countries, diagnosis of MS relies more on clinical diagnostic criteria and less on MRI evidence, as it is not easily accessible. This makes it even more difficult to distinguish between MS and other inflammatory demyelinating diseases (1,4,5).

Clinical Presentation	Additional Evidence Needed for MS Diagnosis
Two or more attacks AND EITHER objective clinical evidence of 2 or more lesions OR objective clinical evidence of one lesion with reasonable historical evidence of a prior attack	None; clinical evidence is enough. Additional evidence such as brain MRI is desirable but must be consistent with MS.
Two or more attacks with objective clinical evidence of 1 lesion	Dissemination in space exhibited by either MRI or further clinical attack involving different part of the CNS.
One attack with objective clinical evidence of 2 or more lesions	Dissemination in time demonstrated by either MRI or additional clinical attack or the presence of CSF-specific oligoclonal bands.
One attack with objective clinical evidence of 1 lesion (also known as clinically isolated syndrome).	Dissemination in space exhibited by either an additional clinical attack involving a different CNS site or MRI. AND Dissemination in time demonstrated by either MRI or additional clinical attack or the presence of CSF-specific oligoclonal bands.

Table 1: The 2017 McDonald criteria for MS diagnosis (6)

If the 2017 McDonald Criteria is fulfilled with no better explanation for the clinical presentation, MS will be diagnosed. However, if MS is suspected through CIS but the 2017 McDonald Criteria are not met, MS will be a possible diagnosis until a better explanatory diagnosis is met during the evaluation.

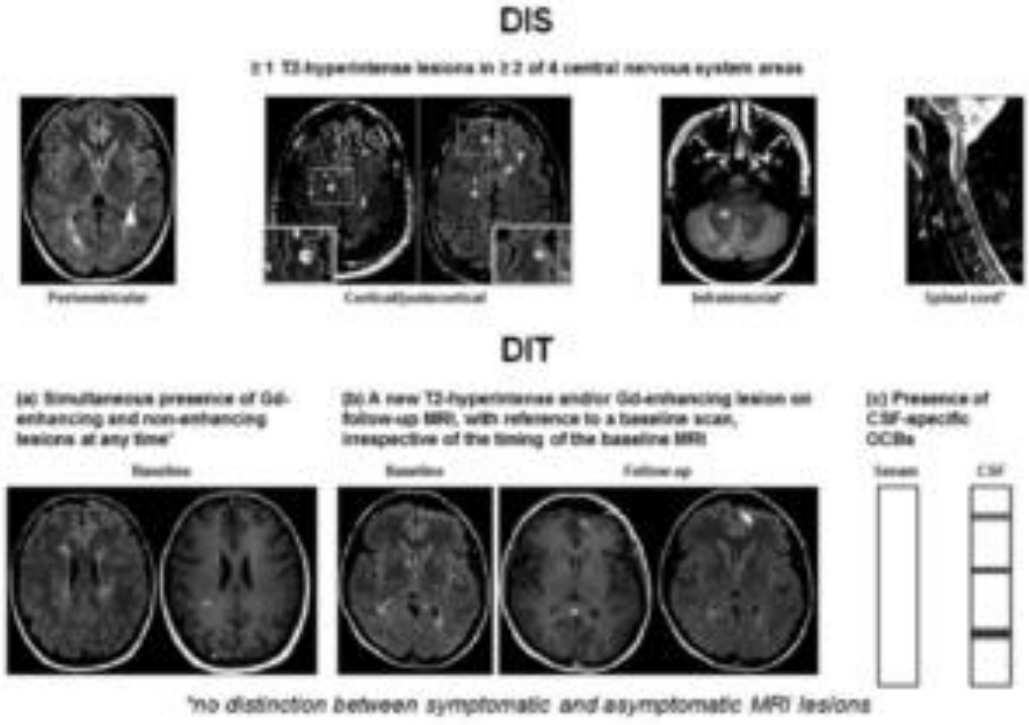
Brain MRI should be done in all patients for whom the diagnosis of MS is being considered unless MRI isn't possible. In addition, spinal cord MRI/ CSF examination must be performed in patients with inadequate previous findings supporting MS, patients with a presentation other than typical CIS, or presenting with atypical features. If tests are negative, alternative diagnoses should be considered before diagnosing MS.

Clinical diagnosis based on objective clinical findings for two attacks is the best. In the absence of documented objective neurological findings, historical evidence for one past attack can include events with symptoms and evolution characteristics of a previous inflammatory demyelinating attack. However, at least one attack should be supported by objective findings. objective evidence is described in panel 1.

The presence of CSF-specific oligoclonal bands is not exactly diagnostic for dissemination in time but can substitute for the requirement for demonstration of this measure.

MRI dissemination criteria in space and time are described in panel 1.

Panel 1: Understanding dissemination in space, time and Objective clinical/paraclinical evidence.
1. **Dissemination in space (DIS)** can be defined as the development of lesions in more than one distinct anatomical location within the central nervous system. It requires the detection of at least one T2-hyperintense lesion in at least two of these areas in the CNS; periventricular, juxtacortical, infratentorial, and the spinal cord. This can be proven if there is enough clinical evidence of these two lesions/areas affected, or if there is clinical evidence of one lesion and historical evidence of a second lesion as mentioned in the table above.
2. **Dissemination in time (DIT)** reduces misdiagnosis of monophasic illness by requiring that the CNS lesions develop over time, this means comparing a patient's baseline MRI with a follow-up MRI. What must be seen in DIT are gadolinium-enhancing and non-enhancing lesions, or the appearance of a new T2-hyperintense or gadolinium-enhancing lesion on a follow-up MRI. The revised 2017 McDonald criteria added that a positive CSF for two or more CSF-specific oligoclonal bands can be a substitute for DIT in patients with no baseline MRI, this suggests that oligoclonal bands are an independent predictor of a second clinical attack (7).
3. **Objective clinical/paraclinical** evidence is the association between the CNS lesion and the typical presenting symptom of the MS attack. It could be an abnormal neurological exam, MRI, OCT or neurophysiological exam that corresponds with the symptoms and anatomical location of the lesion. Examples include optic disc pallor, p100 latency prolongation on visual evoked potentials, T2 hyperintensity of the optic nerve or a relative afferent pupillary defect in a patient presenting with optic neuritis symptoms, internuclear ophthalmoplegia in a patient presenting with diplopia, or hemisensory syndrome suggesting myelitis (6,7).



(Figure 1) Criteria for dissemination in space and dissemination in time in a patient with clinically isolated syndrome (a) a simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time, (b) a new T2-hyperintense and/or gadolinium-enhancing lesion on a follow-up MRI scan, with reference to a baseline scan, irrespective of timing of baseline of the MRI, or (c) Presence of cerebrospinal fluid-specific oligoclonal bands (lower row)(8)

Typical clinical presentation

MS is predominantly seen in early adulthood; this subsequently affects their quality of life which leads to patients seeking medical help and answers.

Multiple sclerosis can affect any part of the central nervous system making the signs, symptoms, and course of the disease extremely variable amongst patients. This adds to the difficulty of incorrect diagnosis because some MS symptoms may overlap with other demyelinating diseases. Imaging that is consistent with dissemination in space and time based on the 2017 McDonald criteria alongside typical symptoms are key components in accurately diagnosing MS. So, to accurately diagnose a patient with multiple sclerosis they must present with at least two attacks of typical MS syndromes; this includes optic neuritis, myelitis, brainstem, and cerebellar syndromes (7).

Optic neuritis

Optic neuritis is defined as an inflammation of the optic nerve. It has multiple different causes, one of those causes includes multiple sclerosis. It is more predominantly seen in white people. The diagnosis and treatment depend on the cause because of the many differential diagnoses for optic neuritis (9). The patient will present with subacute blurry vision or even loss of vision, which can be associated with pain and evolves over hours to days (10). Optic neuritis in multiple sclerosis is caused by acute demyelination of the optic nerve, it is the presenting symptom in about a fifth of MS patients (11). These patients typically present with an acute, unilateral, painful decrease in visual acuity that peaks within a few days and subsides within a few weeks (10).

There is an association between the incidence of optic neuritis and multiple sclerosis risk variant HLA-DRB1*1501, suggesting the relation between risk factors for MS and the cause of optic neuritis in areas of the world where MS is commonly seen. There is also evidence that relapsing CNS demyelinating diseases that are characterized by optic nerve involvement have a relation with serum aquaporin-4 (AQP4) autoantibodies (12,13).

Myelitis

Patients with MS may present with a band-like tightening sensation around their chest or abdomen (MS “hug”), this is a typical symptom of myelitis, suggesting the involvement of the posterior columns of the spinal cord. Myelitis in MS is usually partial and subacute. This corresponds with the typical imaging and neuropathological appearance of MS, which is the involvement of patchy asymmetric inflammatory-demyelinating lesions in the spinal cord. By contrast, complete transverse myelitis is the Inflammation and demyelination across both sides of one segment or level of the spinal cord resulting in symptoms of neurological disconnection and dysfunction below the level of the demyelinating area, such as impairment of motor, sensory, bowel, or bladder functions, it may also be accompanied with pain and absent reflexes (14–16).

Brainstem and cerebellar syndromes

The brainstem is commonly involved in multiple sclerosis. Around 15% of patients with PPMS will present with progressive cerebellar or brainstem syndrome, characterized most prominently by gradual worsening ataxia (17). The most common brainstem presentation in MS is diplopia (cranial nerves III, IV, VI involvement) due to internuclear ophthalmoplegia which may be bilateral, facial weakness or myokymia (cranial nerve VII involvement), vertigo (cranial nerve VIII or a lesion anywhere in the vestibular pathways), or bulbar (medullary) symptoms such as dysphagia, dysarthria, tongue weakness (cranial nerves IX, X, XII involvement) and ataxia (cerebellar lesion).

Facial weakness due to facial nerve involvement may accompany eye movement abnormalities. Usually due to multiple localizations, including the brainstem, cervical cord, and subcortical and cortical sensory pathways (18).

Diplopia may also suggest sixth cranial palsy and is not specific to MS. Third cranial nerve palsy is more suggestive of other causes. If the patient presents with persistent hiccups, nausea, or vomiting it's more suggestive of neuromyelitis Optica spectrum disorder (NMOSD) which is caused by a lesion in the area postrema. Usually, when a patient presents with hyperacute cerebellar symptoms this suggests a vascular cause rather than MS.

Patients may present with symptoms that are less specific to multiple sclerosis and may be seen in other demyelinating diseases. However, this doesn't disapprove the need for further evaluation and testing for MS.

Some atypical symptoms:

Motor symptoms

Weakness due to the involvement of the corticospinal tract can be seen in about 89% of MS patients at some point in the course of their disease. Weakness is often accompanied by symptoms of an upper motor neuron lesion, such as hyperreflexia, positive response in Babinski and Chaddock reflexes, and spasticity (19). In the absence of weakness; stiffness, spam, cramping, and gait impairment may be present. When there are spinal cord or brainstem lesions, tonic seizures may occur which are usually confined to one side of the body (20).

Cognitive impairment

Cognitive impairment is seen in all subtypes of multiple sclerosis, although, it is more common in progressive MS than in relapsing MS (1). Cognitive impairment accompanies other symptoms of MS so it cannot be used alone to diagnose MS, as other CNS lesions may also be accompanied by cognitive impairment.

Imbalance, Bowel and bladder dysfunction, Sensory impairment, Depression, and Fatigue are some other atypical symptoms of MS.

A patient with MS will usually present with attacks of neurological dysfunction including numbness, tingling, weakness, vision loss, gait abnormalities, incoordination, imbalance, and bladder dysfunction. This does not mean that every patient will present

with the same symptoms as they vary considerably between patients, depending on where in the CNS is the neurological involvement. If the patient has RRMS then these symptoms would be completely gone, and they'd be neurologically stable between attacks.

Phenotypic subtypes of multiple sclerosis

There are three phenotypic subtypes of multiple sclerosis: relapsing-remitting MS (RRMS), progressive MS (primary or secondary), and clinically isolated syndrome (CIS) (21).

Clinically isolated syndrome (CIS) is when a patient presents with MS after a single event or attack. These patients present with an acute demyelinating attack, but the MRI conducted does not fully meet the criteria for RRMS. In this case, DIS can be satisfied with clinical evidence of only one lesion incorporating the patient's MRI, or if there is any evidence of another lesion during neurological examination.

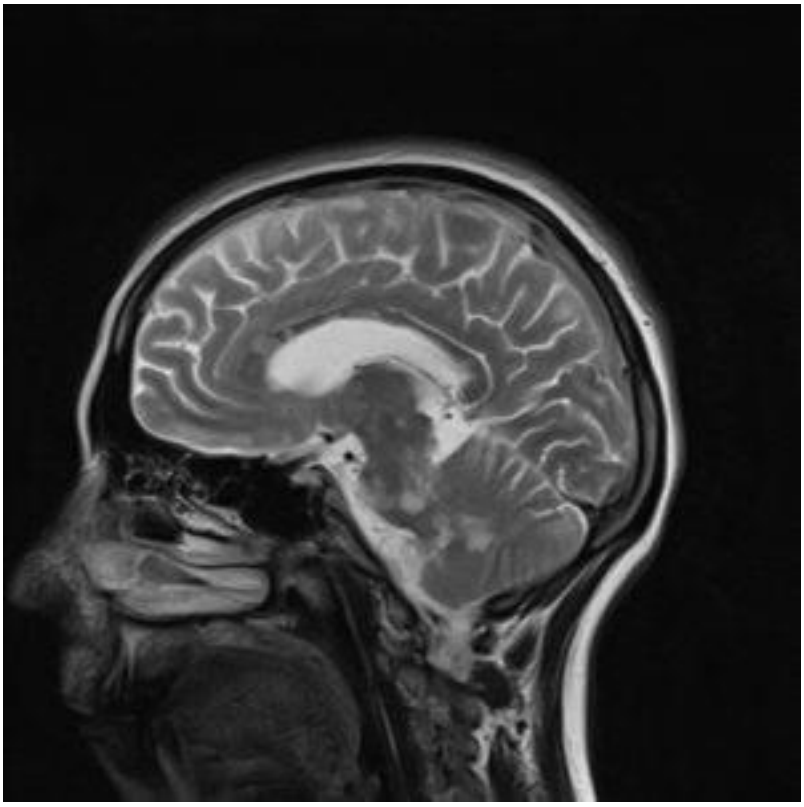
A CIS diagnosis does not exclude the possibility of CIS progressing into RRMS, or any other classification of MS. A brain MRI at the presentation of the first demyelinating attack can predict the development of MS, as well as the type and extent of disability eventually (1,22,23).

85% of patients diagnosed with MS showed RRMS features characterized by recurring symptoms followed by their total or partial disappearance (4). MS relapses/attacks occur due to demyelination evolving over 24 hours which persists from days to weeks, patients then relatively improve (2). Relapsing-remitting MS is defined by the International Panel on the Diagnosis of multiple sclerosis as 'patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with a duration of at least 24 h, in the absence of fever or infection' (8).

This pattern of RRMS can become increasingly progressive after an initial relapse in 50% of untreated patients 10-15 years into the course of the disease, this stage is defined as secondary-progressive MS (24). It is usually difficult to define the point of transition. SPMS is characterized by a gradual decline in neurological functions, usually involving the areas of the CNS that were previously involved during the relapse stage. At first, patients with SPMS experience will have relapsing and remitting symptoms, but over time it turns into an insidious progression of the disease without any remission.

Some research is shedding light on better characterizing the point of transition from RRMS to SPMS or even predicting it by imaging and laboratory biomarkers as a way of distinguishing between SPMS and RRMS. These biomarkers are IL-17 and INF-gamma, which are pro-inflammatory cytokines increased in RRMS. TGF-beta1 is another

biomarker, it is decreased in RRMS and has immunosuppressant activity. This could potentially prove that different cytokines are responsible for RRMS compared to SPMS but is still under research and needs further validation (25).



(Figure 2) extensive brainstem and cerebellar involvement, case courtesy of Dr Bita (26)

Primary Progressive multiple sclerosis (PPMS) represents 10-15% of MS cases and is characterized at the time of disease onset by a slow decline in neurological functions and has no relapses or remissions. In contrast, SPMS usually occurs after relapse and not from the beginning of the disease. (27)

Table 2. 2017 McDonald criteria for the diagnosis of MS in patients with a disease course characterized by having been progressed from onset (primary progressive multiple sclerosis) (28)

Primary progressive multiple sclerosis can be diagnosed based on cases with · ≥1 year of disability progression which can be determined either prospectively or retrospectively.
With two of the following:

- ≥1 T2-hyperintense lesion characteristic of multiple sclerosis in one or more of the following regions: periventricular, cortical or juxtacortical, or infratentorial
- ≥2 T2-hyperintense lesions in the spinal cord
- Presence of CSF-specific oligoclonal bands

Pathogenesis and Etiology

The exact pathogenesis of multiple sclerosis is still not fully understood but there has been recent evidence proving the relationship between genetics (e.g., HLA DRB1*15:01) and MS. other factors that contribute to the development of MS include environmental factors (e.g., vitamin D deficiency), immunizations, emotional and physical stressors, diet and lifestyle (e.g., Cigarette smoking). Environmental factors have a bigger role in susceptibility to MS contrary to what most people think. Both the innate and adaptive immune systems are known to contribute to the pathogenesis of MS. New treatment targets are now being developed due to the discovery that B cells have a major role in the disease (29).

Environmental risk factors

Vitamin D deficiency, infectious agents, and cigarette smoking have been shown to contribute to the pathogenesis of multiple sclerosis. Some physicians say that obesity might also be a risk factor but that it could be due to vitamin D deficiency. Therefore, correcting vitamin D levels is important in reducing the risk of MS. On the other hand, Vitamin D deficiency in neonates hasn't shown any correlation with the incidence of MS. The incidence of the disease increases with the increase of smoking duration, this is seen more in men than in women (30–34).

Exposure to infectious agents; *usually Epstein-Barr virus infection as a young adult* increases the risk of developing the disease. Others may say that the *hygiene hypothesis* is related. The more pathogens and infectious agents a growing child are exposed to, the less likely they are to develop allergies and autoimmune diseases when they are older. Because of that, some may say that people who were raised in conditions where they were not exposed to many pathogens have a higher risk of developing MS later on in life (35,36).

Genetic factors

It has been observed that the incidence of Multiple sclerosis increases within families. This suggests that genetics have a significant role in the development of MS. Carriers of DRB1*15:01 are three times more likely to develop MS than non-carriers of this allele; it

is known as the strongest association with MS susceptibility. Recent population-based studies have estimated a sibling of a patient with MS has a sevenfold increase in the risk of developing the disease. Environmental factors have also been shown to interact with genetic risk (e.g., HLA), thus increasing the overall risk of developing MS (37). More specifically, the HLA region on chromosome 6 has been noted to have significant associations with most autoimmune diseases in humans. And ever since the 1970s, the connection between serotype DR2 (HLA-DR15 and HLA-DR16 serotype) and multiple sclerosis has been established (38,39).

In addition to clear MS genetic variants, a genome-wide association study (GWAS) has identified the first two non-HLA genetic variants with minor effects, including genes in IL2RA and IL7RA (40).

Work up and Diagnosis

Diagnosis of MS requires a combination of findings during clinical history, neurological exam, MRI, and the exclusion of other possible inflammatory demyelinating diseases. CSF, urodynamic studies of the bladder, and OCT are usually supportive for the diagnosis. Some patients may come between attacks so all the symptoms might not be present, some may present with persisting fatigue or heat sensitivity between attacks so that is something physicians must take into account (41).

MRI

The most sensitive tool to diagnose MS is MRI, it detects brain and spinal cord lesions. It is also necessary for the exclusion of other diseases (42). The presence or absence of red flags in the MRI will help guide the differential diagnosis, which includes metabolic diseases, toxicity, malignancy, and infiltrative processes (1). This is important in preventing the misdiagnosis of multiple sclerosis as any other demyelinating disease. The specific guidelines for the clinical implementation of the brain and spinal cord MRI were mentioned above (McDonald criteria 2017).

Lumbar puncture

CSF may show the presence of IgG oligoclonal bands in CSF that are absent in serum, with an elevated IgG index in multiple sclerosis patients (43), The presence of CSF-specific oligoclonal bands doesn't demonstrate dissemination in time but can substitute the requirement for demonstration of this measure.

Treatment and management

Treatment of multiple sclerosis (MS) is divided into 3 groups: treatment of exacerbations, slowing the progression of the disease with disease-modifying therapies (DMTs), and symptomatic relief therapies.

Relapse management

A real relapse occurs when a patient experiences a new symptom not experienced before. A pseudo-relapse is when an acute attack of physical or emotional stress exacerbates their already existing symptoms. Treatment of acute relapses aims to speed recovery from neurologic deficits, alleviate the severity of the attack and lessen or eliminate potentially persistent deficits.

Corticosteroids are the first-line treatment modality for MS relapses. The use of corticosteroids over time shortens the time to recover from an acute attack, reduces symptoms, and improves motor function (44). If patients don't respond to corticosteroids and are still experiencing severe relapses, plasmapheresis should be used (45). Although relapses are uncommon during pregnancy, if it occurs, intravenous immunoglobulin can be used safely during pregnancy. Methylprednisolone can also be given to pregnant women as it is the preferred drug because it is metabolized before crossing the placenta (46,47).

Treatment with low doses of carbamazepine or related agents often provides rapid and substantial relief for motor symptoms of MS (48).

Disease-Modifying Therapies

There is no cure for multiple sclerosis, so the aim is to reduce the progression of the disease. There are several disease-modifying therapies (DMTs) available, an example of DMTs (are Interferon Beta, Glatiramer Acetate, Natalizumab, Fingolimod, Dimethyl Fumarate).

Prognosis

MS on its own is rarely fatal, but the secondary complications of MS-like difficulties swallowing, respiratory infections, and bladder infections may decrease the patient's life expectancy by 10-15 years. However, with the continuous development of newer therapies; these complications may be outdated.

References

1. Sand IK. Classification, diagnosis, and differential diagnosis of multiple sclerosis. Curr Opin Neurol. 2015;28(3):193–205.
2. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. Clin Med J R Coll Physicians London. 2017;17(6):530–6.

3. Correale J, Gaitán MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. Brain. 2017;140(3):527–46.
4. Msif. Atlas of MS 2013: Mapping Multiple Sclerosis Around the World. Mult Scler Int Fed. 2013;1–28.
5. Brownlee WJ, Swanton JK, Altmann DR, Ciccarelli O, Miller DH. Earlier and more frequent diagnosis of multiple sclerosis using the McDonald criteria. J Neurol Neurosurg Psychiatry. 2015;86(5):584–5.
6. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Position Paper Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. 2018;17(February).
7. Solomon BAJ. Diagnosis, Differential Diagnosis, and Misdiagnosis of Multiple Sclerosis. 2019;(1):611–35.
8. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011 Feb;69(2):292–302.
9. Toosy AT, Mason DF, Miller DH. Optic neuritis. Lancet Neurol [Internet]. 2014;13(1):83–99. Available from: http://dx.doi.org/10.1016/S1474-4422(13)70259-X
10. The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group. Arch Ophthalmol (Chicago, Ill 1960). 1991 Dec;109(12):1673–8.
11. Balcer LJ. Clinical practice. Optic neuritis. N Engl J Med. 2006 Mar;354(12):1273–80.
12. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet (London, England). 2004 Dec;364(9451):2106–12.
13. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med. 2005;202(4):473–7.
14. Cordonnier C, de Seze J, Breteau G, Ferriby D, Michelin E, Stojkovic T, et al. Prospective study of patients presenting with acute partial transverse myelopathy. J Neurol. 2003 Dec;250(12):1447–52.
15. Bourre B, Zéphir H, Ongagna J-C, Cordonnier C, Collongues N, Debette S, et al. Long-term Follow-up of Acute Partial Transverse Myelitis. Arch Neurol [Internet]. 2012 Mar 1;69(3):357–62. Available from: https://doi.org/10.1001/archneurol.2011.949
16. Miller DH, Weinshenker BG, Filippi M, Banwell BL, Cohen JA, Freedman MS, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler. 2008 Nov;14(9):1157–74.
17. Miller DH, Leary SM. Primary-progressive multiple sclerosis. Lancet Neurol. 2007 Oct;6(10):903–12.
18. Miller DH, Chard DT, Ciccarelli O. Clinically isolated syndromes. Lancet Neurol [Internet]. 2012;11(2):157–69. Available from: http://dx.doi.org/10.1016/S1474-4422(11)70274-5
19. Swingler RJ, Compston DA. The morbidity of multiple sclerosis. Q J Med. 1992 Apr;83(300):325–37.
20. MATTHEWS WB. Tonic seizures in disseminated sclerosis. Brain. 1958 Jun;81(2):193–206.
21. Lublin FD. New multiple sclerosis phenotypic classification. Eur Neurol. 2014;72(suppl 1):1–5.
22. O'Riordan JI, Thompson AJ, Kingsley DP, MacManus DG, Kendall BE, Rudge P, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain. 1998 Mar;121 (Pt 3:495–503.
23. Tintoré M, Rovira A, Río J, Nos C, Grivé E, Téllez N, et al. Baseline MRI predicts future attacks and disability in clinically isolated syndromes. Neurology. 2006 Sep;67(6):968–72.
24. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology. 1996 Apr;46(4):907–11.
25. Pasquali L, Lucchesi C, Pecori C, Metelli MR, Pellegrini S, Iudice A, et al. A clinical and laboratory study evaluating the profile of cytokine levels in relapsing remitting and secondary progressive multiple sclerosis. J Neuroimmunol. 2015 Jan; 278:53–9.
26. Extensive brainstem and cerebellar involvement.
27. Hawker K. Progressive multiple sclerosis: characteristics and management. Neurol Clin. 2011 May;29(2):423–34.
28. Carroll WM. 2017 McDonald MS diagnostic criteria: Evidence-based revisions. Vol. 24, Multiple sclerosis (Houndmills, Basingstoke, England). England; 2018. p. 92–5.
29. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet [Internet]. 2018;391(10130):1622–36. Available from: http://dx.doi.org/10.1016/S0140-6736(18)30481-1
30. Marrie RA. Environmental risk factors in multiple sclerosis aetiology. Lancet Neurol. 2004 Dec;3(12):709–18.
31. Ramanujam R, Hedström A-K, Manouchehrinia A, Alfredsson L, Olsson T, Bottai M, et al. Effect of Smoking Cessation on Multiple Sclerosis Prognosis. JAMA Neurol. 2015 Oct;72(10):1117–23.
32. Ascherio A, Munger KL. Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention-An Update. Semin Neurol. 2016 Apr;36(2):103–14.
33. Ascherio A, Munger KL, White R, Köchert K, Simon KC, Polman CH, et al. Vitamin D as an early predictor of multiple sclerosis activity and progression. JAMA Neurol. 2014 Mar;71(3):306–14.
34. Ueda P, Rafatnia F, Bäärnhielm M, Fröbom R, Korzunowicz G, Lönnerbro R, et al. Neonatal vitamin D status and risk of multiple sclerosis. Ann Neurol. 2014 Sep;76(3):338–46.
35. Levin LI, Munger KL, Rubertone M V, Peck CA, Lennette ET, Spiegelman D, et al. Temporal relationship between elevation of epstein-barr virus antibody titers and initial onset of neurological symptoms in multiple sclerosis. JAMA. 2005 May;293(20):2496–500.
36. Bach J-F. The Effect of Infections on Susceptibility to Autoimmune and Allergic Diseases. N Engl J Med [Internet]. 2002 Sep 19;347(12):911–20. Available from: https://doi.org/10.1056/NEJMra020100
37. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol [Internet]. 2016;13(1):26–36. Available from: http://dx.doi.org/10.1038/nrneurol.2016.187

38. Inoko H, Kulski JK. An update of the HLA genomic region, locus information and disease associations: 2004. 2004;631–49.
39. Patsopoulos NA, Barcellos LF, Hintzen RQ, Schaefer C, Duijn CM Van, Noble JA, et al. Fine Mapping the Genetic Association of the Major Histocompatibility Complex in Multiple Sclerosis: HLA and Non-HLA Effects. 2013;9(11).
40. Hafler DA, Compston A, Sawcer S, Lander ES, Daly MJ, De Jager PL, et al. Risk alleles for multiple sclerosis identified by a genomewide study. N Engl J Med. 2007 Aug;357(9):851–62.
41. Gelfand JM. Multiple sclerosis: Diagnosis, differential diagnosis, and clinical presentation. [Internet]. 1st ed. Vol. 122, Handbook of Clinical Neurology. Elsevier B.V.; 2014. 269–290 p. Available from: http://dx.doi.org/10.1016/B978-0-444-52001-2.00011-X
42. Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: progress and challenges. Lancet (London, England). 2017 Apr;389(10076):1336–46.
43. Huss AM, Halbgebauer S, Öckl P, Trebst C, Spreer A, Borisow N, et al. Importance of cerebrospinal fluid analysis in the era of McDonald 2010 criteria: a German-Austrian retrospective multicenter study in patients with a clinically isolated syndrome. J Neurol. 2016 Dec;263(12):2499–504.
44. Frohman EM, Shah A, Eggenberger E, Metz L, Zivadinov R, Stüve O. Corticosteroids for multiple sclerosis: I. Application for treating exacerbations. Neurother J Am Soc Exp Neurother. 2007 Oct;4(4):618–26.
45. Cortese I, Chaudhry V, So YT, Cantor F, Cornblath DR, Rae-Grant A. Evidence-based guideline update: Plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2011 Jan;76(3):294–300.
46. Ferrero S, Pretta S, Ragni N. Multiple sclerosis: management issues during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2004 Jul;115(1):3–9.
47. Winkelmann A, Rommer PS, Hecker M, Zettl UK. Intravenous immunoglobulin treatment in multiple sclerosis: A prospective, rather-blinded analysis of relapse rates during pregnancy and the postnatal period. CNS Neurosci Ther. 2019 Jan;25(1):78–85.
48. Espir ML, Millac P. Treatment of paroxysmal disorders in multiple sclerosis with carbamazepine (Tegretol). J Neurol Neurosurg Psychiatry. 1970 Aug;33(4):528–31.

Article Topic: Intracerebral Hemorrhage (ICH).

Author: Mohammad Ahmad Sawaftah.

Editor: Omar Jbarh.

Reviewer: Ethar Hazaimeh.

keywords: Cerebrovascular accident, hemorrhagic stroke, intracerebral hemorrhage.

Overview and Epidemiology:

Stroke is an acute vascular injury of the brain tissue, causing impaired blood delivery either due to ischemia or hemorrhage (intracerebral hemorrhage ICH and subarachnoid hemorrhage) ([1]. It accounts for the major numbers of deaths annually and is also a leading cause of disability globally [2].

In 2017, more than 100 million cases of stroke were reported worldwide, around 80% of them were ischemic stroke, and the rest were classified as hemorrhagic stroke (17.9 million cases of intracerebral hemorrhage and 9.3 million cases of subarachnoid hemorrhage). Although intracerebral hemorrhage does not have the highest prevalence rate, it does have the highest mortality rate compared to the other types (around 50% of stroke deaths) [3].

Intracerebral hemorrhage is defined as bleeding inside the brain's parenchymal tissue, its spectrum of presentation is wide and varies depending on the blood vessel supplying the site of the lesion. It could be motor or somatosensory deficit, loss of consciousness, cognitive dysfunction, headache, psychological changes, etc. The presentation does not differentiate the type being ischemia or bleeding, that's why non-contrast CT is essential, to determine the etiology and subsequently the management [4].

Pathogenesis and Etiologies

Trauma

Direct blood vessels injury that could be anywhere in the brain.

Hypertension

The main cause of ICH in adults affecting the small vessels is due to long standing hypertension, causing fibrinoid necrosis and lipo-hyalinosis of the vessel walls, making it weak and leaky [4].

Amyloid angiopathy

It is the main cause of spontaneous ICH in elderly, affecting small vessels due to amyloid deposition with aging, making the blood vessels weaker and fragile [5].

Arteriovenous malformations

The main cause of spontaneous ICH in children [6].

Iatrogenic

Reperfusion therapy after ischemic stroke can be complicated by reperfusion injury, one of these injuries could be hemorrhage [7][8].

CNS tumors

ICH is a common consequence of brain tumors, could be due to tumor cells invading the cerebral blood vessels, or vascular endothelial growth from the tumor itself. More common in metastatic brain lesions (Thyroid papillary carcinoma, Hepatocellular carcinoma), but primary brain tumors can cause it as well (pituitary adenoma, polycystic astrocytoma, glioblastoma) [9][10].

Vasculitis

An inflammation of cerebral vessels can be Primary angiitis of CNS (without involvement of systemic vasculitis) or secondary vasculitis (with vasculitis affecting other organs like SLE, RA, Bechet disease) [11].

Risk Factors

1. **Hypertension.** [4]
2. **Smoking.** [12]
3. **Low LDL and cholesterol:** although hyperlipidemia is a risk factor for ischemic stroke, low LDL and cholesterol are considered risk factors for ICH. [13]
4. **Bleeding tendency:** as a result of using anticoagulation drugs, especially warfarin and Tissue plasminogen activator *(*tPA) which have a higher risk of causing ICH than direct oral anticoagulants ([14]. Coagulopathies as well (inherited coagulopathies, neoplasia related coagulopathy, acute leukemia, etc.) [15].
5. **Substances and drugs**: like cocaine or amphetamines [16].
6. **Age**: due to higher risk of having hypertension [4] and amyloid angiopathy [5].
7. **Male gender** [12].
8. **High alcohol consumption** [12].
9. **Chronic kidney disease:** low glomerular filtration rate of the kidney is associated with increased intracerebral hemorrhage [17].
10. **Genetic factors: although** the genetic factor is considered a weak influencer on ICH cases, APOE (seen in many ethnicities) and PMF1 (more in Europe) genes are counted [18].

Clinical presentations and complications

Cerebrovascular accident presentations are somehow classical، and it couldn't be determined whether it is the ischemic or hemorrhagic type, it could be widely scattered according to the affected blood vessel and the area that is supplied by that vessel, on the other hand it could consist of multiple symptoms and signs depending on how much the hematoma has spread .The presentation could consist of headache ،loss of consciousness ،altered mental status, hypersomnia, cognitive disturbances, psychological problems [4] focal and neurological deficit; cranial nerves motor or sensory function loss motor, or somatosensory defects.

Intracerebral hemorrhage is divided according to the location of the hemorrhage into lobar (cortical and subcortical areas) and non-lobar (deep brain structures; like thalamus, Pons, or cerebellum) [19]:

- **Lobar ICH** is caused due to cerebral amyloid angiopathy, AV malformations, tumors and less commonly hypertension, commonly seen in elderly people. Presentation is according to the affected cortical lobe. Visual problems if occipital lesions are the ones affected, sensory loss due parietal lobe involvement, hearing, and language dysfunction if temporal lobe, and decrease in memory function along with emotional and personality disturbance in frontal bleeding

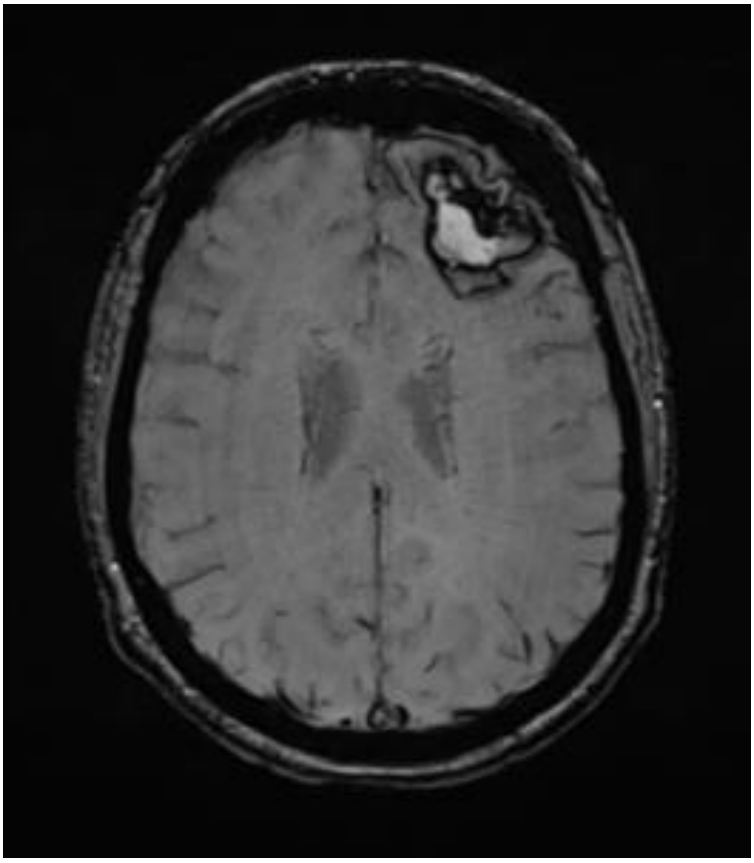


Figure 1: T1 weighted MRI showing a lobar Intracerebral hemorrhage ICH (20)

- **Non-lobar ICH** is also referred to as Hypertensive intracerebral hemorrhage. Mainly affects the internal capsule and basal ganglia, but also seen at the cerebellum and brain stem.
  Presentation is according to the area of the brain affected, internal capsule lesions will cause motor or sensory defect or both, motor voluntary control and movement impairment is seen in basal ganglia hemorrhage cases, vertigo and ataxia are linked to cerebellar bleeding, hypersomnia and motor or sensory symptoms are seen in thalamic hemorrhages.

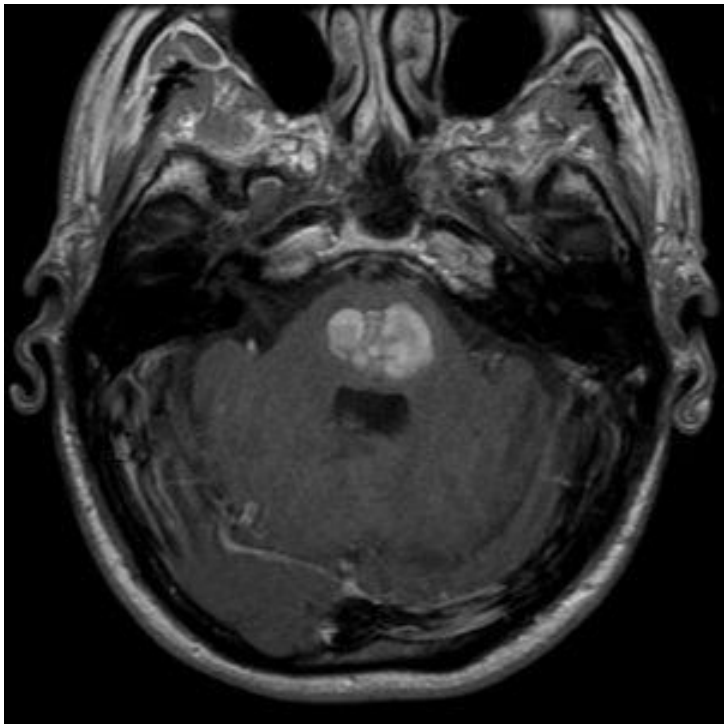


Figure 2: T1 weighted MRI showing pontine hemorrhage, which is considered as deep or non-lobar Intracerebral hemorrhage ICH (21).

Along with the clinical presentation of the ICH, possible complications can also happen and participate with the clinical picture overall:

1. **Brain edema and elevated intracranial pressure:** either during the first day around the bleeding area and is associated with the hematoma expansion, or after several weeks [22]. High ICP happens due to brain edema, large hematoma, or hydrocephalus, presents as headache, dilated pupils, and confusion, and sometimes Cushing's triad can also be seen (hypertension, bradycardia, and irregular respirations) [23].

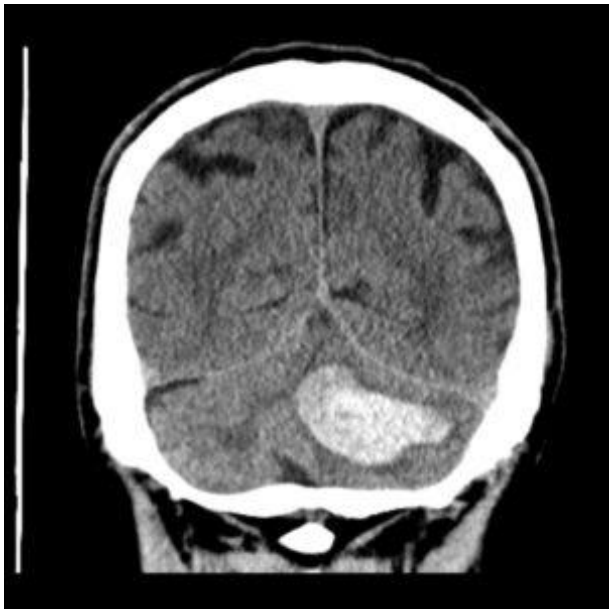


figure3: acute cerebellar hemorrhage surrounded by vasogenic edema (24).

2. **Cerebral ventricles compression and hydrocephalus and IVH:** presents with vomiting, headache, and visual impairment.
   Happens due to hemorrhage compressing the CSF pathway or intraventricular hemorrhage and may require shunting of the CSF in some cases [23].
3. **Hematoma expansion:** presents as deterioration of the case presentation and new neurological impairment, commonly seen during the first day, especially those on anticoagulants [23].
4. **Seizures: more** frequently seen in cortical and subcortical hemorrhages, could be early due to irritations of the cerebral cortex, or later on due to scaring of the cortex [25].
5. **Infection:** respiratory and UTI are commonly seen post ICH, respiratory infection is very important and highly correlated with the mortality rate, happens due to coma, intubation, and dysphagia [26].
6. **Deep venous thrombosis:** ICH is frequently complicated with DVT especially in Asian ethnic group and females [27].

Workup and diagnosis

Although stroke diagnosis is clinical, distinguishing between the types of strokes is hard using the clinical presentation alone. Hence, further investigations are important as a workup for ICH patients:

- Laboratory tests: platelets count to find if there is a low platelets level. [15] PT and PTT: searching for coagulopathy. [15]
- Drug screening: should be suspected in young adults. [16]
- Serum glucose: hypo or hyperglycemia should be corrected. [41]

- EEG: to detect any epileptiform waves [25].

Imaging modalities [28]:

Non-contrast CT scan

Non-contrast CT is found to be very practical and very sensitive, making it the imaging modality of choice in acute stroke that can differentiate ischemic from hemorrhagic strokes. This is a very crucial step in these cases because the management is going to be different from ischemic stroke (thrombolytics are contraindicated is this case). Hyperdense lesions on CT represent the hemorrhagic sites, in very acute stages of the case, and what makes it more practical is that it also detects the extension of the bleeding volume along with the site of the lesion, and possible complications can be revealed as well.

Figure 4: frontal lobe Intracerebral hemorrhage caused by coagulopathy (29).

Volume calculations

ABC/2 method is a commonly used method to estimate the ICH volume and was found to be very predictable to the outcome of the patient:
1- A is the longest diameter of the lesion.
2- B is the perpendicular diameter of the hemorrhage to A.
3-C is the number of the CT slices that show the hemorrhage multiplied by the number of slices.

If the estimated volume was more than 30mL, in that case there is a high possibility for a poor outcome. Although ABC/2 method is practical and useful in real practice, it still has its own falls. It assumes that the hemorrhage is ellipsoid with smooth dimensions,

and not all the hemorrhages have regular or smooth edges, in fact all the hemorrhages will have irregularities, especially ICH due to oral coagulation drugs or coagulopathies, that puts the method in overestimation error.

Some would use Alternatives to ABC/2 formula such as 2.5ABC/6 in order to decrease the overestimation error and improve the accuracy [30].

CT scan and lesion aging and complications:

Regarding the aging of the hemorrhage, CT is also helpful during this part of the assessment using Hounsfield units. For example, during the first 2 days of the hemorrhage the CT will reveal a hyperdense lesion, and sometimes in large hematomas especially coagulopathy related or post-thrombolytic therapy ones it can show blood-fluid levels, which are horizontal lines easily differentiated and separate hypodense bloody serum layered above hyperdense settled blood, that could be seen on CT scan or MRI early on. One of the early markers that could be detected in the early 72 hours is the peripheral edema that appears as a hypodense area surrounding the lesion itself. Those early changes are frequently detected before the lesion's density decreases with time and lesions size shrink down.

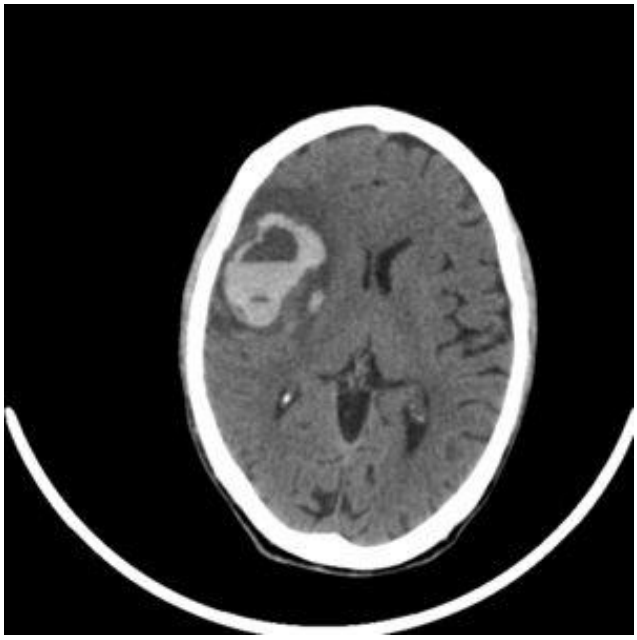


Figure 5: an early onset of ICH showing a blood-fluid level is evident that may be due to coagulation disorder or anticipating, with peripheral edema surrounding the hemorrhage (31).

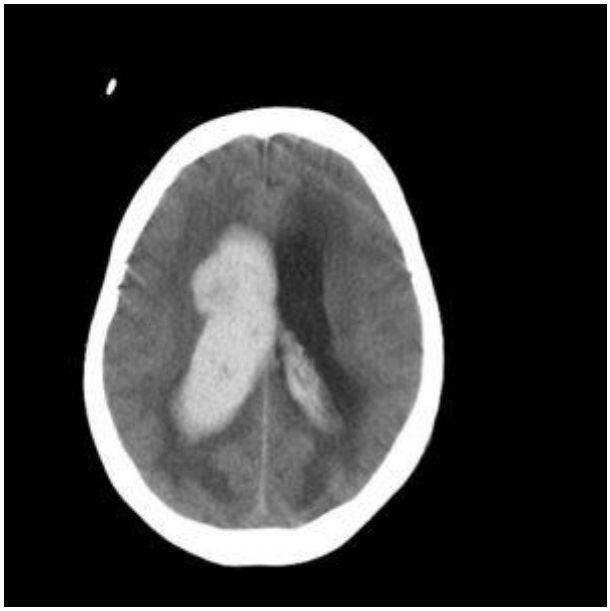


Figure 6: intraventricular hemorrhage due to ICH extension (32).

CT scan can also be helpful in identifying some complications after the ICH, like IVH and hydrocephalus
secondary to ICH extension, and are associated with bad outcomes of cases.

CT angiography (CTA)

CTA is usually done in cases when vascular pathology is suspected, such as AV malformation or tumor that might cause the hemorrhage especially in lobar ICH, young age or absence of significantly known risk factors.

Figure 7B: AV malformation that caused ICH in a young patient revealed by CTA axial section (33).

Figure 7 A: AV malformation that caused ICH in a young patient revealed by CTA sagittal section (33).

Spot sign

Showing contrast enhancement at the lesion itself is called a spot sign. It has a very predictive outcome to the case, because the risk of hematoma expansion occurring increases when it appears, especially during the first 3 hours of symptom onset, appearance of spot sign increases the mortality rate as well.

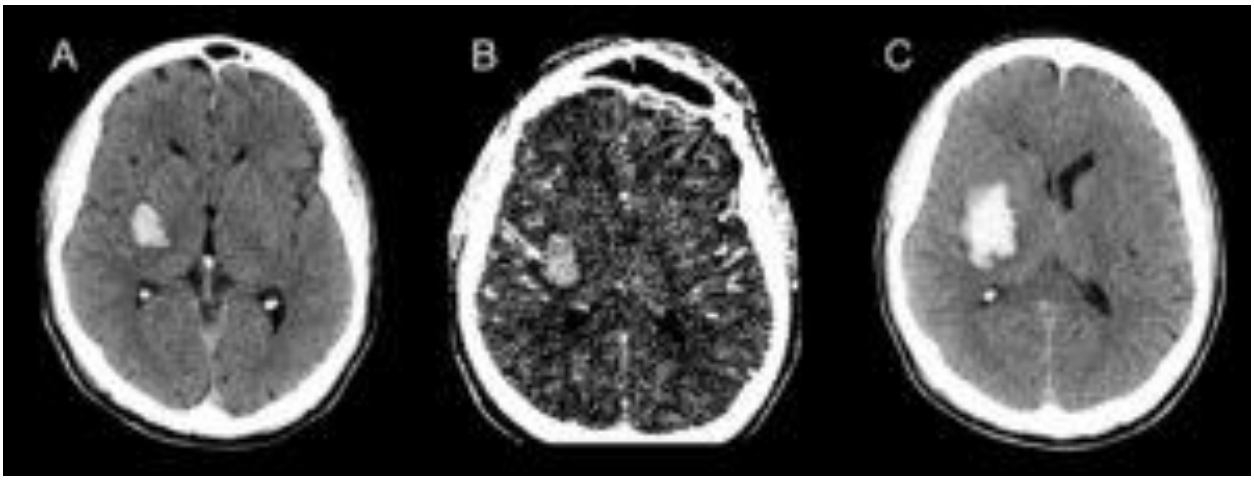


Figure 8: A: non contrast CT showing hemorrhagic lesion; B: CTA showing the spot sign, which is a hyperdense spot inside the hemorrhagic lesion; C: hemorrhagic expansion after the spot sign has appeared (34).

MRI Brain

Although NCCT is more practical, and sometimes there are certain difficulties resulting in MRI not being an option, such as pacemaker placement and so on. MRI is still a sensitive tool for diagnosis of ICH, even 20 minutes after the onset of symptoms. In fact, susceptibility-weighted or gradient echo MRI are considered more sensitive than NCCT in subacute cases and is the best modality to detect the actual aging of the ICH lesion, due to high sensitivity of molecular changes of hemoglobin in the lesion.

Aging of the lesion using MRI [35]:

MRI is sensitive to hemoglobin changes inside the brain's parenchyma, the composition of the lesion will form, either intracellular oxyhemoglobin (during the first 24 hours), intracellular deoxyhemoglobin (from days 1-3), intracellular methemoglobin (after day 3 till day 7), extracellular methemoglobin (from days 7-28), or hemosiderin (>28 days).

Those molecular changes are important because they will cause the radiological changes on the MRI at T1 or T2 sequence as the following:

1. **Hyperacute stage** (before 24 hours): lesion will appear as isointense lesion at T1, isointense-hyperintense at T2.
2. **Acute stage** (from days 1-3): lesion will stay isointense at T1, however at T2 it will appear hypointense.
3. **Early subacute stage** (from days 3-7): lesion becomes hyperintense at T1, although it will stay hypointense at T2.
4. **Late subacute stage** (from days 7-28): lesion is hyperintense at both T1 and T2.
5. **Chronic stage** (after day 28): the intensity of both MRI sequences will drop over time.

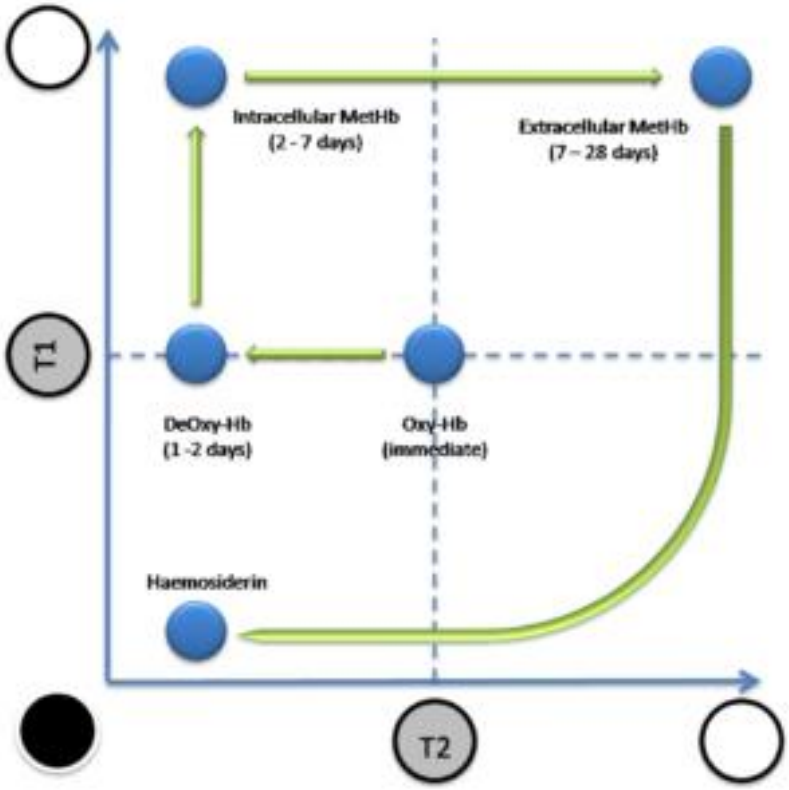


Figure 9: this graph shows the hemoglobin color changes in T1 and T2 over time.

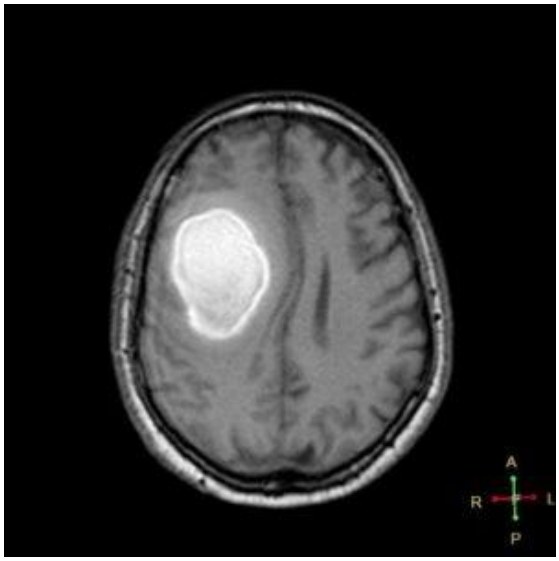


figure 10 A: subacute hypertensive ICH in T1 sequence (36).

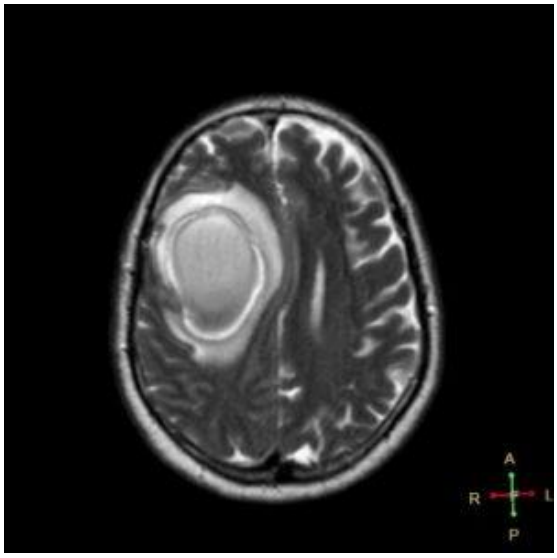


Figure 10 B: subacute hypertensive ICH in T2 sequence (37).

Figures 10A and f10B are showing the same lesion for the same patient at the same time ،during this subacute phase where methemoglobin is extracellular (between day 7 and day 14), both sequences are hyperintense MRI also has a high capability to detect the underlying causes of the hemorrhages such as AV malformations or tumors, making it a very useful imaging option in lobar ICH, young patients with no clear risk factors directed towards a certain etiology and micro bleeds that are related to vascular pathologies like hypertensive ICH and CAA that could not be detected easily by CT.

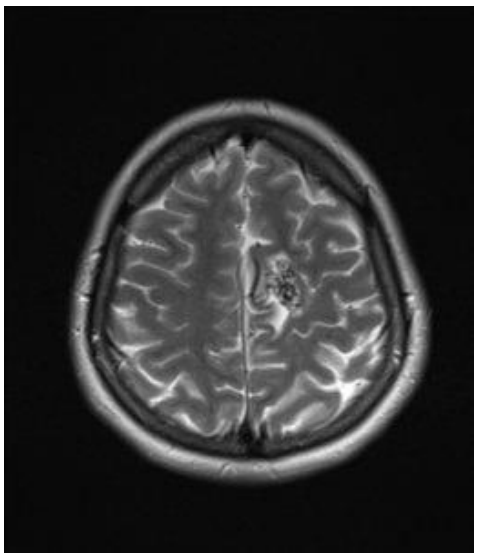


figure 11: This is a T2 weighted MRI showing AV malformation at the current section for a patient that had a hemorrhagic stroke (38).

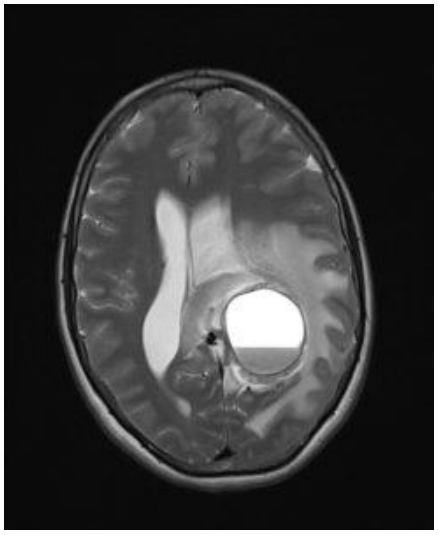


Figure 12: Cystic glioblastoma with cerebral hemorrhage(39).

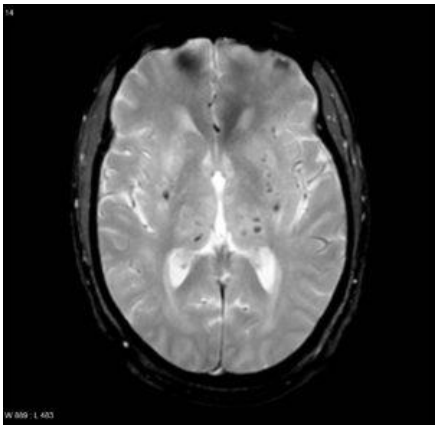


Figure 13: Microbleeds due to chronic hypertension, which are silent small cerebral hemorrhages, a sign for vascular pathology due to hypertension or CAA (40).

Treatment and Management

1. **Cardiopulmonary support:** management initially should be focused on Airway, breathing, circulation and neurological deficit. Cardiopulmonary support is important, and screening for possible MI is required since in such cases patients may have concurrent MI, shock, etc. [41][42].
2. **Intubation should be taken in consideration** to secure the airways in patients with a high risk of aspiration, or when Po2 < 60 mmHg or Pco2 > 50 mmHg [41][42].
3. **Neurological assessment and Glasgow coma scale** as a baseline for follow up and to get an idea about the severity and prognosis [42].
4. **Blood labs** should be sent: (CBC, KFT, coagulation profile, electrolytes and serum glucose [42].

5. **Urgent Imaging** to differentiate ischemic from hemorrhagic strokes by CT or MRI [41].
6. **Blood pressure control:** intensive blood pressure lowering is considered a safe approach when systolic blood pressure >220 mmHg, or when mean arterial pressure >150 mmHg. It also has a better outcome in cases where SBP ranges between 150-220. Acute hypertension treatment should then be considered to drop the SBP to 140 mmHg, but contraindications of treatment should be considered, kidney and neurological follow up must be obtained as well.
   Short acting drugs are preferred to prevent overshoot hypotension, like Labetalol and nicardipine. Vasodilators such as hydralazine and Nitroprusside must be avoided due to their side effect of increasing the ICP [41][42].
7. **Dysphagia screening:** dysphagia screening must be done to all patients before starting oral intake; this will prevent aspiration or pneumonia [41].
8. **Correction the coagulopathy:** FFP, platelet transfusion, vitamin K administration depending on the coagulation problem present [15][41][42].
   - Thrombocytopenia: platelet transfusion is indicated in severe low platelet count situation, when the count is less than 50000-100000µ
   - ICH in patients taking IV heparin or LMWH: IV protamine sulfate is used as a reversal of the coagulopathy, with close vital signs monitoring because it can cause hypotension.
   - ICH due to warfarin: warfarin causes increased INR value and correcting this elevation is the aim to decrease the hemorrhage tendency. Achieved by stopping warfarin, administering IV vitamin K infusion, using either FFP or PCCs, since vit K alone needs 2 hours to give a reversal action. PCC is generally preferred over FFP and considered more practical since it doesn't require cross-matching and large volumes to correct the INR to the target value (<1.5), has faster correction ability of INR than FFP, and has less complications than FFP. After giving drugs INR should be monitored for follow up.
   - ICH due to new anticoagulants: direct thrombin inhibitor (dabigatran) or factor Xa inhibitors (including rivaroxaban, apixaban, and edoxaban). Idarucizumab, a humanized monoclonal antibody fragment against dabigatran (direct thrombin inhibitor) is approved by FDA for emergency situations.
     Andexanet Alfa (Andexxa) is an antidote for patients treated with rivaroxaban, apixaban and edoxaban.
9. **Fever:** fever is commonly seen in ICH patients, especially those with IVH. It is related to the higher possibilities of hematoma spreading causing worse outcomes [41].
10. **ICH and DVT prophylaxis:** Intermittent pneumatic compression has a better outcome in preventing DVT in comparison with the graduated compression stocking which did not give beneficial results in DVT prevention. That is why

intermittent pneumatic compression is recommended in all ICH cases in the first days of admission [41].

11. **Treatment for edema and high ICP** is done by a using a dehydrant agent like mannitol, hyperventilation and keeping the head elevated at 30° to optimize cerebral perfusion and ICP. Steroids should not be used [22].
12. **Correction of the blood glucose level:** hyperglycemia in ICH is associated with bad results, and decreasing the glucose levels in hyperglycemia decreases the hematoma spreading risk. As a rule for glucose monitoring, treat low or high blood glucose [41].
13. **Seizures:** is possible event after hemorrhagic stroke, either clinical convulsions or epileptiform EEG changes in unconscious patients, that's why EEG is recommended in cases with altered mental status or unconsciousness.
    Many antiseizure drugs can be used in these cases, although phenytoin and valproic acid should be avoided due to worsening of neurological outcome and increase in the mortality rate. New antiseizure drugs have safer profile and less drug interactions like Levetiracetam and Lacosamide on the other hand. Overall, post-ICH prophylactic antiepileptic drugs are not recommended [25][41].
14. **ICH patients should be admitted to the neurological ICU,** or dedicated stroke unit, for closer follow up and monitoring of the case, and this has shown better functional outcome, and less mortality rate than the regular ward admissions [42].
15. **Rehabilitation** should be considered for all patients who suffer from hemorrhagic stroke to help improve the disabilities and recover from them (since ICH is a leading cause of these disabilities). It will furthermore help the patients have a better functional life even without being fully recovered from the disability [41].
16. **Atrial fibrillation and ICH [43]** Atrial fibrillation are normally associated with a higher risk of ischemic stroke. Thus, coagulation therapy is considered in AF patients. On the other hand, anticoagulation is associated with hemorrhagic stroke. Hence, balancing the risk of having ischemic and hemorrhagic strokes made us develop a new way to manage those patients with AF and a history of ICH. Has-bled score is an important method to evaluate this case. Has**-bled score:**
    Has-bled score is a score developed to evaluate the risk of major bleeds that the atrial fibrillation patient could encounter in one year due to anticoagulation drugs. The score helps cluster the patients into low and high-risk patients and take a better discussion toward anticoagulation medications.

Clinical features	explanation	score
Hypertension	>160 mmHg systolic blood pressure	1 point
Abnormal kidney function	Dialysis, or Kidney transplant, or Cr >2.26 mg/dL	1 point
Abnormal liver function	Cirrhosis, or bilirubin ≥2 the normal value, or ALT/AST/ALP ≥3 the normal value	1 point
Stroke	Prior history of stroke	1 point
Bleeding	Prior history of major bleeding or predisposition to bleeding	1 point
Liable INR	Abnormal INR value	1 point
Elders	>65 years	1 point
Drugs	Increase the risk of bleeding like NSAIDs or aspirin	1 point
Alcohol	8 or more drinks/week	1 point
Total		0-9

Has-bled score 3 or more indicates a high-risk patient of bleeding, anticoagulants should be used with caution but not necessarily stop the drugs. Instead, clinicians can work more on the modifiable risk factors. Score of 5 or more is associated with a risk of bleeding of >12.5% during the year.

Prognostic Factors

Hemorrhagic stroke is considered a serious disease with bad morbidity and mortality rates; it also causes a nonfunctional life to many people worldwide. There are some scoring systems for prognosis predictions, such as ICH score and FUNC score that are frequently used [42]:

- ICH score: it's used for 30-days mortality rate for ICH patients. Correlating the age of the patient, the hemorrhage volume and location, the presence of IVH, and the initial GCS with the prognosis [42].

Element	Score
GCS	
3-4	2
5-12	1
13-15	0
ICH volume	
>30 mL	1
<30 mL	0
Present IVH	1
No IVH	0
Infratentorial ICH	
yes	1
no	0
Age	
>80	1
<80	0
Total score	0-6

ICH score	Percentage of 30-days mortality rate
0	0%
1	13%
2	26%
3	72%
4	97%
5 or 6	100%

The higher the ICH score the higher the mortality rate will be. With a>70% mortality rate for ICH score of 3, and almost a 100% ICH score of 4 or more.

- **FUNC score:** used for 90-days functional independence. Very similar to ICH score components, but it includes pre-ICH cognitive status into consideration [42].

Element	Score
GCS	
9 or more	2
<9	0
ICH volume	
<30 mL	4
30-60 mL	2
>60 mL	0
ICH location	
Lobar	2
Deep	1
Infratentorial	0
Age	
<70	2
70-79	1
>80	0
Pre-ICH cognitive impairment	
No	1
Yes	0
Total score	0-11

FUNC score	Chances of functional independence
0-4	0%
5-7	29%
8	48%
9-10	75%
11	95%

The higher the FUNC score the higher the chances are for the patient to have good functional outcomes. In fact, 4 or less FUNC score have 0% chance to achieve functional independence. Those with >8 FUNC score on the other hand have more than 75% chance of functional independence.

ICHs prognosis might worsen and have a higher complication and mortality rate due to the following situations:

- ICH due to coagulopathy especially warfarin. Which has a worse prognosis due to the larger hematoma occurring in these cases [15]
- Pneumonia post -ICH is associated with poor prognosis [26].
- Hydrocephalus complication after ICH is correlated with bad outcomes [44].
- Large sized hematoma [45].
- Old age [45].
- Initial low GCS [45].
- Hemorrhage volume more than 30 cc. [45]
- Hyperglycemia with ICH. [46]
- Spot sign: it has a poor prognostic factor, gives higher risk of hematoma spread [28].

Prevention [41][47]

Blood pressure control: controlling hypertension is considered the main action for prevention. It decreases the risk of having hemorrhagic stroke, and recurrence of the event later on.

Anticoagulation: Aspirin is not recommended for primary prevention of ischemic stroke. Because it increases the risk of having cerebral hemorrhage, but continuing antiplatelet drugs in high-risk ischemic stroke patients that had recent hemorrhagic stroke did not show meaningful change in the risk of recurrence of the hemorrhage. Direct oral anticoagulants are superior in atrial fibrillation cases for prevention compared to warfarin and have a lower risk of causing ICH. The recommended timing to resume anticoagulation therapy in anticoagulants induced ICH is still unknown. Physicians must carefully balance the risks of recurrent ICH and thromboembolism in individual patients.

Steering away from smoking, alcohol drinking >2 drinks/day and illicit drugs are good lifestyle risk factor changes. Treating obstructive sleep apnea is also beneficial.

Blood glucose control: glucose level correction is recommended. Treating hyperglycemia prevents bad outcomes as well.

Recent research

- Although Covid-19 patients are at a risk of thrombotic events during the disease. Anticoagulation drugs (either as therapeutic or prophylactic doses), puts the patients at risk of having ICH with cerebral herniation or cortical ICH [48].

- Stroke patients are at an elevated risk of having disabilities that sometimes become permanent. However, DVT is more common in ICH and SAH than in ischemic stroke [49].
- In a non-randomized study testing platelet transfusion in patients under antiplatelet therapy and seeing the effect on hematoma expansion, the results showed no significant risk of hematoma expansion [50].
- Relapsing polychondritis is a rare disease in rheumatology. Presents usually as hearing loss due to auricular chondritis, but also can cause aortic aneurysm. extremely rare but reported cerebral vasculitis due to the disease, causing hemorrhagic stroke [51].

References

1. NHLBI,stroke. (n.d.). https://www.nhlbi.nih.gov/health-topics/stroke
2. Katan, M., & Luft, A. (2018). Global Burden of Stroke. Seminars in Neurology, 38(2), 208–211. https://doi.org/10.1055/s-0038-1649503
3. Virani, S. S., Alonso, A., Benjamin, E. J., Bittencourt, M. S., Callaway, C. W., Carson, A. P., Chamberlain, A. M., Chang, A. R., Cheng, S., Delling, F. N., Djousse, L., Elkind, M. S. V, Ferguson, J. F., Fornage, M., Khan, S. S., Kissela, B. M., Knutson, K. L., Kwan, T. W., Lackland, D. T., … Tsao, C. W. (2020). Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation, 141(9), e139–e596. https://doi.org/10.1161/CIR.0000000000000757
4. Unnithan, A. K. A., & Mehta, P. (2020). Hemorrhagic Stroke.
5. Charidimou, A., Boulouis, G., Gurol, M. E., Ayata, C., Bacskai, B. J., Frosch, M. P., Viswanathan, A., & Greenberg, S. M. (2017). Emerging concepts in sporadic cerebral amyloid angiopathy. Brain : A Journal of Neurology, 140(7), 1829–1850. https://doi.org/10.1093/brain/awx047
6. Hutchinson, M. L., & Beslow, L. A. (2019). Hemorrhagic Transformation of Arterial Ischemic and Venous Stroke in Children. Pediatric Neurology, 95, 26–33. https://doi.org/10.1016/j.pediatrneurol.2019.01.023
7. Piccardi, B., Arba, F., Nesi, M., Palumbo, V., Nencini, P., Giusti, B., Sereni, A., Gadda, D., Moretti, M., Fainardi, E., Mangiafico, S., Pracucci, G., Nannoni, S., Galmozzi, F., Fanelli, A., Pezzati, P., Vanni, S., Grifoni, S., Sarti, C., … Inzitari, D. (2018). Reperfusion Injury after ischemic Stroke Study (RISKS): single-centre (Florence, Italy), prospective observational protocol study. BMJ Open, 8(5), e021183. https://doi.org/10.1136/bmjopen-2017-021183
8. Mokin, M., Kan, P., Kass-Hout, T., Abla, A. A., Dumont, T. M., Snyder, K. V, Hopkins, L. N., Siddiqui, A. H., & Levy, E. I. (2012). Intracerebral hemorrhage secondary to intravenous and endovascular intraarterial revascularization therapies in acute ischemic stroke: an update on risk factors, predictors, and management. Neurosurgical Focus, 32(4), E2. https://doi.org/10.3171/2012.1.FOCUS11352
9. Fujita, K., & Matsumoto, S. (1980). [Intracerebral hemorrhage in brain tumors (author's transl)]. No shinkei geka. Neurological surgery, 8(10), 929–934.
10. Lieu, A. S., Hwang, S. L., Howng, S. L., & Chai, C. Y. (1999). Brain tumors with hemorrhage. Journal of the Formosan Medical Association = Taiwan Yi Zhi, 98(5), 365–367.
11. Vasculitis foundation, Central nervous system vasculitis. (n.d.). https://www.vasculitisfoundation.org/education/forms/central-nervous-system/
12. An, S. J., Kim, T. J., & Yoon, B.-W. (2017). Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. Journal of Stroke, 19(1), 3–10. https://doi.org/10.5853/jos.2016.00864
13. Mustanoja, S., Strbian, D., Putaala, J., Meretoja, A., Curtze, S., Haapaniemi, E., Sairanen, T., Hietikko, R., Sirén, J., Kaste, M., & Tatlisumak, T. (2013). Association of prestroke statin use and lipid levels with outcome of intracerebral hemorrhage. Stroke, 44(8), 2330–2332. https://doi.org/10.1161/STROKEAHA.113.001829
14. Emiru, T., Bershad, E. M., Zantek, N. D., Datta, Y. H., Rao, G. H. R., Hartley, E. W., & Divani, A. A. (2013). Intracerebral hemorrhage: a review of coagulation function. Clinical and Applied Thrombosis/Hemostasis : Official Journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis, 19(6), 652–662. https://doi.org/10.1177/1076029612454938
15. Quinones-Hinojosa, A., Gulati, M., Singh, V., & Lawton, M. T. (2003). Spontaneous intracerebral hemorrhage due to coagulation disorders. Neurosurgical Focus, 15(4), E3. https://doi.org/10.3171/foc.2003.15.4.3
16. Tsatsakis, A., Docea, A. O., Calina, D., Tsarouhas, K., Zamfira, L.-M., Mitrut, R., Sharifi-Rad, J., Kovatsi, L., Siokas, V., Dardiotis, E., Drakoulis, N., Lazopoulos, G., Tsitsimpikou, C., Mitsias, P., & Neagu, M. (2019). A Mechanistic and Pathophysiological Approach for Stroke Associated with Drugs of Abuse. Journal of Clinical Medicine, 8(9). https://doi.org/10.3390/jcm8091295

17. Bos, M. J., Koudstaal, P. J., Hofman, A., & Breteler, M. M. B. (2007). Decreased glomerular filtration rate is a risk factor for hemorrhagic but not for ischemic stroke: the Rotterdam Study. Stroke, 38(12), 3127–3132. https://doi.org/10.1161/STROKEAHA.107.489807
18. Chen, Y.-C., Chang, K.-H., & Chen, C.-M. (2018). Genetic Polymorphisms Associated with Spontaneous Intracerebral Hemorrhage. International Journal of Molecular Sciences, 19(12). https://doi.org/10.3390/ijms19123879
19. Aguilar, M. I., & Brott, T. G. (2011). Update in intracerebral hemorrhage. The Neurohospitalist, 1(3), 148–159. https://doi.org/10.1177/1941875211409050
20. Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 42228. (n.d.-b). lobar-haemorrhage-1. https://radiopaedia.org/articles/lobar-haemorrhage
21. Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 10224. (n.d.-a). pontine hemorrhage. https://radiopaedia.org/articles/pontine-haemorrhage?lang=us
22. Zheng, H., Chen, C., Zhang, J., & Hu, Z. (2016). Mechanism and Therapy of Brain Edema after Intracerebral Hemorrhage. Cerebrovascular Diseases (Basel, Switzerland), 42(3–4), 155–169. https://doi.org/10.1159/000445170
23. complications of ICH, Minneapolis clinic of neurology. (n.d.). https://minneapolisclinic.com/patient-resources/intracerebral-hemorrhage-hemorrhagic-stroke/
24. Case courtesy of Dr David Cuete, Radiopaedia.org, rID: 27193. (n.d.). cerebellar-haemorrhage and vasogenic edema. https://radiopaedia.org/articles/intracerebral-haemorrhage?lang=us
25. Doria, J. W., & Forgacs, P. B. (2019). Incidence, Implications, and Management of Seizures Following Ischemic and Hemorrhagic Stroke. Current Neurology and Neuroscience Reports, 19(7), 37. https://doi.org/10.1007/s11910-019-0957-4
26. Lord, A. S., Langefeld, C. D., Sekar, P., Moomaw, C. J., Badjatia, N., Vashkevich, A., Rosand, J., Osborne, J., Woo, D., & Elkind, M. S. V. (2014). Infection after intracerebral hemorrhage: risk factors and association with outcomes in the ethnic/racial variations of intracerebral hemorrhage study. Stroke, 45(12), 3535–3542. https://doi.org/10.1161/STROKEAHA.114.006435
27. de Freitas, G. R., & Nagayama, M. (2009). Deep venous thrombosis after intracerebral hemorrhage, gender and ethnicity: a challenge for therapeutic approaches. Cerebrovascular Diseases (Basel, Switzerland), 27(4), 320–321. https://doi.org/10.1159/000202007
28. Macellari, F., Paciaroni, M., Agnelli, G., & Caso, V. (2014). Neuroimaging in intracerebral hemorrhage. Stroke, 45(3), 903–908. https://doi.org/10.1161/STROKEAHA.113.003701
29. Case courtesy of Dr Ian Bickle, Radiopaedia.org, rID: 76781. (n.d.). frontal-lobe-haematoma. https://radiopaedia.org/cases/frontal-lobe-haematoma
30. Dr Rohit Sharma and Dr Evyn Arnfield et al. (n.d.). ABC/2. https://radiopaedia.org/articles/abc2
31. Case courtesy of Dr Mohammad Farghali Ali Tosson, Radiopaedia.org, rID: 52302. (n.d.). intracranial-haemorrhage-with-blood-fluid level. https://radiopaedia.org/cases/intracranial-haemorrhage-with-fluid-fluid-level-1
32. Case courtesy of Dr Jeremy Jones, Radiopaedia.org, rID: 6223. (n.d.). intracerebral-haemorrhage-with-ventricular-extension. https://radiopaedia.org/cases/intracerebral-haemorrhage-with-ventricular-extension?lang=us
33. Case courtesy of Dr Stefan Ludwig, Radiopaedia.org, rID: 13919. (n.d.). cerebral-arteriovenous-malformation. https://radiopaedia.org/articles/cerebral-arteriovenous-malformation
34. Case courtesy of A/Professor Christen Barras, Radiopaedia.org, rID: 24481. (n.d.). intracranial-haemorrhage-cta-spot-sign. https://radiopaedia.org/articles/ct-angiographic-spot-sign-intracerebral-haemorrhage?lang=us
35. Al, D. D. J. B. and A. P. F. G. et. (n.d.). hemorrhage on MRI. https://radiopaedia.org/articles/haemorrhage-on-mri
36. Case courtesy of Dr Ahmed Abdrabou, Radiopaedia.org, rID: 22749. (n.d.). hypertensive-intracerebral-haemorrhage T1. https://prod-images-static.radiopaedia.org/images/3251974/11274cdbb5fa0a305ab53bdf31ecc8_big_gallery.jpg
37. Case courtesy of Dr Ahmed Abdrabou, Radiopaedia.org, rID: 22749. (n.d.-b). hypertensive-intracerebral-haemorrhage T2. https://prod-images-static.radiopaedia.org/images/3252272/8529f95080ca7ef6f3cdc52aa00916_big_gallery.jpg
38. Case courtesy of Dr Bita Abbasi, Radiopaedia.org, rID: 22709. (n.d.). cerebral-arteriovenous-MRI. https://radiopaedia.org/articles/cerebral-arteriovenous-malformation
39. Case courtesy of Dr Abdulrahman Abdo Ali Abbas , Radiopaedia.org, rID: 78910. (n.d.). hemorrhagic-cystic-glioblastoma. https://radiopaedia.org/articles/haemorrhagic-intracranial-tumours
40. Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 4564. (n.d.-c). chronic-hypertensive-encephalopathy. https://radiopaedia.org/articles/cerebral-microhaemorrhage
41. Hemphill, J. C. 3rd, Greenberg, S. M., Anderson, C. S., Becker, K., Bendok, B. R., Cushman, M., Fung, G. L., Goldstein, J. N., Macdonald, R. L., Mitchell, P. H., Scott, P. A., Selim, M. H., & Woo, D. (2015). Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke, 46(7), 2032–2060. https://doi.org/10.1161/STR.0000000000000069
42. Morotti, A., & Goldstein, J. N. (2016). Diagnosis and Management of Acute Intracerebral Hemorrhage. Emergency Medicine Clinics of North America, 34(4), 883–899. https://doi.org/10.1016/j.emc.2016.06.010
43. Stanton, R. J., Eckman, M. H., Woo, D., Moomaw, C. J., Haverbusch, M., Flaherty, M. L., & Kleindorfer, D. O. (2020). Ischemic Stroke and Bleeding: Clinical Benefit of Anticoagulation in Atrial Fibrillation After Intracerebral Hemorrhage. Stroke, 51(3), 808–814. https://doi.org/10.1161/STROKEAHA.119.027370
44. Bhattathiri, P. S., Gregson, B., Prasad, K. S. M., & Mendelow, A. D. (2006). Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. Acta Neurochirurgica. Supplement, 96, 65–68. https://doi.org/10.1007/3-211-30714-1_16

45. Al-Mufti, F., Thabet, A. M., Singh, T., El-Ghanem, M., Amuluru, K., & Gandhi, C. D. (2018). Clinical and Radiographic Predictors of Intracerebral Hemorrhage Outcome. Interventional Neurology, 7(1–2), 118–136. https://doi.org/10.1159/000484571
46. Saxena, A., Anderson, C. S., Wang, X., Sato, S., Arima, H., Chan, E., Muñoz-Venturelli, P., Delcourt, C., Robinson, T., Stapf, C., Lavados, P. M., Wang, J., Neal, B., Chalmers, J., & Heeley, E. (2016). Prognostic Significance of Hyperglycemia in Acute Intracerebral Hemorrhage: The INTERACT2 Study. Stroke, 47(3), 682–688. https://doi.org/10.1161/STROKEAHA.115.011627
47. Diener, H.-C., & Hankey, G. J. (2020). Primary and Secondary Prevention of Ischemic Stroke and Cerebral Hemorrhage: JACC Focus Seminar. Journal of the American College of Cardiology, 75(15), 1804–1818. https://doi.org/10.1016/j.jacc.2019.12.072
48. Dogra, S., Jain, R., Cao, M., Bilaloglu, S., Zagzag, D., Hochman, S., Lewis, A., Melmed, K., Hochman, K., Horwitz, L., Galetta, S., & Berger, J. (2020). Hemorrhagic stroke and anticoagulation in COVID-19. Journal of Stroke and Cerebrovascular Diseases : The Official Journal of National Stroke Association, 29(8), 104984. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104984
49. Ji, R., Li, G., Zhang, R., Hou, H., Zhao, X., & Wang, Y. (2019). Higher risk of deep vein thrombosis after hemorrhagic stroke than after acute ischemic stroke. Journal of Vascular Nursing : Official Publication of the Society for Peripheral Vascular Nursing, 37(1), 18–27. https://doi.org/10.1016/j.jvn.2018.10.006
50. Mengel, A., Stefanou, M.-I., Hadaschik, K. A., Wolf, M., Stadler, V., Poli, K., Lindig, T., Ernemann, U., Grimm, F., Tatagiba, M., Ziemann, U., & Poli, S. (2020). Early Administration of Desmopressin and Platelet Transfusion for Reducing Hematoma Expansion in Patients With Acute Antiplatelet Therapy Associated Intracerebral Hemorrhage. Critical Care Medicine, 48(7), 1009–1017. https://doi.org/10.1097/CCM.0000000000004348
51. Chaucer, B., Demanes, A., Stone, A., & Kakollu, V. (2020). Hemorrhagic Stroke in Relapsing Polychondritis: A Rare Complication of a Rare Disease. In Case reports in rheumatology (Vol. 2020, p. 7464503). https://doi.org/10.1155/2020/7464503

Article topic: Neuromyelitis Optica Spectrum Disorder (NMOSD).

Author: Nadine Absy.

Editor: Aroob Awwad

Reviewer: Ethar Hazaimeh

Keywords: Neuromyelitis Optica, Aquaporin 4, antibody, Devic's disease.

Overview

Neuromyelitis Optica spectrum disorder (NMOSD) is a rare but serious inflammatory demyelinating disease of the central nervous system. It is characterized by its classical clinical presentation of myelitis (inflammation of the long segments of the spinal cords) and optic neuritis (often severe and bilateral). The disease may also present with brainstem syndromes, including but not limited to, area postrema syndrome in which patients suffer from episodes of intractable nausea, vomiting and hiccups. (1) Previously, the disease was referred to as Devic's disease since it was first described by Eugène Devic and his student Fernand Gault in 1894. (2)

Epidemiology

While NMOSD may occur at any age, the mean age of onset is around 40 years, and about 15-20% of patients present to pediatricians or geriatric physicians. In accordance with other autoimmune diseases, females have a higher susceptibly to have NMOSD-AQP4 than males (3:1-9:1). (). (3,4)

Interestingly, in regions where multiple sclerosis had a lower prevalence, such as Asia, NMSOD represented a greater proportion of central nervous system demyelinating diseases. This is important to note since the disease should be considered in the differential diagnosis when assessing patients from those regions.

Pathogenesis and Etiology

It is known that most patients with NMOSD have AQP4-IgG, those immunoglobulins can pass the blood brain barrier and bind to AQP4 channels that are located on the end-feet of astrocytes. Their binding initiates a cascade of immunologically mediated inflammation that causes secondary demyelination. (5) The cascade involves the recruitment and activation of the complement system, which results in complement-dependent-cytotoxicity. Antibody-dependent cytotoxicity is also triggered, by the activation of effector cells. (6)

Studies conducted on biopsies and autopsies of patients with NMOSD demonstrate that lesions show loss of myelin, infiltration of inflammatory cells and have both axonal and astrocytic loss. (7) Contrary to MS (multiple sclerosis), AQP4 immunostaining is not found within NMSOD lesions and there are no cortical lesions. (8)

Diagnosis

NMSOD's neurologic manifestations may mimic those of multiple sclerosis. It is vital to distinguish between these two disorders owing to the differences in both therapeutic and diagnostic implications. This distinction was made possible by the discovery of a specific biomarker for neuromyelitis Optica (NMO), namely the aquaporin-4 water channel (AQP4) which was detected through AQP4-Abs. (9)

The current classification (NMOSD) resulted from the recognition that patients can have more restricted forms of the disease (e.g.: recurring transverse myelitis that is not accompanied by optic neuritis) or symptoms surpassing the optic nerve and spinal cord (e.g.: area postrema syndrome). (10)

It is noteworthy to mention that around 20% of patients are seronegative for AQP4-IgG, and a proportion of those seronegative patients have myelin oligodendrocyte glycoprotein antibodies (i.e.: MOG-IgG seropositive).(11) Since AQP4 NMOSD is a disease of astrocytes while MOG NMOSD is a disease of oligodendrocytes, certain controversies have arisen regarding what basis to consider for diagnosis.
Diagnostic criteria are divided into syndrome-based (NMSOD) or biomarker-based (AQP4-IgG, MOG-IgG), currently the 2015 International Panel for NMO Diagnosis criteria is used, as the name implies, a set of criteria used to diagnose (NMOSD) (10,12). It based on a combination of clinical, laboratory, and neuroimaging findings, Table 1.

Table 1. 2015 International Panel for NMO Diagnosis criteria for neuromyelitis optica spectrum disorders.

Diagnostic criteria for NMOSD with AQP4-IgG: 1. No less than 1 core clinical characteristic 2. Positive test for AQP4-IgG using best obtainable detection method. 3. Exclusion of alternative diagnosis
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unidentified AQP4-IgG status: 1. No less than 2 core clinical characteristics arising due to one or more clinical attacks and meeting all the following requirements: a. No less than 1 core clinical characteristic must be optic neuritis, acute myelitis with longitudinal extensive transverse myelitis (LETM), or area postrema syndrome. b. Dissemination in space (2 or more differing core clinical characteristics) c. Fulfillment of additional MRI requirements, as appropriate 2. Negative tests for AQP4-IgG using best obtainable detection methods. 3. Exclusion of alternative diagnosis

Core clinical characteristics 1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome: an episode of hiccups or nausea and vomiting that is otherwise unexplained 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or rather acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions. 6. Symptomatic cerebral syndrome accompanied by NMOSD-typical brain lesions
Further MRI necessities for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status 1. Acute optic neuritis necessitates brain MRI showing (a) normal findings or only non-specific white matter lesions OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion spreading over > ½ optic nerve length or lesion involving optic chiasm. 2. Acute myelitis: necessitates associated intramedullary MRI lesion extending over >/= 3 adjoining longitudinally extensive transverse myelitis segments (LETM) or >/= 3 adjoining segments of focal spinal cord atrophy in patients with history compatible with acute myelitis 3. Area postrema syndrome necessitates accompanying dorsal medulla/area postrema lesions. 4. Acute brainstem syndrome requires associated periependymal brainstem lesions

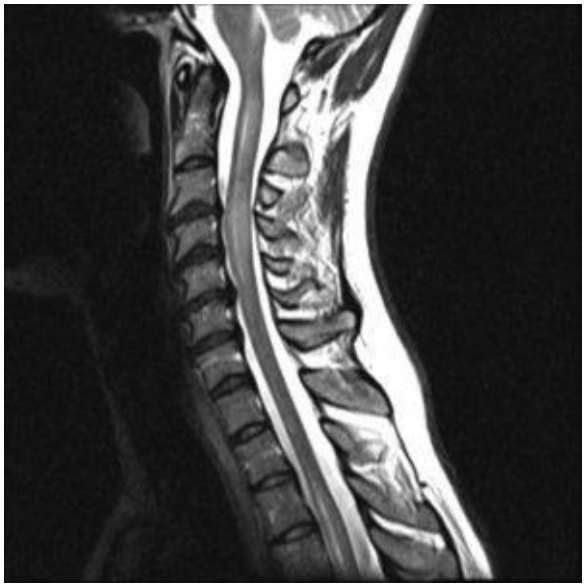


Figure 1.a Transverse myelitis, Case courtesy of Assoc Prof Frank Gaillard (13)

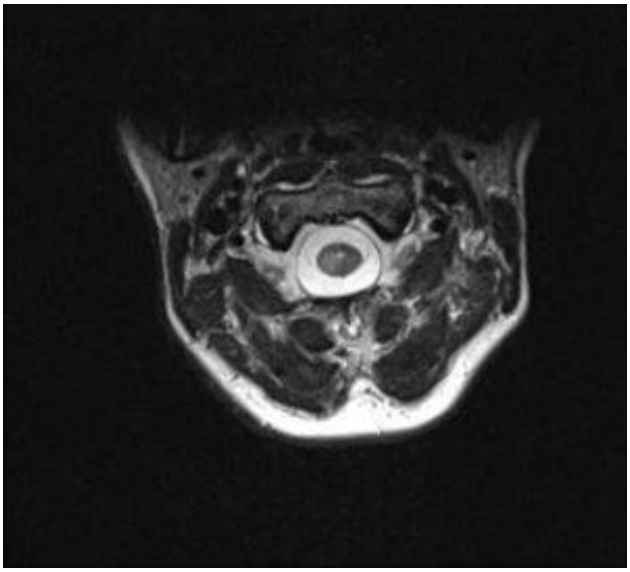


Figure 1.b Transverse myelitis, Case courtesy of Assoc Prof Frank Gaillard. (14)

Figure 1 demonstrates the longitudinally extensive involvement of the cervicothoracic cord. Spinal cord lesion (LESCL) of an abnormal T2 signal with cord swelling. The central cord is involved. No hemorrhage.

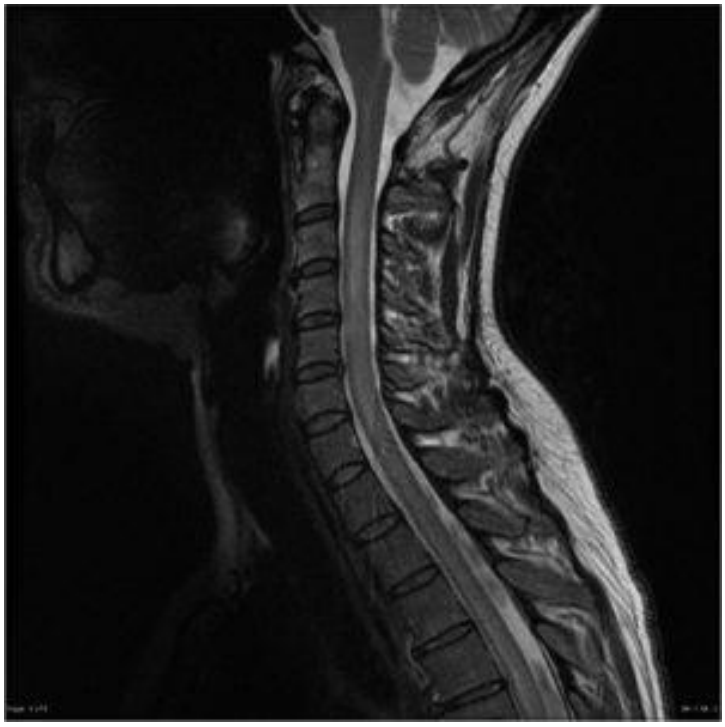


Figure 2. The cord demonstrates a longitudinally extensive spinal cord lesion, with high T2 signal involving almost the entire cord. Case courtesy of Assoc Prof Frank Gaillard.

Clinical presentation

Principally, the three classic clinical presentations for NMOSD are: optic neuritis, transverse myelitis, and area postrema syndrome. (15) Most patients have a relapsing course, and some patients have severe attacks that result in lasting neurological deficits that persist even after prolonged periods of remission. A distinction that may be significant in separating MS from NMSOD, is that in the latter a secondary progressive course is exceedingly rare. (16)

The bouts of transverse myelitis may present with conventional findings of myelitis including numbness, weakness, bladder or bowel dysfunction, and Lhermitte phenomenon (electric shock like sensation extending down the spine or extremities when the neck is flexed). The progression of these symptoms beyond 1 month should warrant concerns for alternative diagnosis. Another point to highlight in the differences between MS and NMOSD is that unlike MS the attacks of myelitis in NMOSD are often disabling. Episodes of painful involuntary flexion called tonic spasms may occur after episodes of myelitis. Those tonic spasms are triggered by movement, they last less than 1

minute and respond well to low doses of carbamazepine and occur frequently with NMSOD. (17)

Area postrema syndrome, the third cardinal feature, results in bouts of intractable nausea and vomiting that may or may not be accompanied by hiccups. (10) The bouts may be a patient's first presentation and may cause the patient to initially believe the condition is due to a pathology in the gastrointestinal system. (18) furthermore, they may occur in isolation, be accompanied by other brainstem features or develop into a myelitis episode. (19) At times, NMOSD presents in paraneoplastic contexts. (5)

Autoimmune disorders, such as systemic lupus erythematosus, Sjögren syndrome, and antiphospholipid antibody syndrome, were found to frequently coincide with NMSOD. This association warrants AQP4-IgG testing if the patient presents with optic neuritis, transverse myelitis, or intractable vomiting in patients with any of these systemic autoimmune disorders. If a positive result ensues, this would confirm the existence of an autoimmune neurologic disorder along with the rheumatologic disorder, in lieu of a neurologic manifestation of one of these disorders.(20) Noticeably, patients who have both NMSOD and antiphospholipid antibodies or the syndrome might have an increased risk of have developing clotting disorders (resulting in deep vein thrombosis, miscarriages and other manifestations).(21) Myasthenia gravis (MG) was also found to coexist frequently with NMSOD. Usually, MG would precede a NMSOD diagnosis by years or decades. (22)

As mentioned before 20% of patients are seronegative for AQP4 most of those patients have MOG antibodies. Other than NMSOD that is seronegative for AQP4-IgG these patients present with optic neuritis, acute disseminated encephalomyelitis, transverse myelitis, and brainstem demyelinating episodes.

Summary of clinical features

Cardinal clinical features (15,18,23,24)

- Transverse myelitis, classically longitudinally extensive (involving three or more vertebral segments; frequently followed by tonic spasms and rarely elements of pain or pruritus present)
- Optic neuritis (usually severe and may be bilateral at times)
- Bouts of intractable nausea and vomiting or hiccups due to involvement of area postrema.

Other Clinical Features (25–34)

- Narcolepsy
- Hydrocephalus

- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- Differing hypothalamic presentations (e.g., anorexia)
- Acute myopathy with elevated serum CK levels (hyperCKemia)
- Brainstem syndromes (such as, ophthalmoplegia, hearing loss, opsoclonus or myoclonus)
- Myeloradiculitis
- Encephalopathy (similar to acute disseminated encephalomyelitis; or posterior reversible encephalopathy syndrome)
- Cognitive dysfunction (of subcortical pattern)

Treatment and Management

It is important to keep in mind while approaching the management of NMSOD, that the disorder has high attack related disability, poor prognosis, and a generally high risk of mortality in patients who remain untreated. (35)

The principles of treatment are based on the evidence on the role of humoral immunity in the pathogenesis of the disease

Acute attacks

Initially patients might be given a high dose of intravenous methylprednisolone, which is given daily over 3-5 days in 1-gram doses. If patients suffer from symptoms that are severe and unresponsive to glucocorticoids, the suggested “rescue” treatment is plasma exchange. (36) This management protocol applies to both seronegative and seropositive NMOSD.

Attack prevention

Recurrent attacks are one of the features of NMOSD; these attacks often lead to accumulated disability since there is little to no recovery after each attack unlike MS. Hence, long-term immunotherapy is indicated for those diagnosed with NMOSD. In patients who are seropositive for AQP4-IgG treatment with monoclonal antibodies such as eculizumab, inebilizumab and satralizumab is recommended, rather than other immunosuppressant drugs.(36)However, many clinicians use rituximab, mycophenolate mofetil, azathioprine and other immunotherapies. Drugs containing antibodies targeting IL-6 which plays a role in the pathogenesis of the disease are being trialed. (37)

It is recommended that immunosuppression is continued for at least five years in patients who have AQP4 antibodies, even if the patient had only one previous attack since those patients would have a high risk of relapse or developing NMOSD.(38) Due to

the devastating nature of the disease, some physicians recommend life-long therapy as the appropriate way of approach. Others suggest that the severity of attacks and disability should guide physicians to treatment durations.

The risks of long-term immunosuppression are not yet established well enough. Retinal infections caused by opportunistic microorganisms such as toxoplasmosis and cytomegalovirus may present similarly to optic neuritis attacks. (39) Studies are needed to explore whether maintenance immunotherapy can be stopped safely, so reducing the risk associated with long-term suppression of the immunity. Currently, other approaches are under development amongst which are: AQP4 blocking antibodies used on animal models and inhibitors of neutrophils (sivelstat) or eosinophils (cetirizine). (40)

Risk Factors

No well-established risk factors are known. However, patients with NMOSD are likely to have a history of other autoimmune diseases, malignancy, or recent non-neurological systemic diseases all of which may trigger the onset of NMOSD or predispose the patient to developing the disorder. (41)

Prognosis

Recurrent attacks lead to the accumulation of motor, sensory, visual, and bladder deficits. Thus, causing a stepwise deterioration in the patient's condition. Attacks or relapses usually worsen over a number of days and patients take several weeks to months to recover, though never fully since attacks leave significant sequels each time. A worse outcome is expected according to the number of replaces during the first two years, being older at the onset of disease, the severity of the first attack, and if the patient has associated autoimmune disorders. (42–44) It is noteworthy to mention that these prognostic factors require confirmation via larger prospective studies.

Respiratory failure due to neurogenic causes is a frequent secondary cause of mortality. In general, mortality rates tend to be high in patients with NMOSD. (36) Due to the progress in both the diagnosis and treatment of NMOSD patients, mortality rates are expected to decrease. In patients with optic neuritis that is recurrent, retrospective evidence has shown that seropositivity for AQP4-IgG is linked to worse visual outcomes. (24)

Recent updates (clinical trials)

A recent study that compared the usage of intravenous methylprednisolone (IVMP) with succeeding plasma exchange (PLEX) that is used as an add-on and the combination of concurrent IVMP and PLEX in patients suffering from severe attacks of NMOSD. The study found that early treatment with PLEX ought to be implemented in those with severe acute attacks since the outcome and response were better than their counterparts. (45)

Another recent clinical trial explored the efficacy and safety of satralizumab as monotherapy in NMOSD found that the immunosuppressive agent reduced the rate of relapse compared with placebo and had an overall satisfactory safety profile. Both seropositive and seronegative patients were included in the trial. (46)

References

1. Huda S, Whittam D, Bhojak M, Chamberlain J, Noonan C, Jacob A. Neuromyelitis optica spectrum disorders. Clin Med. 2019 Mar;19(2):169–76.
2. Jarius S, Wildemann B. The history of neuromyelitis optica. J Neuroinflammation. 2013 Jan;10:8.
3. Hor JY, Asgari N, Nakashima I, Broadley SA, Leite MI, Kissani N, et al. Epidemiology of Neuromyelitis Optica Spectrum Disorder and Its Prevalence and Incidence Worldwide. Front Neurol. 2020;11:501.
4. Quek AML, McKeon A, Lennon VA, Mandrekar JN, Iorio R, Jiao Y, et al. Effects of age and sex on aquaporin-4 autoimmunity. Arch Neurol. 2012 Aug;69(8):1039–43.
5. Pittock SJ, Lennon VA. Aquaporin-4 autoantibodies in a paraneoplastic context. Arch Neurol. 2008 May;65(5):629–32.
6. Wu Y, Zhong L, Geng J. Neuromyelitis optica spectrum disorder: Pathogenesis, treatment, and experimental models. Mult Scler Relat Disord. 2019 Jan;27:412–8.
7. Lucchinetti CF, Guo Y, Popescu BFG, Fujihara K, Itoyama Y, Misu T. The pathology of an autoimmune astrocytopathy: lessons learned from neuromyelitis optica. Brain Pathol. 2014 Jan;24(1):83–97.
8. Popescu BFG, Guo Y, Jentoft ME, Parisi JE, Lennon VA, Pittock SJ, et al. Diagnostic utility of aquaporin-4 in the analysis of active demyelinating lesions. Neurology. 2015 Jan;84(2):148–58.
9. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet (London, England). 2004 Dec;364(9451):2106–12.
10. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015 Jul;85(2):177–89.
11. Waters PJ, McKeon A, Leite MI, Rajasekharan S, Lennon VA, Villalobos A, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. Neurology. 2012 Feb;78(9):665–71; discussion 669.
12. Hacohen Y, Palace J. Time to separate MOG-Ab-associated disease from AQP4-Ab-positive neuromyelitis optica spectrum disorder. Neurology [Internet]. 2018 May 22;90(21):947 LP – 948. Available from: http://n.neurology.org/content/90/21/947.abstract
13. radiopedia. Transverse myelitis.
14. axial section.
15. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology. 1999 Sep;53(5):1107–14.
16. Wingerchuk DM, Pittock SJ, Lucchinetti CF, Lennon VA, Weinshenker BG. A secondary progressive clinical course is uncommon in neuromyelitis optica. Neurology. 2007 Feb;68(8):603–5.
17. Kim S-M, Go MJ, Sung J-J, Park KS, Lee K-W. Painful tonic spasm in neuromyelitis optica: incidence, diagnostic utility, and clinical characteristics. Arch Neurol. 2012 Aug;69(8):1026–31.
18. Apiwattanakul M, Popescu BF, Matiello M, Weinshenker BG, Lucchinetti CF, Lennon VA, et al. Intractable vomiting as the initial presentation of neuromyelitis optica. Ann Neurol. 2010 Nov;68(5):757–61.
19. Asgari N, Skejoe HPB, Lennon VA. Evolution of longitudinally extensive transverse myelitis in an aquaporin-4 IgG-positive patient. Neurology [Internet]. 2013 Jul 2;81(1):95 LP – 96. Available from: http://n.neurology.org/content/81/1/95.abstract
20. Wingerchuk DM, Weinshenker BG. The emerging relationship between neuromyelitis optica and systemic rheumatologic autoimmune disease. Mult Scler. 2012 Jan;18(1):5–10.
21. Guerra H, Pittock SJ, Moder KG, Fryer JP, Gadoth A, Flanagan EP. Frequency of Aquaporin-4 Immunoglobulin G in Longitudinally Extensive Transverse Myelitis With Antiphospholipid Antibodies. Mayo Clin Proc. 2018 Sep;93(9):1299–304.
22. McKeon A, Lennon VA, Jacob A, Matiello M, Lucchinetti CF, Kale N, et al. Coexistence of myasthenia gravis and serological markers of neurological autoimmunity in neuromyelitis optica. Muscle Nerve. 2009 Jan;39(1):87–90.

23. Kanamori Y, Nakashima I, Takai Y, Nishiyama S, Kuroda H, Takahashi T, et al. Pain in neuromyelitis optica and its effect on quality of life: a cross-sectional study. Neurology. 2011 Aug;77(7):652–8.
24. Matiello M, Lennon VA, Jacob A, Pittock SJ, Lucchinetti CF, Wingerchuk DM, et al. NMO-IgG predicts the outcome of recurrent optic neuritis. Neurology. 2008 Jun;70(23):2197–200.
25. Viegas S, Weir A, Esiri M, Kuker W, Waters P, Leite MI, et al. Symptomatic, radiological and pathological involvement of the hypothalamus in neuromyelitis optica. J Neurol Neurosurg Psychiatry. 2009 Jun;80(6):679–82.
26. Suzuki K, Nakamura T, Hashimoto K, Miyamoto M, Komagamine T, Nagashima T, et al. Hypothermia, hypotension, hypersomnia, and obesity associated with hypothalamic lesions in a patient positive for the anti-aquaporin 4 antibody: a case report and literature review. Arch Neurol. 2012 Oct;69(10):1355–9.
27. Iorio R, Lucchinetti CF, Lennon VA, Costanzi C, Hinson S, Weinshenker BG, et al. Syndrome of inappropriate antidiuresis may herald or accompany neuromyelitis optica. Neurology. 2011 Oct;77(17):1644–6.
28. Baba T, Nakashima I, Kanbayashi T, Konno M, Takahashi T, Fujihara K, et al. Narcolepsy as an initial manifestation of neuromyelitis optica with anti-aquaporin-4 antibody. Vol. 256, Journal of neurology. Germany; 2009. p. 287–8.
29. Suzuki N, Takahashi T, Aoki M, Misu T, Konohana S, Okumura T, et al. Neuromyelitis optica preceded by hyperCKemia episode. Neurology. 2010 May;74(19):1543–5.
30. Kremer L, Mealy M, Jacob A, Nakashima I, Cabre P, Bigi S, et al. Brainstem manifestations in neuromyelitis optica: a multicenter study of 258 patients. Mult Scler. 2014 Jun;20(7):843–7.
31. Hage RJ, Merle H, Jeannin S, Cabre P. Ocular oscillations in the neuromyelitis optica spectrum. J neuro-ophthalmology Off J North Am Neuro-Ophthalmology Soc. 2011 Sep;31(3):255–9.
32. Takai Y, Misu T, Nakashima I, Takahashi T, Itoyama Y, Fujihara K, et al. Two cases of lumbosacral myeloradiculitis with anti-aquaporin-4 antibody. Neurology. 2012 Oct;79(17):1826–8.
33. Blanc F, Noblet V, Jung B, Rousseau F, Renard F, Bourre B, et al. White matter atrophy and cognitive dysfunctions in neuromyelitis optica. PLoS One. 2012;7(4):e33878.
34. Clardy SL, Lucchinetti CF, Krecke KN, Lennon VA, O'Toole O, Weinshenker BG, et al. Hydrocephalus in neuromyelitis optica. Neurology. 2014 May;82(20):1841–3.
35. Collongues N, de Seze J. Current and future treatment approaches for neuromyelitis optica. Ther Adv Neurol Disord. 2011 Mar;4(2):111–21.
36. Sellner J, Boggild M, Clanet M, Hintzen RQ, Illes Z, Montalban X, et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. Eur J Neurol. 2010 Aug;17(8):1019–32.
37. Araki M, Matsuoka T, Miyamoto K, Kusunoki S, Okamoto T, Murata M, et al. Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: a pilot study. Neurology. 2014 Apr;82(15):1302–6.
38. Carroll WM, Fujihara K. Neuromyelitis optica. Curr Treat Options Neurol. 2010 May;12(3):244–55.
39. George JS, Leite MI, Kitley JL, Jones N, Cortes N, Donati M, et al. Opportunistic infections of the retina in patients with aquaporin-4 antibody disease. JAMA Neurol. 2014 Nov;71(11):1429–32.
40. Flanagan EP, Weinshenker BG. Neuromyelitis optica spectrum disorders. Curr Neurol Neurosci Rep. 2014 Sep;14(9):483.
41. Akaishi T, Takahashi T, Fujihara K, Misu T, Abe M, Ishii T, et al. Risk factors of attacks in neuromyelitis optica spectrum disorders. J Neuroimmunol. 2020 Jun;343:577236.
42. Ghezzi A, Bergamaschi R, Martinelli V, Trojano M, Tola MR, Merelli E, et al. Clinical characteristics, course and prognosis of relapsing Devic's Neuromyelitis Optica. J Neurol. 2004 Jan;251(1):47–52.
43. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica: clinical predictors of a relapsing course and survival. Neurology. 2003 Mar;60(5):848–53.
44. Kitley J, Leite MI, Nakashima I, Waters P, McNeillis B, Brown R, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. Brain. 2012 Jun;135(Pt 6):1834–49.
45. Songthammawat T, Srisupa-Olan T, Siritho S, Kittisares K, Jitprapaikulsan J, Sathukitchai C, et al. A pilot study comparing treatments for severe attacks of neuromyelitis optica spectrum disorders: Intravenous methylprednisolone (IVMP) with add-on plasma exchange (PLEX) versus simultaneous ivmp and PLEX. Mult Scler Relat Disord. 2020 Feb;38:101506.
46. Traboulsee A, Greenberg BM, Bennett JL, Szczechowski L, Fox E, Shkrobot S, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. Lancet Neurol. 2020 May;19(5):402–12.

Article Topic: Myasthenia gravis.

Author: Basel Abbas Asad Ghwini.

Editor: Yaman Oudat, Aroob Awwad.

Reviewer: Ethar Hazaimeh.

Keyword: autoimmune, acetylcholine receptors, antibodies, myasthenia gravis.

Overview and epidemiology

Thomas Willis wrote about a woman who lost her ability to speak in his book "De anima brutorum," the book was published in 1672[1], he was the first to write a description about myasthenia gravis (MG), on the other hand Wilks was the first person who report myasthenia gravis in 1877[2]. At the end of 19th century, Erb and Goldflam described the myasthenia gravis clinical symptoms. [3] It was named Erb-Goldflam syndrome for several years. In 1895, Jolly used the name of myasthenia gravis and explained myasthenic reaction of muscle [3].

Myasthenia gravis is an autoimmune chronic disease in which antibodies are directed against acetylcholine receptors or against proteins involved in the clustering of acetylcholine receptors (MuSK, LRP-4, or agrin) in the postsynaptic membrane at the neuromuscular junction and leads to skeletal muscle weakness and fatigue[4,5].

The prevalence is about 140 cases per million[6,7], with an annual incidence estimated to be between ten and thirty per million[6,8]. the peak of incidence is different between men and women, with a bimodal distribution, women is more commonly affected under the age of forty, and men more commonly affected over the age of fifty[6,9]. The frequency of myasthenia gravis in the elderly seems to be rising recently, attributed to enhanced awareness of the disease in recent decades[6].

Pathogenesis and etiology

When action potential travel through alpha motor neurons and reaches the presynaptic boutons, which contains acetylcholine loaded synaptic vesicles[10], depolarization of presynaptic membrane opens voltage gated calcium channels, causing the calcium ions to influx, calcium then docking of the synaptic vesicles to the presynaptic terminals, enabling release of Ach into the synaptic cleft, binding of acetylcholine to acetylcholine receptors on the muscle membrane leads to sodium and potassium flux across the junctional membrane, leading to depolarization of endplate. If the motor endplate

potential (EPP) reaches threshold, voltage gated sodium channels located at the underside of the folds are opened, resulting in sodium influx and therefore the generation of an “all or none” muscle fiber action potential that spreads bidirectionally through the muscle fiber. In myasthenia gravis patients, A reduction of AChR molecules causing “reduced safety factor,” and the number of AChRs contacted may be inadequate to drive the EPP to threshold, causing failure of neuromuscular transmission[6,11].

The disease is divided into several sub-groups because the clinical manifestations of myasthenia gravis vary according to the age of onset, the antibody involved and the presence of thymic pathology [12].

A. Pure ocular form

Around 15% of myasthenia gravis patients present with only ocular symptoms[12], due to high percentage of patients with initial ocular manifestation in the first year of onset, minimally 2 years delay without generalization is needed to classify a patient as a pure ocular form. 50% of these patients present antibodies not detectable by a classical assay but often demonstrable in a cell-based assay “CBA”[13].

B. Generalized form with anti AChR antibodies.

Around 85% of myasthenia gravis patient displays this form[12]. There is no apparent correlation between the level of antibodies and the severity of the disease. Thymic abnormalities are usually found in these patients, and the maximum titers of antibodies are seen in patients with thymic follicular hyperplasia, the anti-AChR antibodies belong to the IgG1 and IgG3 subclasses[14]. The patients with AChR antibodies can be divided into two sub-groups:

- Early onset myasthenia gravis “EOMG”, the onset before the age of 50 and it is to women, thymic follicular hyperplasia found in women[15].
- Late onset myasthenia gravis “LOMG”, the onset after the age of 50, most patients generalized and severe symptoms like bulbar involvement [16].

C. The forms without classical anti-AChR antibodies

- **The form with anti-MuSK antibodies**

Around 5% of patients with myasthenia gravis has this antibody kind[17], the patients are typically female, and they have serious form of the disease with common muscular atrophy, the respiratory muscles are commonly affected, but ocular symptoms and thymic abnormalities are unusual. The anti-MuSK antibodies belong to the IgG4 subclass[18].

- **The form with anti-LRP4 antibodies**

Around 12-50%of the seronegative population presents antibodies to LRP4. These antibodies were detected in a subgroup of patients who were double seronegative for AChR and MuSK[19].

- **The form with clustered AChR antibodies**

Around 5% of the myasthenia gravis patients has no recognized antibodies[12]. The antibodies can be discovered by cell-based assay, in which AChRs are assembled, the clinical pattern is similar to myasthenia gravis with classical anti-AChR antibodies involving ocular and generalized form; thymic hyperplasia may be present[13].

D. Neonatal myasthenia gravis

There is a possibility of aggravation of the myasthenic symptoms in 20-40% of females throughout the first 3 months. In 10-20% of the cases, the newborn will display a transient neonatal myasthenia (TNM) that could last a few days to 3 months. This disease is because of the passive transfer of the antibodies from the mother, the anti-AChR antibodies[20].

Clinical presentation

Clinically, patients with myasthenia gravis will have nonspecific features of weakness and fatigability which are fluctuating in nature, these symptoms will get worse as the day goes on or with exercise, indicative of the loss of function of AChRs, and improves with rest[21].

Patients with myasthenia gravis will also have a different pattern of weakness due to the vulnerability of certain muscle groups. Most of the patients will initially present with ocular symptoms like ptosis and diplopia but with no pupillary abnormalities [21](figure1). About 50% of patients will have ocular symptoms, and that is why an ophthalmologist initially sees most patients. Around 90% of patients eventually have ocular manifestation within 1 to 2 years[22]. Bulbar muscle weakness shows dysarthria, dysphagia, or chewing difficulties. Limp (appendicular)muscle weakness caused by myasthenia gravis is rare.

Exacerbation of symptoms appears with infection, pregnancy, menses, heat exposure. exacerbation that needs mechanical respiratory support is called myasthenia crisis [22]. the occurrence of some severe symptoms like shortness of breath, ineffective cough, choking, and rapid motor deterioration indicate MG crisis which is an emergency and needs immediate hospitalization in intensive care.[12]

On neurological examination there may be positive findings of gaze palsy, which can be unilateral, and bilateral ptosis which will reduce facial expression and affect smile, lower lip may be slightly everted, jaw may drop, dysarthria and dysphonia can be present, hyperacusis due to weakness of inner ear stapedius muscle [22], Chewing difficulties may present because of jaw fatigue ,also swallowing may be affected due to pharyngeal muscle weakness [21] . limp weakness is usually proximal and asymmetrical, the flexor muscles of neck weaken early [22].

Figure 1: Bilateral asymmetrical ptosis in MG patients (24).

Table 1: MG classified corresponding to the distribution and severity by myasthenia gravis foundation of America clinical classification [23]:		
Class 1	Any ocular muscle weakness, all other muscle strength is normal	
Class 2	mild generalized	2a-> mainly limp axial muscles
		2b-> mainly oropharyngeal /respiratory muscles
Class 3	moderate generalized	3a-> mainly limp axial muscles
		3b->mainly oropharyngeal /respiratory muscles
Class 4	severe generalized	4a-> mainly limp axial muscles
		4b->mainly oropharyngeal /respiratory muscles
Class 5	intubation	

Diagnosis

To diagnose a patient with myasthenia gravis may be somehow challenging because of fluctuation character and as the fatigue is a common symptom of various neuromuscular disorders[23].

Serologic testing is the first diagnostic step for MG. anti-acetylcholine receptor antibodies assay, purified AChR from obtained skeletal muscle is labeled with radio iodine alpha bungarotoxin[23]. Its sensitivity to generalized form of myasthenia gravis is about 85 percent, and to ocular form is about 50 percent. For patient with similar grade of weakness the serum concentration of acetylcholine antibodies differs broadly among myasthenia gravis patients. To diagnose myasthenia gravis clinical features are essential along with elevated concentration of antibodies in patient serum, although other diseases may have elevated serum AChR antibodies like autoimmune liver disease,

systemic lupus, and in patients with thymoma, as well as in RA patients whom receiving penicillamine[25].there are many other assays somehow increase the sensitivity like AChR-blocking antibodies which measures the capability of patient serum to inhibit cholinergic ligands binding , or AChR-modulating antibodies which measures the capability of patient serum to induce modulation of AChR in cell cultures[26].

The low affinity anti -acetylcholine receptor antibodies in which antibodies binds to AChRs clustered on the surface of cells other than muscle is shown in about 66 percent generalized form MG patients who were negative for antibodies on all standard assays [AChR, MuSK][13].

Anti-striated muscle antibodies are highly related with thymoma, around 75 to 80 percent of myasthenia gravis patients along with thymoma are positive, in some cases it can be positive in non-thymomatous patients like in old patients[27]. There might be a correlation between the presence of anti-titin or anti-ryanodine antibodies and late-onset form of myasthenia gravis specifically with more severe disease[28].

One of noninvasive and cost-effective tools in diagnosing myasthenia gravis is ice pack test, which involves the application of a packet of ice onto the eyes for about 5 minutes, if ptosis resolves, the test is considered positive.[29]

One of short acting acetylcholine inhibitor which is Edrophonium chloride works by extending the duration of action of acetylcholine within the NMJ, it is used for patients suspected to possess myasthenia gravis. The edrophonium test, includes intravenous administration of edrophonium and then observation for progression in muscle strength (figure2), the edrophonium test sensitivity in MG diagnosis varies between 71% to 95% for generalized form[30].

Figure 2: edrophonium test A bilateral ptosis in MG patient B IV edrophonium administration.

Electrophysiological test can determine the exhaustion of neuromuscular transmission that caused by a diminished number of functional AChRs. Most frequently used is repetitive nerve stimulation in which repeated supramaximal electrical stimulation of a nerve is performed with recording of the compound muscle action potential in a subsequent muscle. There is 80% reduction in the amplitude or the area of the compound muscle action potential following repetitive nerve stimulation in patients with generalized form of myasthenia gravis , but less than fifty percent in patients with ocular form myasthenia gravis[31].

Single-fiber electromyography [SFEMG] is a highly specialized manner that allows for recording of electrical potentials from single muscle fiber[31]. It can be considered if clinical suspicion for myasthenia gravis is high and all other testing were negative[32],SFEMG can determine neuromuscular jitter, which is variation in the time electrical potential takes to reach the threshold for muscle fiber, in myasthenia gravis patients SFEMG shows abnormal jitter in 95-99 percent of patients if appropriate muscle are tested[31], but SFEMG is not specific only to myasthenia gravis, other abnormalities in nerve or even in muscle can be seen[23].

Chest CT scan is helpful in presence of thymoma, a generalize myasthenia gravis patient with anti-AChR antibodies needs to monitor the thymus every 5 year if the patient is not thymectomized[12].

Figure 3: CT scan of the mediastinum of a young woman clinically demonstrate features of MG with anterior mediastinal thymoma type 2B, Case courtesy of Assoc Prof Frank Gaillard (33).

Differential diagnosis of MG

Include other neuromuscular junction disorders [34]:

- lambert Eaton myasthenic syndrome
- Botulism
- Congenital myasthenic syndrome
- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) may encourage myasthenia gravis.
- Mitochondrial neuromuscular disorders
- Motor neuron disease
- Brainstem ischemia
- Organophosphate poisoning

Disease	Clinical features	Diagnostic test
Progressive external ophthalmoplegia	Progressive ptosis and ophthalmoplegia fixed weakness	EMG muscle biopsy
Amyotrophic lateral sclerosis	Asymmetric muscle weakness and atrophy Fasciculation and hyperreflexia normal eye movements	EMG nerve conduction velocities
Lambert-Eaton myasthenic syndrome	Proximal, symmetric hip and shoulder weakness Paresthesia Dry mouth Hyporeflexia	Repetitive nerve stimulation Anti-Hu and anti-calcium channel antibodies
Periodic paralysis	Intermittent generalized limb weakness after exertion or intake of high carbohydrate food	Potassium level during attack Muscle biopsy
Polymyositis, dermatomyositis	Proximal, symmetric limb weakness with or without skin rash	Serum CK EMG muscle biopsy
Guillain-Barre syndrome	Ascending, symmetric limb weakness and areflexia	nerve conduction velocities and F wave CSF study
Botulism	Generalized limb weakness Pupillary dilatation Hyporeflexia	Repetitive nerve stimulation
Multiple sclerosis	**Bilateral internuclear ophthalmoplegia Upper motor neuron signs**	**Magnetic resonance imaging of head CSF study**

Table 2: differentiation of myasthenia and other neurological disorders[22]

Treatment

Treatment of myasthenia gravis is individualized, the overall goal of treatment is to restore the normal function and to minimize adverse effect of the disease, treatment choice depends on many factors including the distribution, duration, and the severity of the disease[34]. There might be complications associated with treatment, the risk of having this complication is increased with age, gender, medical comorbidities, and compliance of the patient[34].

Plasma exchange and IVIG

Plasma exchange is used to decrease the number of circulating antibodies and shows improvement in myasthenia gravis patient specifically the acquired form[35].it is used as a short-term treatment for severe cases, myasthenia gravis crisis, or prior thymectomy or another surgical procedure and in refractory cases of myasthenia gravis[34]. PE series consist of 5 to 6 exchanges of 2 or 3 liters on different days[34]. Many side effects could be happened from PE includes paresthesia because of hypocalcemia and hypotension[36].

The use of IVIg improve the muscle strength specially in severe cases, patient with septicemia and prior to surgeries, common side effect may include chills, headache, and fever. Some serious side effect may include renal toxicity, volume overload, aseptic meningitis and stroke but they are rare, Decreasing the rate of infusion may improve some side effects[23]. IVIGs is administered as 10% solution, with standard dosage is 2 gm/kg over 2 to 5 days[34].practice parameter analyzed all controlled studies of thymectomy in myasthenia gravis patients, and the results were baffled by baseline variances between surgical and nonsurgical groups[37]. In a random trial compare between efficacy IVIg an PE, it supports the use of IVIg in treatment of myasthenia gravis patients[38].

Drugs for Symptomatic Therapy

There are several strategies to treat myasthenia gravis patients which includes improving the effect of acetylcholine by using cholinesterase inhibitors, get rid of AChR antibodies by plasma exchange or intravenous IG, thymectomy, immunosuppression[23].

first-line medication used to treat myasthenia gravis patients is a drug that inhibits acetylcholine esterase function, due to its safety, rapid onset, few side effects. Pyridostigmine is the most used AChEI, it works as a symptomatic therapy by increasing

the amount of ACh in the synaptic cleft of NMJ, starting dose of 30 to 60 every 4-6 hours[34].

doses beyond 120 mg every 4 hours are not often effective and more likely to give cholinergic side effects include diarrhea, sweating, bradycardia, stomach cramps, increased secretions[39,40].

Immunosuppressive Drug Therapy

Corticosteroids are commonly used in myasthenia gravis, prednisone is used as a first choice in treating myasthenia gravis, indicated to generalized form or ocular form myasthenia gravis patients that cholinesterase inhibitors were not enough to control their symptoms[23],admenstration of prednisone is mostly at high doses 0.75-1.0 mg/kg/day for quite a few months at first, then gradual tapering off the dose. The improvement needs about 2-4 weeks to be observed[23]. Around 30-50% of patients showed transient worsening of symptoms when given high daily prednisone dose [41]. corticosteroids have side effects in every system of the body like DM, osteoporosis, and obesity[42]. for most of the patients, azathioprine is added to corticosteroids, this combination will reduce the side effects and enhance the results, in case of contraindication for corticosteroids, azathioprine can be given as a monotherapy. The long-term treatment is safe an all patients[43].

Most guidelines recommend mycophenolate mofetil for mild or moderate myasthenia gravis, the mechanism of action of this drug is by inhibiting purine synthesis and interference with B-cell and T-cell proliferation. Methotrexate, cyclosporine, and tacrolimus are alternative secondary immunosuppressive drugs[43].

MEDICATION	TOME TO ONSET	DOSE	SIDE EFFECTS	NOTES
SHORT TERM				
Pyridostigmine	20 min x 4h	30–60 mg tid	Diarrhea, bradycardia	Cholinergic crisis Caution in bronchial asthma. For night or morning weakness, may use 180 mg "Timespan"
IVIG	Improvement within 2wk	2 g/kg divided over 4 or 5 infusions	Tachycardia, hyper/hypo-tension Rare: fluid overload or thrombosis	
Plasmapheresis	Days to 1 wk	5 or 6 total exchanges of 2to 3 Leach, every other day	Hypotension Arrhythmias	
INTERMEDIATE TERM				
Glucocorticoids (prednisone)		20–40 mg/d	Osteoporosis, weight gain, mood disturbances, acne	Check for latent TB prior to starting any immunosuppressants
Cyclosporine (Neoral)		2 mg/kg bid	Nephrotoxic	
Tacrolimus		0.035 mg/kg bid	Nephrotoxic, liver toxicity	
LONG TERM				
Mycophenolate	Months to 1 year	1 or 1.5 g bid	GI upset	Give "Myfortic" 720 mg bid if GI problems with mycophenolate
Azathioprine	Many months		Infections, diarrhea, nausea	Never give with allopurinol-Myelotoxic
Rituximab	May benefit within weeks, or may require a second course of 4 treatments 2 or 3 month later	375 mg/m2 weekly for 4wk	Headache, fever, diarrhea, flushing	Premedicate with methylprednisolone 50–100 mg, Benadryl. Better for anti-MuSK than for anti-AChR Ab MG

Abbreviations: bid, twice daily; GI, gastrointestinal; IVIG, intravenous immunoglobulin; TB, tuberculosis; tid, three times daily. Table 3: myasthenia gravis treatment plan[5]

Thymectomy

Thymectomy is indicated for removal of a thymic tumor or as a treatment for MG. Thymic tumors can spread locally so they must be removed. Thymomas in general respond to corticosteroids treatment as well, for generalized myasthenia gravis thymectomy is recommended as a treatment, previous studies show that 1/3 of patients had excellent results, 1/3 improve, and 1/3 obtain no clinical benefit. Thymectomy should never be done as an emergent procedure, the earlier it performed, the more rapidly its benefits realized[5].

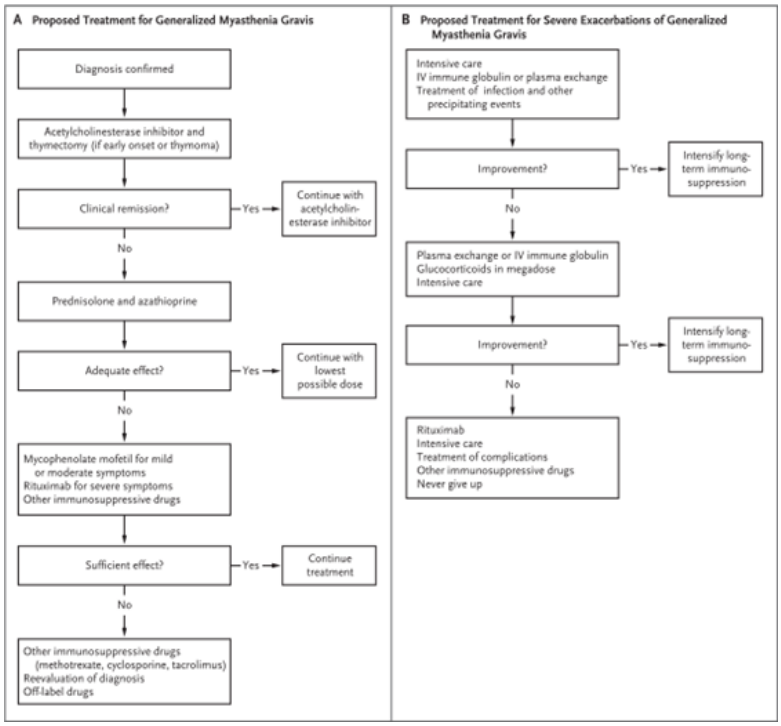


Figure 4: Algorithms for generalized MG treatment and for severe exacerbation for generalized disease43.

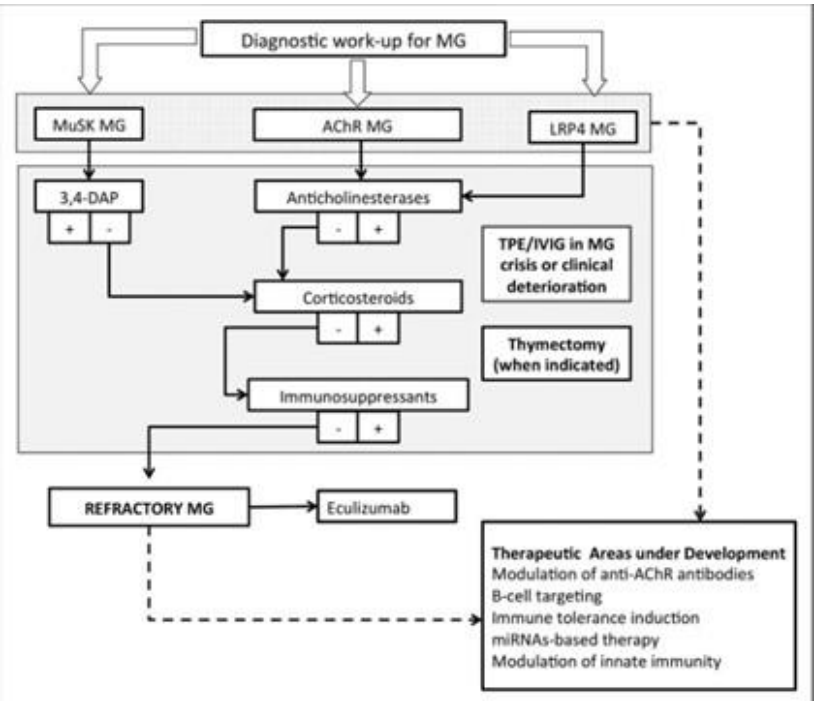


Figure 5: Flowchart summary of treatment strategies for the main serological subtypes of MG5

Refractory Myasthenia gravis

Even though most of myasthenia gravis patients respond to treatment listed above, some patients do not respond to these agents, or cannot tolerate their side effect, treatment for those patients should try to remove the autoimmune response, by giving them high doses of cyclophosphamide to reboot their immune system. Many of them shows good results. This method necessitates special attention and should be performed under supervision of experts in the area of hematology/oncology[5]. Other choice can be given to those patients is Eculizumab, which is recombinant humanized monoclonal antibody that binds to the C5 complement protein and prevent the formation of C5b-9 membrane attack complex, candidates for this therapy are those with severe or refractory disease despite receiving adequate immunotherapies or can not tolerate their side effects, meningococcal vaccine should be given prior therapy administration[44].

Myasthenic crisis

It is life-threatening manifestation of myasthenia gravis, weakness develop within minutes to days and involve flaccid tetra paresis, severe dyspnea, respiratory failure, and aspiration. Rapid progressive weakness of respiratory muscles is the main symptom. The early diagnosis and treatment the better outcome, treatment includes early intubation, it is essential to secure the airway, pyridostigmine or neostigmine to relief symptoms, plasmapheresis, or immunoglobulins. Corticosteroids and azathioprine should be optimized. rituximab can be a choice for escalation[45].

Prognosis

Early in the coarse of myasthenia gravis, symptoms fluctuate and sometimes remit, even though such remission are rarely permanent, there are three major stages, an active stage described as relapses and remissions last about 7 years is followed by an inactive stage last about 10 years, the inactive stage is characterized by less disease volatility, however patients may have aggravation related to many causes, ultimate stage of “burned-out” disease, untreated weakness may become fixed in relation to muscle atrophy.[34]

References

1. Mimenza-Alvarado A, Tellez-Zenteno J, Garcia-Ramos G, Estañol B. [The history of myasthenia gravis. Men and ideas.]. *Neurologia*. Published online June 2007.
2. SPECIAL ARTICLE. *J Am Med Assoc*. 1953;153(14):1273-1280. doi:10.1001/jama.1953.02940310041010
3. Capone L, Gentile R, Schoenhuber R. Thymus and Myasthenia Gravis. Pathophysiological and Clinical Features. In: Lavini C, Moran CA, Morandi U, Schoenhuber R, eds. *Thymus Gland Pathology: Clinical, Diagnostic, and Therapeutic Features*. Springer Milan; 2008:89-98. doi:10.1007/978-88-470-0828-1_8
4. Mantegazza R, Bernasconi P, Cavalcante P. Myasthenia gravis: from autoantibodies to therapy. *Curr Opin Neurol*. 2018;31(5):517-525. doi:10.1097/WCO.0000000000000596

5. Willcox N. Myasthenia gravis. *Curr Opin Immunol*. 1993;5(6):910-917. doi:10.1016/0952-7915(93)90105-2
6. Atsuko H, Mutsumi I, Masanobu U. Myasthenia Gravis の. 東京女子医科大学雑誌. 2008;78(臨時増刊号):E178-E181.
7. Heldal AT, Owe JF, Gilhus NE, Romi F. Seropositive myasthenia gravis: a nationwide epidemiologic study. *Neurology*. 2009;73(2):150-151. doi:10.1212/WNL.0b013e3181ad53c2
8. Andersen JB, Heldal AT, Engeland A, Gilhus NE. Myasthenia gravis epidemiology in a national cohort; combining multiple disease registries. *Acta Neurol Scand Suppl*. 2014;(198):26-31. doi:10.1111/ane.12233
9. Mantegazza R, Baggi F, Antozzi C, et al. Myasthenia gravis (MG): epidemiological data and prognostic factors. *Ann N Y Acad Sci*. 2003;998:413-423. doi:10.1196/annals.1254.054
10. Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. *J Clin Invest*. 2006;116(11):2843-2854. doi:10.1172/JCI29894
11. Morgutti M, Conti-Tronconi BM, Sghirlanzoni A, Clementi F. Cellular immune response to acetylcholine receptor in myasthenia gravis. *Neurology*. 1979;29(5):734 LP - 734. doi:10.1212/WNL.29.5.734
12. Berrih-Aknin S, Frenkian-Cuvelier M, Eymard B. Diagnostic and clinical classification of autoimmune myasthenia gravis. *J Autoimmun*. 2014;48-49:143-148. doi:10.1016/j.jaut.2014.01.003
13. Leite MI, Jacob S, Viegas S, et al. IgG1 antibodies to acetylcholine receptors in 'seronegative' myasthenia gravis†. *Brain*. 2008;131(7):1940-1952. doi:10.1093/brain/awn092
14. Verschuuren JJGM, Huijbers MG, Plomp JJ, et al. Pathophysiology of myasthenia gravis with antibodies to the acetylcholine receptor, muscle-specific kinase and low-density lipoprotein receptor-related protein 4. *Autoimmun Rev*. 2013;12(9):918-923. doi:10.1016/j.autrev.2013.03.001
15. Eymard B, Berrih-Aknin S. [Role of the thymus in the physiopathology of myasthenia]. *Rev Neurol (Paris)*. 1995;151(1):6-15.
16. Romi F, Aarli JA, Gilhus NE. Myasthenia gravis patients with ryanodine receptor antibodies have distinctive clinical features. *Eur J Neurol*. 2007;14(6):617-620. doi:10.1111/j.1468-1331.2007.01785.x
17. Evoli A, Tonali PA, Padua L, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. *Brain*. 2003;126(Pt 10):2304-2311. doi:10.1093/brain/awg223
18. McConville J, Farrugia ME, Beeson D, et al. Detection and characterization of MuSK antibodies in seronegative myasthenia gravis. *Ann Neurol*. 2004;55(4):580-584. doi:10.1002/ana.20061
19. Zhang B, Tzartos JS, Belimezi M, et al. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. *Arch Neurol*. 2012;69(4):445-451. doi:10.1001/archneurol.2011.2393
20. Vernet-der Garabedian B, Lacokova M, Eymard B, et al. Association of neonatal myasthenia gravis with antibodies against the fetal acetylcholine receptor. *J Clin Invest*. 1994;94(2):555-559. doi:10.1172/JCI117369
21. Hehir MK, Silvestri NJ. Generalized Myasthenia Gravis: Classification, Clinical Presentation, Natural History, and Epidemiology. *Neurol Clin*. 2018;36(2):253-260. doi:10.1016/j.ncl.2018.01.002
22. Pourmand R. Abstract . -Adult-onset myasthenia gravis is an acquired au- toimmune disorder of neuromuscular transmission in which ace- tylcholine receptor antibodies attack the postsynaptic membrane of the neuromuscular junction . Although the cause of this dis- ease. 1997;(February):70-109.
23. Meriggioli MN. Myasthenia gravis with anti-acetylcholine receptor antibodies. *Front Neurol Neurosci*. 2009;26:94-108. doi:10.1159/000212371
24. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM. Myasthenia gravis. *Nat Rev Dis Prim*. 2019;5(1):30. doi:10.1038/s41572-019-0079-y
25. the-clinical-limits-of-myasthenia-gravis-and-differential-diagnosis.
26. Howard FMJ, Lennon VA, Finley J, Matsumoto J, Elveback LR. Clinical correlations of antibodies that bind, block, or modulate human acetylcholine receptors in myasthenia gravis. *Ann N Y Acad Sci*. 1987;505:526-538. doi:10.1111/j.1749-6632.1987.tb51321.x
27. Romi F, Skeie GO, Gilhus NE, Aarli JA. Striational antibodies in myasthenia gravis: reactivity and possible clinical significance. *Arch Neurol*. 2005;62(3):442-446. doi:10.1001/archneur.62.3.442
28. Romi F, Skeie GO, Aarli JA, Gilhus NE. The severity of myasthenia gravis correlates with the serum concentration of titin and ryanodine receptor antibodies. *Arch Neurol*. 2000;57(11):1596-1600. doi:10.1001/archneur.57.11.1596
29. Kearsey C, Fernando P, D'Costa D, Ferdinand P. The use of the ice pack test in myasthenia gravis. *JRSM Short Rep*. 2010;1(1):14. doi:10.1258/shorts.2009.090037
30. Pascuzzi RM. The edrophonium test. *Semin Neurol*. 2003;23(1):83-88. doi:10.1055/s-2003-40755
31. Meriggioli MN, Sanders DB. Advances in the diagnosis of neuromuscular junction disorders. *Am J Phys Med Rehabil*. 2005;84(8):627-638. doi:10.1097/01.phm.0000171169.79816.4c
32. Padua L, Stalberg E, LoMonaco M, Evoli A, Batocchi A, Tonali P. SFEMG in ocular myasthenia gravis diagnosis. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 2000;111(7):1203-1207. doi:10.1016/s1388-2457(00)00307-2
33. Radiopedia. thymoma. https://radiopaedia.org/cases/thymoma-8?lang=us
34. Juel VC, Massey JM. Myasthenia gravis. *Orphanet J Rare Dis*. 2007;2:44. doi:10.1186/1750-1172-2-44
35. Kordas G, Lagoumintzis G, Sideris S, Poulas K, Tzartos SJ. Direct proof of the in vivo pathogenic role of the AChR autoantibodies from myasthenia gravis patients. *PLoS One*. 2014;9(9):e108327. doi:10.1371/journal.pone.0108327
36. Keefe D, Hess D, Bosco J, et al. A rapid, fluorescence-based assay for detecting antigenic modulation of the acetylcholine receptor on human cell lines. *Cytom Part B Clin Cytom*. 2009;76B(3):206-212. doi:https://doi.org/10.1002/cyto.b.20454
37. Gronseth GS, Barohn RJ. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(1):7-15. doi:10.1212/wnl.55.1.7

38. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. *Ann Neurol*. 1997;41(6):789-796. doi:10.1002/ana.410410615
39. Punga AR, Sawada M, Stålberg E V. Electrophysiological signs and the prevalence of adverse effects of acetylcholinesterase inhibitors in patients with myasthenia gravis. *Muscle Nerve*. 2008;37(3):300-307. doi:10.1002/mus.20935
40. Breyer-Pfaff U, Schmezer A, Maier U, Brinkmann A, Schumm F. Neuromuscular function and plasma drug levels in pyridostigmine treatment of myasthenia gravis. *J Neurol Neurosurg Psychiatry*. 1990;53(6):502-506. doi:10.1136/jnnp.53.6.502
41. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. *Ann Neurol*. 1984;15(3):291-298. doi:10.1002/ana.410150316
42. Barnett C, Tabasinejad R, Bril V. Current pharmacotherapeutic options for myasthenia gravis. *Expert Opin Pharmacother*. 2019;20(18):2295-2303. doi:10.1080/14656566.2019.1682548
43. Article R. M 2570. Published online 2016. doi:10.1056/NEJMra1602678
44. Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of Myasthenia Gravis. *Neurol Clin*. 2018;36(2):311-337. doi:10.1016/j.ncl.2018.01.011
45. Stetefeld H, Schroeter M. SOP myasthenic crisis. *Neurol Res Pract*. 2019;1:19. doi:10.1186/s42466-019-0023-3

Article topic: Causes of Ischemic Stroke.

Author: Fadi Haddad.

Editor: Yaman Oudat.

Reviewer: Ethar Hazaimeh.

Keywords: Stroke, Classifications, Atherosclerosis, Cardio-embolism.

Introduction

Stroke can be defined as an acute episode of focal neurological deficit (brain, retina, or spinal cord) lasting longer than 24 h, or of any duration if radiological or pathological evidence of infarction or hemorrhage relevant to the symptoms, involving a defined cerebral vascular territory.[1] In the US, the number of adults who ever had a stroke is 7.8 million and the percent of adults who ever had a stroke is 3.1%, and it is ranked as the 5th leading cause of death.[2] It is important to establishing the most likely cause of an ischemic stroke as it influences both short-term and long-term prognoses and it affects treatment decisions.[3] Throughout history, many classifications of strokes have been defined such as; The Trial of Org 10172 in Acute Stroke Treatment (TOAST) Classification, The Spanish Classification system (GEECV/SEN), and The SPARKLE classification.[4-6] TOAST classification shows a logical and clinically oriented system and supports other independent assessments.[4] TOAST classification became the most widely used system to identify the etiology of strokes.[7]

TOAST Classification

TOAST classification has subdivided ischemic stroke into 5 categories: Large-artery atherosclerosis (embolus/thrombosis), Cardio-embolism (high-risk/medium-risk), Small-vessel occlusion (lacune), Stroke of other determined etiology, Stroke of undetermined etiology (Two or more causes identified, Negative evaluation or Incomplete evaluation). It is based on specific clinical, radiological, and laboratory investigations (Table 1), which will help in guiding proper management.

Table 1. Features of TOAST Classification of Subtypes of Ischemic Stroke

Features	Subtype			
	Large-artery atherosclerosis	Cardioembolism	Small-artery occlusion (lacune)	Other cause
Clinical				
Cortical or cerebellar dysfunction	Y	Y	N	Y/N
Lacunar syndrome	N	N	Y	Y/N
Imaging				
Cortical, cerebellar, brain stem, or subcortical infarct >1.5 cm	Y	Y	N	Y/N
Subcortical or brain stem infarct <1.5 cm	N	N	Y/N	Y/N
Tests				
Stenosis of extracranial internal carotid artery	Y	N	N	N
Cardiac source of emboli	N	Y	N	N
Other abnormality on tests	N	N	N	Y

(TOAST): Trial of Org 10172 in Acute Stroke Treatment, (Y): Yes, (N): No

Table 1. Features of TOAST classification of subtypes of Ischemic stroke.

Large Artery Atherosclerosis

Is defined as the presence of well-notable stenosis or occlusion (>50%) due to atherosclerosis of the major arteries of the brain (e.g., Internal carotid artery, and the basilar artery) or a Branch vessel (e.g. Anterior, posterior, and middle cerebral arteries) accompanied by an infarction larger than 15mm in diameter on Computed Tomography (CT) scanning or Magnetic Resonance Imaging (MRI), with clinical findings of cortical, cerebellar or brain stem damage depending on the occulted artery.[8-11] Large Artery Atherosclerosis is the most common cause of stroke forming (37.3%) of cases and in which, the most common territory affected is the territory of the middle cerebral artery (49.6%).[12] The arterial circulation of the brain can be divided into anterior and posterior circulations; regarding the anterior circulation, Middle Cerebral Artery (MCA) is most frequently involved and covers parts of the parietal lobe, the frontal lobe, and the temporal lobe (Figure 1).[13] Anterior Cerebral Artery infarction is a rare entity as it represents 0.5–3% of all ischemic strokes. It occurs most frequently on the left side of the brain, with contralateral hemiparesis or monoparesis as the most common presentation (Figure 2).[14-16] The posterior circulation covers the occipital lobe, cerebellum, and brain stem. The symptoms of which occur according to the involved location (Figure 3).[17]

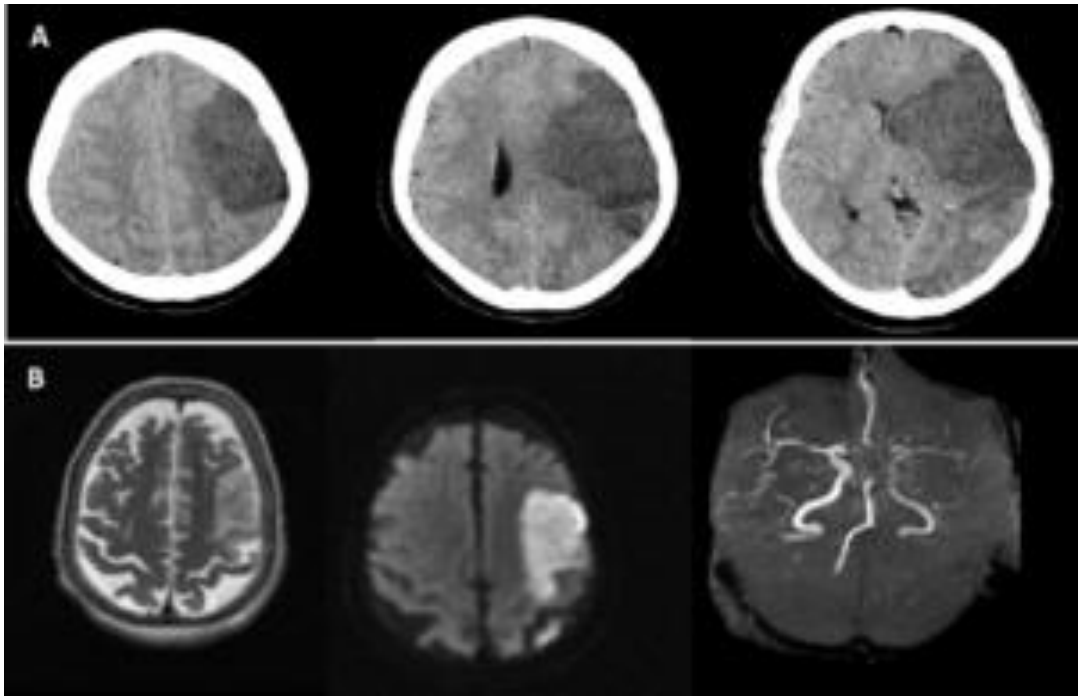


Figure 1. (A) Axial CT scan without contrast of the brain for a 60-years-old female patient presented with acute right-sided weakness showing a progression of MCA territory infarct with marked midline shift.18 (B) Axial T2 and DWI weighted MRI of the brain, and an MRA showing a well-defined area of high T2 signal with diffusion restriction in the left MCA territory. Loss of signal in the left MCA and its branches on the MRA.19

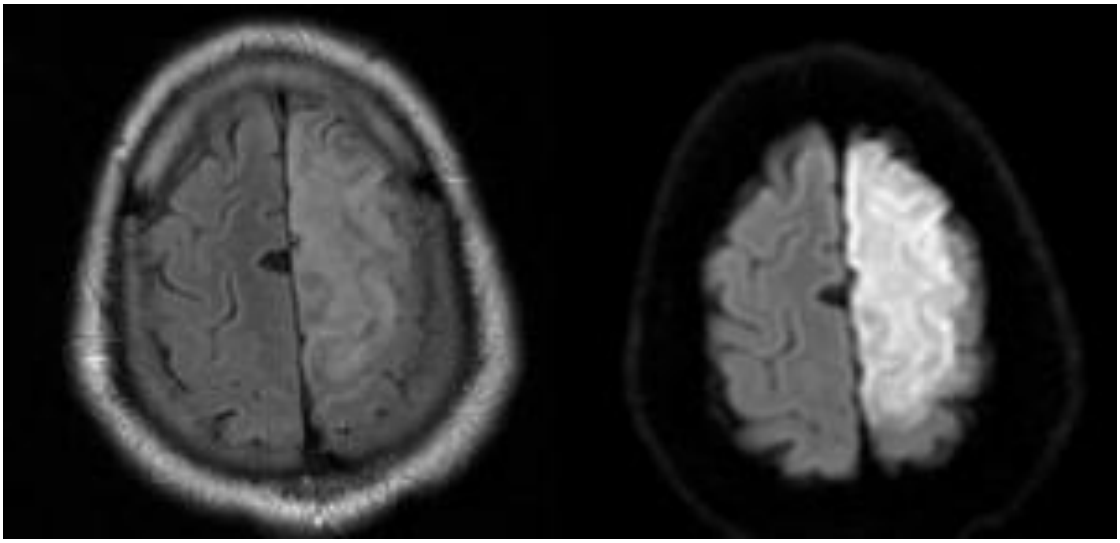


Figure 2. Axial Flair and DWI weighted MRI of the brain for a 50-years-old male presented with acute onset right lower limb weakness, showing DW imaging confirms acute infarction - territorial to left ACA.20

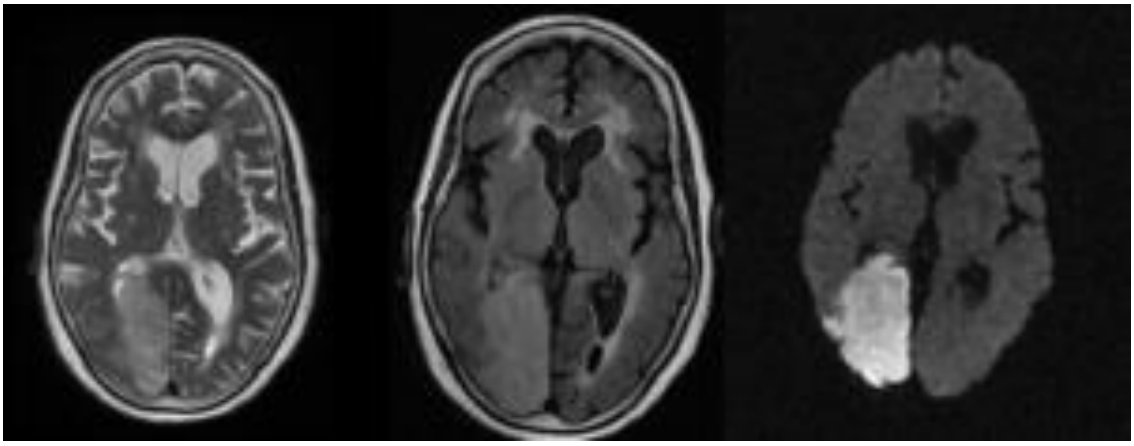


Figure 3. Axial T2. FLAIR and DWI MRI of the brain of an 85-years-old female presented with right-sided weakness and decreased vision showing right-sided PCA territory infarct showing hyperintense T2/FLAIR signals and diffusion restriction. Confluent high signal foci in T2 and FLAIR sequences at subcortical, centrum semiovale, and periventricular white matter of both cerebral hemispheres (Fazekas grade III) depict microvascular ischemic events.21

Cardio-embolism

The findings of Cardio-embolism strokes are similar to those of large artery atherosclerosis but differ as they originate from the heart. They are mostly associated with a variety of conditions including mechanical prosthetic valves, atrial fibrillation or flutter, recent myocardial infarction (<4 weeks), dilated cardiomyopathy, infective endocarditis Regional left ventricular akinesis, or rheumatic heart disease (Figure 4). It accounts for 20-30% of ischemic strokes.[22,23]

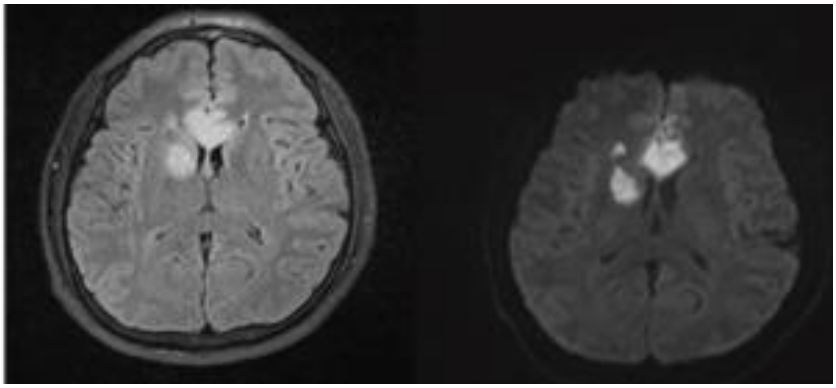


Figure 4. Axial DWI and FLAIR MRI for a 40-years-old male presented with an altered conscious level showing Extensive restricted diffusion in the rostrum, genu, and body of the corpus callosum. Further foci of restricted diffusion of variable size in the right internal capsule, corpus striatum, centrum semiovale, and insula. All consistent with acute infarcts.24

Small-vessel occlusion

Also known as Lacunar Strokes (LS); are defined as small infarctions occurring in the terminal branches of large cortical arteries. The main branches involved are derived from PCA territory. This can be due to a numerous number of causes; hypertension, dyslipidemia, and Diabetes Mellitus (DM). Moreover, it accounts for 20-30% of ischemic strokes.[25-28] They are clinically significant when infarcts are between 5 mm to 15 mm in diameter and involving the deep gray and subcortical white matter (Figure 5).[27]

Figure 5. Axial CT without contrast of the brain showing two small hypoattenuating areas on left thalamic and insular region.29

Strokes of other determined etiology

This kind of stroke accounts for 2-11% of ischemic strokes.[30] It can be due to a variety of causes such as vasculopathy (the most common cause) and is mostly associated with cytomegalovirus (CMV), human immunodeficiency virus (HIV) and Varicella zoster virus (VZV)[31], and hypercoagulable states (e.g. antithrombin III, protein S, and protein C deficiencies) [32,33], hematological disorders representing 1.3% of the causes of all acute strokes[34], right to left vascular shunts[35], and arterial dissections.[36]

Strokes of undetermined etiology

Despite intensive investigation, 25% of ischemic strokes do not any have identified etiologies.[37] This kind of stroke can be due to emboli of undetermined sources because they are not usually detected by conventional imaging techniques. Those causes might

be patent foramen ovale[38], paroxysmal atrial fibrillation[39], aortic arch atherosclerosis[40],3or non-stenosing atherosclerosis of the carotid arteries.[41]

References

1. Hankey GJ. Stroke. *Lancet (London, England)*. 2017;389(10069):641-654.
2. Cerebrovascular Disease or Stroke. 2021; https://www.cdc.gov/nchs/fastats/stroke.htm. Accessed 13- march, 2021.
3. Adams HP, Jr., Biller J. Classification of subtypes of ischemic stroke: history of the trial of org 10172 in acute stroke treatment classification. *Stroke*. 2015;46(5):e114-117.
4. Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35-41.
5. Sobrino García P, García Pastor A, García Arratibel A, et al. [Aetiological classification of ischaemic strokes: comparison of the new A-S-C-O classification and the classification by the Spanish Society of Neurology's Cerebrovascular Disease Study Group]. *Neurologia (Barcelona, Spain)*. 2013;28(7):417-424.
6. Bogiatzi C, Wannarong T, McLeod AI, Heisel M, Hackam D, Spence JD. SPARKLE (Subtypes of Ischaemic Stroke Classification System), incorporating measurement of carotid plaque burden: a new validated tool for the classification of ischemic stroke subtypes. *Neuroepidemiology*. 2014;42(4):243-251.
7. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. *Cerebrovascular diseases (Basel, Switzerland)*. 2009;27(5):493-501.
8. Mukherjee D, Jani ND, Narvid J, Shadden SC. The Role of Circle of Willis Anatomy Variations in Cardio-embolic Stroke: A Patient-Specific Simulation Based Study. *Annals of biomedical engineering*. 2018;46(8):1128-1145.
9. Patel B, Markus HS. Magnetic resonance imaging in cerebral small vessel disease and its use as a surrogate disease marker. *International journal of stroke: official journal of the International Stroke Society*. 2011;6(1):47-59.
10. Sparaco M, Ciolli L, Zini A. Posterior circulation ischaemic stroke-a review part I: anatomy, aetiology and clinical presentations. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2019;40(10):1995-2006.
11. Rennert RC, Wali AR, Steinberg JA, et al. Epidemiology, Natural History, and Clinical Presentation of Large Vessel Ischemic Stroke. *Neurosurgery*. 2019;85(suppl_1):S4-s8.
12. Chung JW, Park SH, Kim N, et al. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and vascular territory of ischemic stroke lesions diagnosed by diffusion-weighted imaging. *Journal of the American Heart Association*. 2014;3(4).
13. Shapiro M, Raz E, Nossek E, Chancellor B, Ishida K, Nelson PK. Neuroanatomy of the middle cerebral artery: implications for thrombectomy. *Journal of neurointerventional surgery*. 2020;12(8):768-773.
14. Kang SY, Kim JS. Anterior cerebral artery infarction: stroke mechanism and clinical-imaging study in 100 patients. *Neurology*. 2008;70(24 Pt 2):2386-2393.
15. Toyoda K. Anterior cerebral artery and Heubner's artery territory infarction. *Frontiers of neurology and neuroscience*. 2012;30:120-122.
16. Kazui S, Sawada T, Naritomi H, Kuriyama Y, Yamaguchi T. Angiographic evaluation of brain infarction limited to the anterior cerebral artery territory. *Stroke*. 1993;24(4):549-553.
17. Kim JS, Caplan LR. Clinical Stroke Syndromes. *Frontiers of neurology and neuroscience*. 2016;40:72-92.
18. Cuete D. MCA infarct and decompressive craniectomy. 2014; https://radiopaedia.org/cases/mca-infarct-and-decompressive-craniectomy-1. Accessed March, 2021.
19. Choudhary DG. Left middle cerebral artery territory infarct. 2010; https://radiopaedia.org/cases/left-middle-cerebral-artery-territory-infarct. Accessed March, 2021.
20. Babu DV. Anterior cerebral artery infarction. 2016; https://radiopaedia.org/cases/anterior-cerebral-artery-infarction?lang=us. Accessed March, 2021.
21. Rasuli DB. Posterior cerebral artery territory infarct. 2021; https://radiopaedia.org/cases/posterior-cerebral-artery-territory-infarct-1?lang=us, 2021.
22. Kamel H, Healey JS. Cardioembolic Stroke. *Circulation research*. 2017;120(3):514-526.
23. Freeman WD, Aguilar MI. Stroke prevention in atrial fibrillation and other major cardiac sources of embolism. *Neurologic clinics*. 2008;26(4):1129-1160, x-xi.
24. Bickle DI. Cardioembolic stroke: ACA and MCA territories. 2018; https://radiopaedia.org/cases/cardioembolic-stroke-aca-and-mca-territories?lang=us. Accessed March, 2021.
25. Regenhardt RW, Das AS, Lo EH, Caplan LR. Advances in Understanding the Pathophysiology of Lacunar Stroke: A Review. *JAMA neurology*. 2018;75(10):1273-1281.
26. Arboix A, Arbe G, García-Eroles L, Oliveres M, Parra O, Massons J. Infarctions in the vascular territory of the posterior cerebral artery: clinical features in 232 patients. *BMC research notes*. 2011;4:329.
27. Regenhardt RW, Das AS, Ohtomo R, Lo EH, Ayata C, Gurol ME. Pathophysiology of Lacunar Stroke: History's Mysteries and Modern Interpretations. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2019;28(8):2079-2097.
28. Caplan LR. Lacunar infarction and small vessel disease: pathology and pathophysiology. *Journal of stroke*. 2015;17(1):2-6.

29. Radswiki. Lacunar infarction. 2010; https://radiopaedia.org/cases/lacunar-infarction?lang=us. Accessed March, 2021.
30. Knight-Greenfield A, Nario JJQ, Gupta A. Causes of Acute Stroke: A Patterned Approach. *Radiologic clinics of North America*. 2019;57(6):1093-1108.
31. Nagel MA, Mahalingam R, Cohrs RJ, Gilden D. Virus vasculopathy and stroke: an under-recognized cause and treatment target. *Infectious disorders drug targets*. 2010;10(2):105-111.
32. Levine SR. Hypercoagulable states and stroke: a selective review. *CNS spectrums*. 2005;10(7):567-578.
33. Hart RG, Kanter MC. Hematologic disorders and ischemic stroke. A selective review. *Stroke*. 1990;21(8):1111-1121.
34. Arboix A, Jiménez C, Massons J, Parra O, Besses C. Hematological disorders: a commonly unrecognized cause of acute stroke. *Expert review of hematology*. 2016;9(9):891-901.
35. Agnoletti G, Boudjemline Y, Ou P, Bonnet D, Sidi D. Right to left shunt through interatrial septal defects in patients with congenital heart disease: results of interventional closure. *Heart (British Cardiac Society)*. 2006;92(6):827-831.
36. Nash M, Rafay MF. Craniocervical Arterial Dissection in Children: Pathophysiology and Management. *Pediatric neurology*. 2019;95:9-18.
37. de Freitas GR, Barreira C. Stroke of undetermined cause and cardiomyopathies: Another piece of the puzzle? *Neurology*. 2020;94(1):14-15.
38. Miranda B, Fonseca AC, Ferro JM. Patent foramen ovale and stroke. *Journal of neurology*. 2018;265(8):1943-1949.
39. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *The New England journal of medicine*. 2014;370(26):2467-2477.
40. Ntaios G, Pearce LA, Meseguer E, et al. Aortic Arch Atherosclerosis in Patients With Embolic Stroke of Undetermined Source: An Exploratory Analysis of the NAVIGATE ESUS Trial. *Stroke*. 2019;50(11):3184-3190.
41. Kamel H, Gialdini G, Baradaran H, et al. Cryptogenic Stroke and Nonstenosing Intracranial Calcified Atherosclerosis. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2017;26(4):863-870.

Article topic: Management of Multiple Sclerosis Relapses.

Author: Obada Al Jayyousi.

Editor: Noor Qasem.

Reviewer: Ethar Hazaimeh.

Keywords: Neurology, Demyelinating, Relapse, MS.

Overview

Despite the increasing number of treatment modalities for Multiple Sclerosis (MS), relapses remain an unpredictable and insufferable aspect of the disease. As such, adequate and efficient treatment of these relapses are of the essence.

Before we can treat a Multiple Sclerosis (MS) Relapse, however, it is important to correctly distinguish it from a pseudo-relapse. We can distinguish a relapse in multiple sclerosis by clinical and radiological findings implying progression and worsening. (1) The clinical picture should suggest a demyelinating involvement of the CNS, with an event duration of no less than 24 hours, where other etiologies are absent, like infection. (2)

A relapse is treated due to the possible manifestations it could encompass on the optic nerve, brainstem, cerebellum, spinal cord, or cerebral hemispheres. (3)

Treatment of Multiple Sclerosis relapses can be divided into prevention and acute management. The primary management acutely is corticosteroids, while other immunomodulatory therapies are used for prevention. (4) Other treatment options include adrenocorticotropic hormonal therapy, plasmapheresis, and IV immunoglobulins. (3)

Management of Multiple Sclerosis relapses is not proven to benefit on the long-term, but evidence shows short-term benefits. (3) However, treatment is still important to relieve any physical or psychological impact acutely.

1. Corticosteroids

The earliest published use of corticosteroids in MS was in 1951(5), however IV methylprednisolone is the last approved medication by the FDA for MS relapses so far. (6) 1000 mg daily IV methylprednisolone for 3 to 5 days is one commonly used steroid regimen.

Corticosteroids show anti-inflammatory and immunosuppressive actions which justifies their use in the autoimmune condition. Mechanisms include direct action of high concentrations of corticosteroids on the plasma membrane (8) (9), plasma membrane corticosteroid receptor binding (8), cytosolic corticosteroid receptor binding and consequent downregulation of pro-inflammatory genes. (10)(11)

Steroids are known to have multiple side effects, including hypertension, hyperglycemia, adrenal crisis, weight gain, moon face, and others. (12) Corticosteroids are indicated acutely for multiple sclerosis if there are no contraindications. Contraindications include being on live "attenuated" vaccines, osteoporosis, diabetes, current systemic infections, and hypersensitivity. (13)

2. Adrenocorticotropic hormone therapy (ACTH)

ACTH therapy, Acthar®Gel, was approved by the FDA in1978. (7) ACTH stimulates the adrenal cortex to produce cortisol via melanocortin receptors. There are 5 receptor types in the melanocortin system, where steroidogenesis is the result of melanocortin receptor2 (MCR2) binding (Figure1). Receptor binding involving the other melanocortin receptor types is associated with anti-inflammatory and immunomodulatory effects through decreasing the levels of pro-inflammatory cytokines (IFN-γ, IL-12, TNF, IL-17) and producing anti-inflammatory cytokines (IL-10). (15-18) (Figure 1)

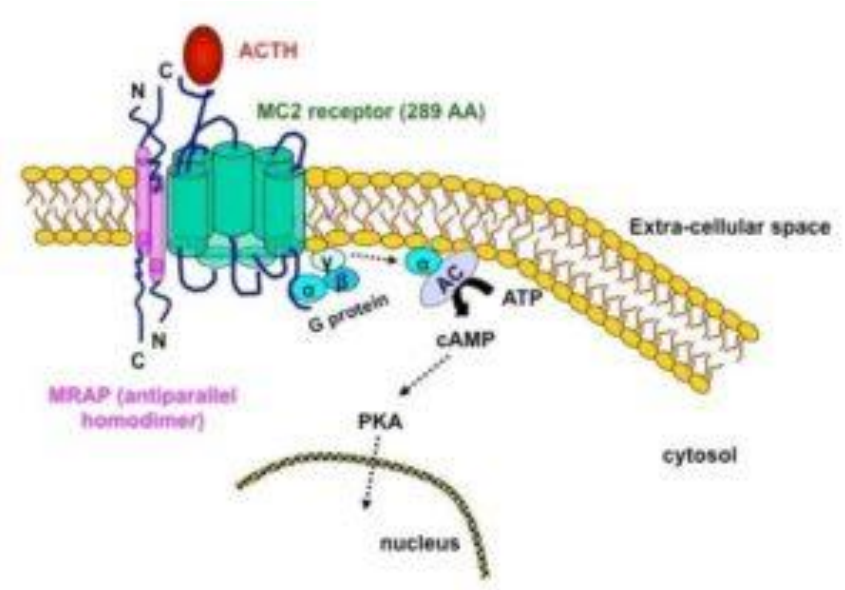


Figure 1, MC2 binding by ACTH. (14)

The Table below (Table 1) summarizes the receptor medicated actions of ACTH on the melanocortin system.

Receptor	Major site of expression	MCR agonist affinity	Function
MCR1	Immune/inflammatory cells, glial cells	ACTH = α-MSH > β-MSH > γ-MSH	Anti-inflammator
MCR2	Adrenal gland	ACTH only	Steroidogenesis
MCR3	Brain Macrophage	ACTH = α-MSH = β-MSH = γ-MSH	Anti-inflammator
MCR4	Brain, spinal cord	ACTH = α-MSH > β-MSH > γ-MSH	Neuroprotection?
MCR5	Adrenal gland, T and B lymphocytes, brain	ACTH = α-MSH > β-MSH > γ-MSH	Immunoregulatio

Table1: ACTH receptor mediated actions via the melanocortin system. (15)

MSH: Melanocyte Stimulation Hormone

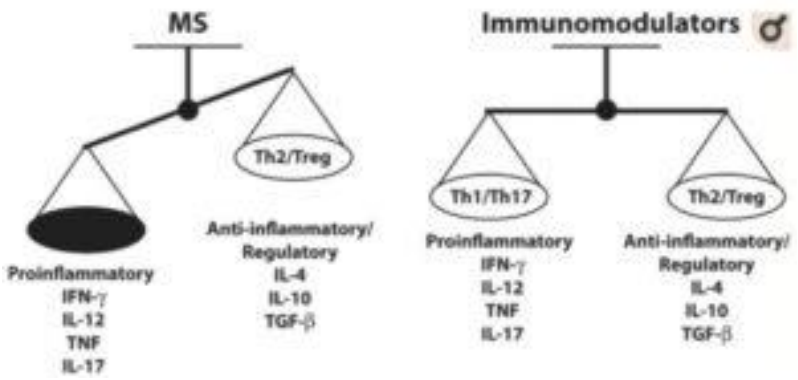


Figure 2, Pro and anti-inflammatory cytokines. (19)

ACTH therapy is indicated for MS relapses when patients don't respond to or can't tolerate corticosteroids. (21) Routes of administration in the form of "ACTHAR Gel" either subcutaneously or intramuscularly. Side effects of ACTH are infections, arterial hypertension, osteoporosis, hypokalemic alkalosis (20)

The contraindications are osteoporosis, peptic ulcer disease, chronic heart failure, and allergy to porcine proteins (3)

3. Plasmapheresis for MS relapses

Plasmapheresis (Figure 3) is a process of plasma exchange where cells are separated using cell separator technology. Immunoglobulin and Immune complex serum levels can be reduced significantly via repeated plasmapheresis. (23)

Plasmapheresis can be used is severe cases of MS relapses that are not responsive to steroid or ACTH therapy. (21) However, there is some but not a great deal of evidence supporting its effectiveness. (24)

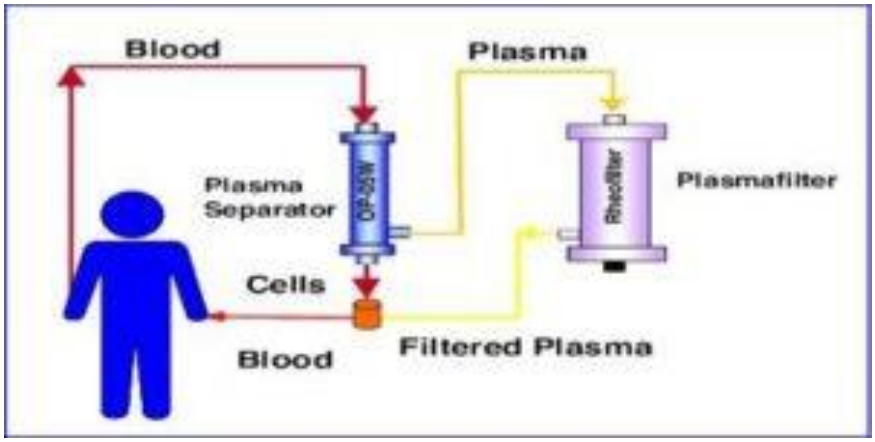


Figure 3, Plasmapheresis. (22).

4. IV immunoglobulins (IVIGs) for MS relapses

IV immunoglobulins can potentially help in the prevention of MS relapses, but considerable evidence has yet to prove its effectiveness, and so cannot be considered first line therapy. IVIG does however, have the advantage of requiring only monthly perfusions and at doses 0.2 -0.4 g/kg has minimal and infrequent side effects. (25)

Managing MS relapses during pregnancy

Therapy involves IV corticosteroids as first line therapy for acute and severe relapses and immunosuppressive drugs (cyclophosphamide, azathioprine, methotrexate etc.) for long term therapy. (26) (27) Furthermore, when steroid therapy isn't tolerable or is contraindicated for pregnant patients, physicians can use IV immunoglobulins, where some evidence shows a corresponding decrease in the risk of childbirth associated MS exacerbations. (28) (29)

Shepherd MS Institute Protocol for MS relapse: (30)

1. To rule out any triggering factors
2. To screen for and treat infections when suspected and refrain from steroid use
3. In the absence of any obvious triggers, the severity of the symptoms and their implications on daily activities should be assessed
4. In case daily life activities aren't seriously affected, observation is done
5. Otherwise, steroid therapy should be tried in the absence of contraindications
6. If contraindications are absent, go for 1g/d of IV methyl prednisone for 3 days with no oral taper or 300 mg of Oral prednisone twice daily for 3 days with no oral taper.

7. Oral lorazepam, 1 mg, can be used for patients with anxiety while on therapy
8. 4 g/kg/d of IVIG for 5 days can be used for those who can't tolerate steroids or those who are pregnant
9. For DM patients, steroids should be used carefully while using sliding scale insulin. IVIG could also be used.

In conclusion, patients of MS relapses deserve every effective treatment approach out there to help them have a better quality of life. Up to this date, corticosteroids, ACTH, plasmapheresis, and IVIGs are deemed the most effective, in that order.

Below are a few clinical trials on the management of MS relapses, for further reading:

- Estrogen therapy showing a potential in management of MS relapses. (32)
- Comparing different disease modifying therapies (dimethyl fumarate, fingolimod, teriflunomide) in their effectiveness of reducing the rate of MS relapses (33)
- Combination of Cyclophosphamide and Interferon beta in reducing MS relapse rate (34)
- Use of Copolymer1 (Copaxone) in reducing MS relapse rate (35)

References

1. Avasarala, J. (2017). Redefining Acute Relapses in Multiple Sclerosis: Implications for Phase 3 Clinical Trials and Treatment Algorithms. Innovations in Clinical Neuroscience, 14(3–4), 38–40. https://pubmed.ncbi.nlm.nih.gov/28584696
2. Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M. S., Fujihara, K., Galetta, S. L., Hartung, H. P., Kappos, L., Lublin, F. D., Marrie, R. A., Miller, A. E., Miller, D. H., Montalban, X., … Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet. Neurology, 17(2), 162–173. https://doi.org/10.1016/S1474-4422(17)30470-2
3. Repovic, P. (2019). Management of Multiple Sclerosis Relapses. Continuum (Minneapolis, Minn.), 25(3), 655–669. https://doi.org/10.1212/CON.0000000000000739
4. Goodin, D. S., Frohman, E. M., Garmany, G. P. J., Halper, J., Likosky, W. H., Lublin, F. D., Silberberg, D. H., Stuart, W. H., & van den Noort, S. (2002). Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology, 58(2), 169–178. https://doi.org/10.1212/wnl.58.2.169
5. Glaser GH, Merritt HH. Effects of ACTH and cortisone in multiple sclerosis. Trans Am Neurol Assoc 1951;56:130–133.
6. Berkovich, R. (2013). Treatment of acute relapses in multiple sclerosis. Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics, 10(1), 97–105. https://doi.org/10.1007/s13311-012-0160-7
7. Questcor Pharmaceuticals, Inc. H.P. Acthar® Gel (repository corticotrophin injection) [prescribing information]. Hayward, CA: Questcor Pharmaceuticals, Inc.; June 2011.
8. Buttgereit, F., Wehling, M., & Burmester, G. R. (1998). A new hypothesis of modular glucocorticoid actions: steroid treatment of rheumatic diseases revisited. Arthritis and Rheumatism, 41(5), 761–767. https://doi.org/10.1002/1529-0131(199805)41:5<761::AID-ART2>3.0.CO;2-M
9. Gold R, Buttgereit F, Toyka KV. Mechanism of action of glucocorticosteroid hormones: possible implications for therapy of neuroimmunological disorders. J Neuroimmunol 2001;117:1– 8
10. Boumpas DT, Chrousos GP, Wilder RL, Cupps TR, Balow JE. Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. Ann Intern Med 1993;119:1198 –1208
11. Adcock IM, Caramori G, Ito K. New insights into the molecular mechanisms of corticosteroids actions. Curr Drug Targets 2006;7: 649 – 660
12. Grennan, D., & Wang, S. (2019). Steroid Side Effects. In JAMA (Vol. 322, Issue 3, p. 282). https://doi.org/10.1001/jama.2019.8506
13. Hodgens A, Sharman T. Corticosteroids. [Updated 2020 Oct 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554612/

14. Angelousi A, Margioris AN, Tsatsanis C. ACTH Action on the Adrenals. [Updated 2020 Jun 13]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279118/
15. Catania, A., Gatti, S., Colombo, G., and Lipton, J.M. (2004) Targeting melanocortin receptors as a novel strategy to control inflammation. Pharmacol. Rev. 56, 1–29.
16. Getting, S.J. and Perretti, M. (2000) MC3-R as a novel target for antiinflammatory therapy. Drug News Perspect. 13, 19–27.
17. Buggy, J.J. (1998) Binding of α-melanocyte-stimulating hormone to its G-protein-coupled receptor on B-lymphocytes activates the Jak/STAT pathway. Biochem. J. 331(Pt 1), 211–216.
18. Taylor, A. and Namba, K. (2001) In vitro induction of CD25+ CD4+ regulatory T cells by the neuropeptide αmelanocyte stimulating hormone (α-MSH). Immunol. Cell Biol. 79, 358–367.
19. Berkovich, R., & Agius, M. A. (2014). Mechanisms of action of ACTH in the management of relapsing forms of multiple sclerosis. Therapeutic Advances in Neurological Disorders, 7(2), 83–96. https://doi.org/10.1177/1756285613518599
20. Riikonen, R., & Donner, M. (1980). ACTH therapy in infantile spasms: side effects. Archives of Disease in Childhood, 55(9), 664–672. https://doi.org/10.1136/adc.55.9.664
21. Ross A., Ben-Zacharia A., Harris C., Smrtka J. (2013) Multiple sclerosis, relapses, and the mechanism of action of adrenocorticotropic hormone. Front Neurol 4: 1–12
22. (n.d.). http://msrblog.com/assign/science/biology/plasmapheresis.html
23. Linker, C. (1983). Plasmapheresis in clinical medicine. The Western Journal of Medicine, 138(1), 60–69. https://pubmed.ncbi.nlm.nih.gov/6601332
24. Cortese, I., Chaudhry, V., So, Y. T., Cantor, F., Cornblath, D. R., & Rae-Grant, A. (2011). Evidence-based guideline update: Plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology, 76(3), 294–300. https://doi.org/10.1212/WNL.0b013e318207b1f6
25. Sorensen, P. S. (2003). The role of intravenous immunoglobulin in the treatment of multiple sclerosis. Journal of the Neurological Sciences, 206(2), 123–130. https://doi.org/10.1016/s0022-510x(02)00343-x
26. Ferrero, S., Pretta, S., & Ragni, N. (2004). Multiple sclerosis: management issues during pregnancy. European Journal of Obstetrics, Gynecology, and Reproductive Biology, 115(1), 3–9.
27. Bodis L, Szupera Z, Pierantozzi M, Bandini F, Sas K, Kovacs L, et al. Neurological complications of pregnancy. J Neurol Sci 1998;153: 279–93.https://doi.org/10.1016/j.ejogrb.2003.10.020

28. Achiron A, Rotstein Z, Noy S, Mashiach S, Dulitzky M, Achiron R. Intravenous immunoglobulin treatment in the prevention of childbirth-associated acute exacerbations in multiple sclerosis: a pilot study. J Neurol 1996;243:25–8.
29. Haas J. High dose IVIG in the post partum period for prevention of exacerbations in MS. Multiple Sclerosis 2000;6(Suppl 2):S18–20.
30. Thrower, B. W. (2009). Relapse management in multiple sclerosis. The Neurologist, 15(1), 1–5. https://doi.org/10.1097/NRL.0b013e31817acf1a
31. Laursen, J. H., Søndergaard, H. B., Sørensen, P. S., Sellebjerg, F., & Oturai, A. B. (2016). Vitamin D supplementation reduces relapse rate in relapsing-remitting multiple sclerosis patients treated with natalizumab. Multiple Sclerosis and Related Disorders, 10, 169–173. https://doi.org/10.1016/j.msard.2016.10.005
32. Gold, S. M., & Voskuhl, R. R. (2009). Estrogen treatment in multiple sclerosis. Journal of the Neurological Sciences, 286(1–2), 99–103. https://doi.org/10.1016/j.jns.2009.05.028
33. Freedman, M. S., Montalban, X., Miller, A. E., Dive-Pouletty, C., Hass, S., Thangavelu, K., & Leist, T. P. (2016). Comparing outcomes from clinical studies of oral disease-modifying therapies (dimethyl fumarate, fingolimod, and teriflunomide) in relapsing MS: Assessing absolute differences using a number needed to treat analysis. Multiple Sclerosis and Related Disorders, 10, 204–212. https://doi.org/10.1016/j.msard.2016.10.010
34. Reggio, E., Nicoletti, A., Fiorilla, T., Politi, G., Reggio, A., & Patti, F. (2005). The combination of cyclophosphamide plus interferon beta as rescue therapy could be used to treat relapsing-remitting multiple sclerosis patients-- twenty-four months follow-up. Journal of Neurology, 252(10), 1255–1261. https://doi.org/10.1007/s00415-005-0857-1
35. Johnson, K. P. (1996). Management of relapsing/remitting multiple sclerosis with copolymer 1 (Copaxone). Multiple Sclerosis (Houndmills, Basingstoke, England), 1(6), 325–326. https://doi.org/10.1177/135245859600100606

Article Topic: Adult Focal Epilepsy.

Author: Leen Sawalha.

Editor: Yaman B. Ahmed.

Reviewer: Ethar Hazaimeh.

Key Words: Adult Focal Epilepsy, Temporal Lobe Epilepsy, Mesial Temporal Lobe Epilepsy, Lateral/Neocortical Temporal Lobe Epilepsy, Frontal Lobe Epilepsy, Hippocampal Sclerosis

Overview and Epidemiology

Epilepsy is a condition characterized by recurrent seizures which are not provoked. It affects about 0.5% - 3% of the world, mostly occurring in extremes of age – young children and the elderly [1].

Adult Focal epilepsy is the most frequent type of epilepsy to be first seen and diagnosed in adulthood. It can appear at any stage of life with the presentation differing depending on the age of the individual. Adult focal epilepsy can be subdivided into the following:

- Temporal lobe epilepsy, which is further divided into mesial and lateral temporal lobe epilepsy
- Frontal lobe epilepsy
- Insular lobe epilepsy
- Cingulate lobe epilepsy
- Parietal lobe epilepsy
- Occipital lobe epilepsy [2].

Pathogenesis and Etiology

Temporal Lobe Epilepsy (TLE) is the most common presentation of focal epilepsy [3], TLE most frequently happens due to [4]:

- Infections
- Mutations
- Hippocampal sclerosis
- Tumors
- Brain injury
- Vascular deformities
- Cryptogenic causes

It is classified into:

- **Mesial Temporal Lobe Epilepsy (MTLE):**

It is the most commonly encountered subdivision of TLE, affecting the parahippocampal gyrus, amygdala, and hippocampus. It is usually associated with hippocampal sclerosis (HS). HS is a condition where gliosis of the hippocampus and neuronal cell death is apparent. Patients undergoing surgery who have HS are more likely to have a better prognosis than those without HS [5][4].

Other conditions that can also cause MTLE include dysembryoplastic neuroepithelioma, focal cortical dysplasia, cysts, heterotopias, cicatrices, heterotopias, cavernous malformations, and vascular deformities [6].

Additionally, MTLE has also been known to be genetically acquired (familial) [7]. Some studies suggest that in order for MTLE to happen, bilateral hippocampal involvement is required for the onset of seizures [8].

- **Lateral/Neocortical Temporal Lobe Epilepsy (LTLE)** is much less frequently seen. It can be familial (autosomal dominant LTLE) or sporadic (idiopathic partial epilepsy). Autosomal dominant LTLE is said to be caused by a genetic mutation in LGI1. This can cause dysfunction in AMPA receptors or potassium channels [2][6].

Frontal Lobe Epilepsy (FLE) can occur due to a multitude of reasons, these include:

- Tumors
- Cortical dysplasia
- Gliosis
- Encephalitis
- Hamartomas and other dysgenetic lesions
- Vascular malformations
- Trauma lesions [9][10]

In addition to that, it can also be caused by genetic mutations (such as CHRNA4 and CHRNB2) that code for nicotinic acetylcholine receptor subunits. This is referred to as autosomal dominant nocturnal frontal lobe epilepsy [9].

Parietal and Occipital Lobe Epilepsy

They are relatively uncommon [2]. One of the most common causes of insular epilepsy is the presence of a low-grade CNS tumor affecting the insula, most significantly gliomas [11].

Cingulate lobe epilepsy can be caused by the following:

- Gliosis
- Cortical dysplasia
- Cavernoma
- Meningioma
- Astrocytoma [12]

Clinical Presentation and Complications

Patients suffering from mesial temporal lobe epilepsy may experience the following symptoms:

- Auras
- Fear
- Olfactory hallucinations
- A feeling of butterflies in their stomach
- Sensations of gastric rising [2]

Symptoms associated with lateral/neocortical temporal lobe epilepsy are varied due to the lobe's extensive connections to other areas of the brain. They are mostly dependent on the area of origin of the seizure [2]. Generally, symptoms include:

- Visual distortions [2]
- Vertiginous symptoms [2]
- Aphasia [13]
- Aura, which can be accompanied by auditory hallucinations [2][13].
- Single-sided clonic jerking of the upper extremities [14].

The clinical manifestations occurring in the frontal lobe in frontal lobe epilepsy are classified depending on location. The following table summarizes the symptoms associated with each area of the frontal lobe.

TABLE 1: Symptoms associated with Frontal Lobe Syndromes [15].

Area	Ictal Behavior
Supplementary sensorimotor	Vocalization Focal/asymmetric tonic posturing Versive movements of the eyes and head Speech arrest
Perirolandic/Primary motor	Vocalization Dysphasia/speech arrest Focal motor seizures which may or may not be accompanied with Jacksonian march
Dorsolateral	Focal tonic/clonic activity Versive movements of the eyes and head Dysphasia/speech arrest
Anterior frontopolar	Versive movements of the eyes and head Forced thinking Absence-like symptoms Motor/speech arrest
Orbitofrontal	Autonomic features Complex motor automatisms Olfactory hallucinations
Cingulate	Autonomic characteristics Vocalization Complex motor automatisms Alterations in mood Distress
Opercular	Symptoms associated with the larynx, mastication, salivation, and swallowing, Dysphasia/speech arrest Epigastric aura, distress Autonomic characteristics Facial clonic activity Gustatory illusions

Insular and cingulate lobe epilepsy are relatively rare. Patients complaining of choking sensations due to contraction of the larynx/oropharynx or painful somatosensory aura should be suspected to be suffering from insular seizures [16][17].

As for cingulate lobe epilepsy, it is very hard to tell apart from other types of focal epilepsies. It is known to have very similar symptoms to temporal and frontal lobe seizures. This is due to the cingulate lobe's extensive connections with those areas [18].

Parietal and occipital lobe epilepsy are uncommon. Symptoms are usually not useful for differentiating these types of epilepsies from frontal and temporal lobe epilepsy (since they also have extensive attachments with these areas) [2].

Occipital lobe epilepsy can manifest with the following symptoms:

- Visual auras [2]
- Ictal blindness [19]
- Movements of the eyes [19]
- Blinking [19]

Parietal lobe epilepsy is characterized by contralateral somatosensory auras (may also be bilateral) [20].

Workup and Diagnosis

Mesial temporal lobe epilepsy is diagnosed by performing an EEG (usually with sleep recording). On the electroencephalogram, spikes can be seen in the temporal lobe's front or tip (especially in mesial temporal lobe epilepsy). Spikes can be noticed while the person is either awake or asleep. A T1 and T2 MRI can also be used to check for discrepancies in the temporal lobe. It is also of great significance that the patient be questioned about the seizures and have them described to the physician.

Moving to neocortical lobe epilepsy, the patterns on EEG closely resemble those of mesial temporal lobe epilepsy but may present with temporal foci leaning more towards the mid or posterior region (electrodes T4/T3 and T6/5 are involved) [2].

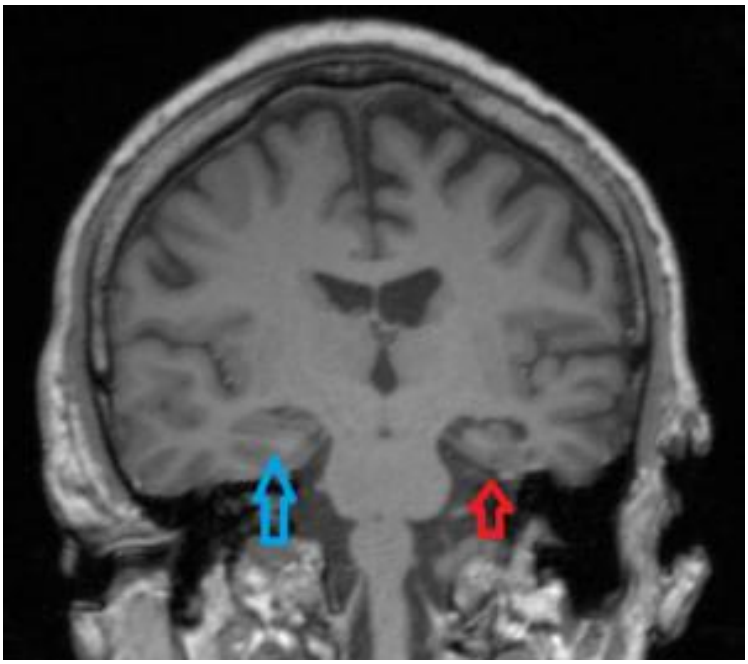


Figure 1: Temporal lobe atrophy, case courtesy of Dr Ian Bickle [22].

As for frontal lobe epilepsy, upon EEG inspection, epileptic activity was noticed in the frontal lobe of 65% of the patients tested. 37% had seizures originating outside the frontal lobe. 17% of patients had seizures on EEG presenting on the contralateral side of the seizure focus, while as 24% of seizure activity was generalized [23]. Bilateral secondary hypersynchrony (which is fast dissemination of interictal spikes between both hemispheres) can also be seen in those suffering from frontal lobe epilepsy. A T1 and T2 MRI can also be used, with the contrast used being reliant on the suspected etiology [2].

An invasive EEG is necessary for identifying insular and cingulate lobe epilepsy in cases where there is no obvious lesion seen on MRI [2].

EEG patterns seen in occipital and parietal lobe epilepsy can either be found focally or seen localized in the frontal and temporal lobe areas due to the abundance of connections found between them. Bilateral hypersynchrony may also be noticed [2].

Treatment and Management

Focal epilepsy can be treated using antiepileptic drugs. Examples of first-line agents used for the treatment of focal epilepsy include carbamazepine, phenytoin, oxcarbazepine, and valproic acid [24].

Additionally, ketogenic diets can be used for the management of epilepsy. A study that included 49 adults on a ketogenic diet concluded that 32 of those adults, who were diagnosed with idiopathic epilepsy, had shown significant improvement [25].

Moreover, vagus nerve stimulation can also be used for the treatment of focal epilepsy. Some studies indicated a decrease in seizures of more than 50% in those receiving this type of treatment [26].

In some cases, epilepsy can be unresponsive to antiepileptic drugs (drug-resistant epilepsy), most notably mesial temporal lobe epilepsy accompanied by mesial temporal sclerosis. The most prevalent surgical procedures done in hope of eliminating the aforementioned type of epilepsy include anterior temporal lobectomy in addition to amygdalohippocampectomy [27].

Risk Factors and Prevention

Alcohol consumption in alcoholics prone to seizures should be avoided. A study indicated that 86% of alcoholics who had previously experienced focal seizures had those seizures occur 48 hours after ceasing alcohol consumption. They concluded that alcohol withdrawal increases the probability of the occurrence of focal seizures [28]. Furthermore, caffeine has been shown to protect and increase susceptibility to seizures based on the dose, whether the administration was chronic or acute, and the stage of development at which caffeine was first given [29].

Nicotine has also been shown to be implicated in the development of convulsive seizures at large doses (30-4 mg/kg). However, this effect was short-lived and disappeared after 10 minutes [30]. Stressful life events can also lead to seizure onset. Some studies showed that people reported seizure onset following major life events [31]. Sleep fragmentation can also be a substrate for the occurrence of intra-sleep seizures [32].

Prognosis

Prognosis vastly depends on the underlying etiology and the presence of comorbidities. Surgery remains to be a great long-term treatment that substantially reduces the recurrence of seizures. However, it is of limited use.

The quality of life for those suffering from epilepsy is severely impacted. Additionally, epilepsy increases the probability of dying prematurely, primarily in those whose seizures prevail [33].

Recent Updates

Recently, genome sequencing techniques have become much more affordable. One method used in epilepsy investigation is known as array comparative genomic hybridization (array-CGH) [34]. This paved the way for precision medicine, which is mainly used for reversing the pathological consequences caused by certain gene mutations. However, disease-specific treatments for epilepsy are not yet widespread [35].

References

[1] P. Kandula and C. Harden, "Epilepsy," in *Encyclopedia of Neuroscience*, L. R. Squire, Ed. Oxford: Academic Press, 2009, pp. 1147–1149.

[2] C. T. Skidmore, "Adult Focal Epilepsies.," *Continuum (Minneap. Minn).*, vol. 22, no. 1 Epilepsy, pp. 94–115, Feb. 2016, doi: 10.1212/CON.0000000000000290.

[3] S. Wiebe, "Epidemiology of Temporal Lobe Epilepsy," *Can. J. Neurol. Sci. / J. Can. des Sci. Neurol.*, vol. 27, no. S1, pp. S6–S10, 2000, doi: DOI: 10.1017/S0317167100000561.

[4] W. McIntosh and J. M Das., "Temporal Seizure," 2020. .

[5] M. Baulac, "MTLE with hippocampal sclerosis in adult as a syndrome.," *Rev. Neurol. (Paris).*, vol. 171, no. 3, pp. 259–266, Mar. 2015, doi: 10.1016/j.neurol.2015.02.004.

[6] J. Engel and N. Salamon, "Temporal Lobe Epilepsy," in *Brain Mapping*, A. W. Toga, Ed. Waltham: Academic Press, 2015, pp. 853–860.

[7] F. Cendes, "Progressive hippocampal and extrahippocampal atrophy in drug resistant epilepsy: review," *Curr. Opin. Neurol.*, vol. 18, no. 2, 2005.

[8] H. V Soper, G. M. Strain, T. L. Babb, J. P. Lieb, and P. H. Crandall, "Chronic alumina temporal lobe seizures in monkeys," *Exp. Neurol.*, vol. 62, no. 1, pp. 99–121, 1978, doi: https://doi.org/10.1016/0014-4886(78)90044-4.

[9] P. Beleza and J. Pinho, "Frontal lobe epilepsy.," *J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas.*, vol. 18, no. 5, pp. 593–600, May 2011, doi: 10.1016/j.jocn.2010.08.018.

[10] C. Kellinghaus, "Frontal lobe epilepsy ," *Epileptic Disord.*, vol. 6, no. 4, pp. 223–239, Dec. 2004.

[11] P. Laoprasert, J. G. Ojemann, and M. H. Handler, “Insular epilepsy surgery.,” *Epilepsia*, vol. 58 Suppl 1, pp. 35–45, Apr. 2017, doi: 10.1111/epi.13682.

[12] R. Alkawadri, N. K. So, P. C. Van Ness, and A. V Alexopoulos, “Cingulate epilepsy: report of 3 electroclinical subtypes with surgical outcomes.,” *JAMA Neurol.*, vol. 70, no. 8, pp. 995–1002, Aug. 2013, doi: 10.1001/jamaneurol.2013.2940.

[13] T. Loddenkemper and P. Kotagal, “Lateralizing signs during seizures in focal epilepsy.,” *Epilepsy Behav.*, vol. 7, no. 1, pp. 1–17, Aug. 2005, doi: 10.1016/j.yebeh.2005.04.004.

[14] J. D. Kennedy and S. U. Schuele, “Neocortical temporal lobe epilepsy.,” *J. Clin. Neurophysiol. Off. Publ. Am. Electroencephalogr. Soc.*, vol. 29, no. 5, pp. 366–370, Oct. 2012, doi: 10.1097/WNP.0b013e31826bd78b.

[15] R. Bagla and C. T. Skidmore, “Frontal lobe seizures.,” *Neurologist*, vol. 17, no. 3, pp. 125–135, May 2011, doi: 10.1097/NRL.0b013e31821733db.

[16] M. F. Kriegel, D. W. Roberts, and B. C. Jobst, “Orbitofrontal and insular epilepsy.,” *J. Clin. Neurophysiol. Off. Publ. Am. Electroencephalogr. Soc.*, vol. 29, no. 5, pp. 385–391, Oct. 2012, doi: 10.1097/WNP.0b013e31826bd82e.

[17] A. Montavont *et al.*, “On the origin of painful somatosensory seizures,” *Neurology*, vol. 84, no. 6, p. 594—601, Feb. 2015, doi: 10.1212/wnl.0000000000001235.

[18] R. Michelucci, E. Pasini, and C. Nobile, “Lateral temporal lobe epilepsies: clinical and genetic features.,” *Epilepsia*, vol. 50 Suppl 5, pp. 52–54, May 2009, doi: 10.1111/j.1528-1167.2009.02122.x.

[19] L. Ferini-Strambi, V. Sansoni, and R. Combi, “Nocturnal frontal lobe epilepsy and the acetylcholine receptor,” *Neurologist*, vol. 18, no. 6, p. 343—349, Nov. 2012, doi: 10.1097/nrl.0b013e31826a99b8.

[20] V. Salanova, F. Andermann, T. Rasmussen, A. Olivier, and L. F. Quesney, “Parietal lobe epilepsy. Clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988.,” *Brain*, vol. 118 (Pt 3, pp. 607–627, Jun. 1995, doi: 10.1093/brain/118.3.607.

[21] H. Klein and C. Joshi, “Temporal Lobe Epilepsy (TLE).” https://www.epilepsy.com/learn/types-epilepsy-syndromes/temporal-lobe-epilepsy-aka-tle.

[22] Radiopaedia, “Temporal lobe atrophy.” .

[23] L. E. Jeha, I. Najm, W. Bingaman, D. Dinner, P. Widdess-Walsh, and H. Lüders, “Surgical outcome and prognostic factors of frontal lobe epilepsy surgery.,” *Brain*, vol. 130, no. Pt 2, pp. 574–584, Feb. 2007, doi: 10.1093/brain/awl364.

[24] A. S. Fauci, *Harrison’s principles of internal medicine*. McGraw-Hill Education, 2015.

[25] C. J. BARBORKA, “KETOGENIC DIET TREATMENT OF EPILEPSY IN ADULTS,” *J. Am. Med. Assoc.*, vol. 91, no. 2, pp. 73–78, Jul. 1928, doi: 10.1001/jama.1928.02700020007003.

[26] Y. Al-Said, S. Baeesa, M. Khalid, M. Abdeen, and H. R. Kayyali, “Vagus nerve stimulation for refractory epilepsy: experience from Saudi Arabia.,” *Ann. Saudi Med.*, vol. 35, no. 1, pp. 41–45, 2015, doi: 10.5144/0256-4947.2015.41.

[27] S. Wiebe, W. T. Blume, J. P. Girvin, and M. Eliasziw, “A randomized, controlled trial of surgery for temporal-lobe epilepsy.,” *N. Engl. J. Med.*, vol. 345, no. 5, pp. 311–318, Aug. 2001, doi: 10.1056/NEJM200108023450501.

[28] H. S. Schwartz, P. R. Yarnell, and G. VanderArk, “Focal motor seizures in patients with alcoholism,” *J. Am. Coll. Emerg. Physicians*, vol. 3, no. 6, pp. 394–396, 1974, doi: https://doi.org/10.1016/S0361-1124(74)80015-8.

[29] R. R. van Koert, P. R. Bauer, I. Schuitema, J. W. Sander, and G. H. Visser, “Caffeine and seizures: A systematic review and quantitative analysis.,” *Epilepsy Behav.*, vol. 80, pp. 37–47, Mar. 2018, doi: 10.1016/j.yebeh.2017.11.003.

[30] H. A. Iha *et al.*, “Nicotine Elicits Convulsive Seizures by Activating Amygdalar Neurons.,” *Front. Pharmacol.*, vol. 8, p. 57, 2017, doi: 10.3389/fphar.2017.00057.

[31] P. Gélisse, P. Genton, P. Coubes, N. P. L. Tang, and A. Crespel, “Can emotional stress trigger the onset of epilepsy?,” *Epilepsy Behav.*, vol. 48, pp. 15–20, Jul. 2015, doi: 10.1016/j.yebeh.2015.05.010.

[32] R. Manni, E. Zambrelli, R. Bellazzi, and M. Terzaghi, “The relationship between focal seizures and sleep: an analysis of the cyclic alternating pattern.,” *Epilepsy Res.*, vol. 67, no. 1–2, pp. 73–80, 2005, doi: 10.1016/j.eplepsyres.2005.08.008.

[33] R. D. Thijs, R. Surges, T. J. O’Brien, and J. W. Sander, “Epilepsy in adults.,” *Lancet (London, England)*, vol. 393, no. 10172, pp. 689–701, Feb. 2019, doi: 10.1016/S0140-6736(18)32596-0.

[34] M. Kharbanda, J. Tolmie, and S. Joss, “How to use… microarray comparative genomic hybridisation to investigate developmental disorders.,” *Arch. Dis. Child. Educ. Pract. Ed.*, vol. 100, no. 1, pp. 24–29, Feb. 2015, doi: 10.1136/archdischild-2014-306022.

[35] A. Orsini, F. Zara, and P. Striano, “Recent advances in epilepsy genetics,” *Neurosci. Lett.*, vol. 667, pp. 4–9, 2018, doi: https://doi.org/10.1016/j.neulet.2017.05.014.

Article topic: Status Epilepticus.

Author: Farah Moh'd Sbeih Fuad Awayes

Editor: Yaman B. Ahmed.

Reviewer: Ethar Hazaimeh

Keywords: Epilepsy, Status Epilepticus, Epilepsy Emergencies.

Introduction

Status Epilepticus (SE) is a neurological emergency; it varies in definition due to lack of a clear understanding of its pathophysiology but according to recent guidelines it is said to be "5 min or more of (i) continuous clinical and/or electrographic seizure activity or (ii) recurrent seizure activity without recovery (returning to baseline) between seizures" with a notable morbidity and mortality rates [1].

SE can be classified in various ways but as recommended by The Neurocritical Care Society, it is classified as convulsive and non-convulsive [1]. Convulsive SE is a generalized tonic-clonic activity that is easily identified, while the non-convulsive SE does not show an obvious activity and is further divided into simple and complex depending on its effect on the consciousness and mental status [2].

Refractory SE is defined as SE that is resistant to two antiepileptic drugs (AED) where one of them is benzodiazepine [3].

Super refractory SE is referred to as the SE that occurs after the initiation or cessation of anesthetic therapy and may last 24 hours or more [4].

Epidemiology

The incidence of SE lies between 18-41 patients per 100,000 per year [5]. Non-convulsive SE affects up to 10% of patients with the greatest risk in patients who have had previous epilepsy, elderly patients, and patients with sepsis [6]. The mortality of SE increases with increasing age and it ranges from 19% to 26% [5]. About 40% develop subsequent epilepsy attacks after their first episode of SE [7].

Pathophysiology

SE happens when the mechanism that stops the seizure fails because there is either inefficient inhibition due to decreased γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter, or due to excessive stimulation from excitatory amino acids like glutamate and its analogues [8].

As SE persists, more calcium enters the neurons via NMDA receptor which leads to the activation of many enzymes like NADPH oxidase, nitric oxide synthase, and calpains; this can generate reactive oxygen species which can cause cell damage or accumulate in the mitochondria causing ATP depletion [9,10].

Etiology

There are wide possible etiologies that can cause SE, and they can be divided into:

- Acute symptomatic: an acute neurological or a systemic cause like stroke, metabolic disturbances, CNS infection, and others [11,12].
- Remote symptomatic: like traumatic brain injury and brain tumors [11,12].
- Epileptic patients taking inadequate antiseizure drug doses [11,12].
- Unknown/Cryptogenic when there is no clear etiology found [11,12].

Diagnosis

All patients require a thorough history and physical examination with consideration to the patient's clinical and mental state, neuroimaging with a non-contrast head Computed Tomography (CT) scan, and basic laboratory studies like complete blood count (CBC), blood glucose level, serum electrolytes (sodium, potassium, calcium, and magnesium), AED blood levels if known to have previous seizures.

Depending on the clinical presentation, patients may need brain Magnetic Resonance Imaging (MRI), a lumbar puncture, a toxicology panel, and other laboratory studies.

Electroencephalography (EEG) is a vital test where electrodes attached to a patient's head detect electrical impulses generated. In a non-convulsive SE, the waves' amplitude is higher compared to a normal EEG with regular patterns (Figure 1). After administering an anesthetic drug, a suppressed pattern will be noticed (Figure 2), this is useful when prescribing the desired drug dose to the patient [13].

Figure (1): An EEG of a patient with non-convulsive SE [13].

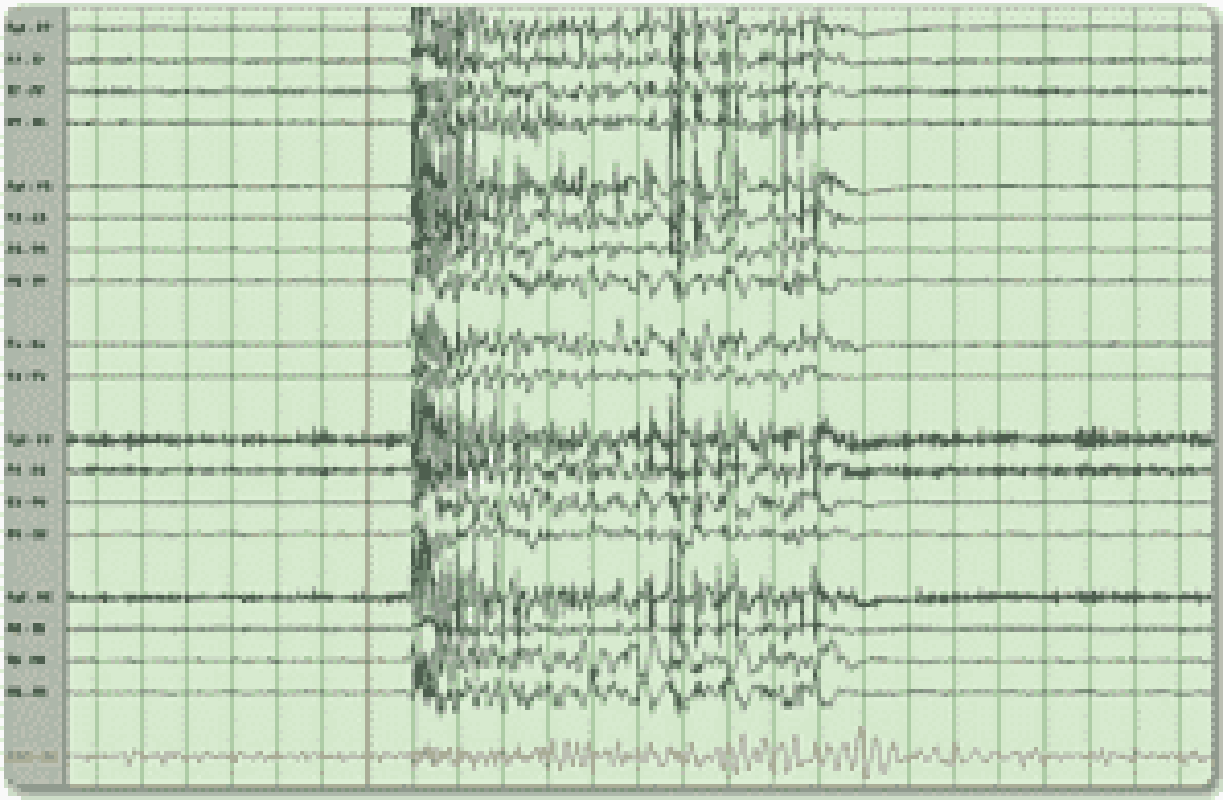


Figure (2): An EEG with a suppressed pattern of a patient after administering an anesthetic drug [13].

Management

Once an etiology has been figured, it must be controlled rapidly with a clear management plan. According to the American Epilepsy Society, guidelines are summarized in Figure (3) [14].

Prognosis

Prognosis is influenced greatly by the underlying cause; other factors include the patient's history of chronic illnesses, the duration in which the episode lasts, and the patient's age [8].

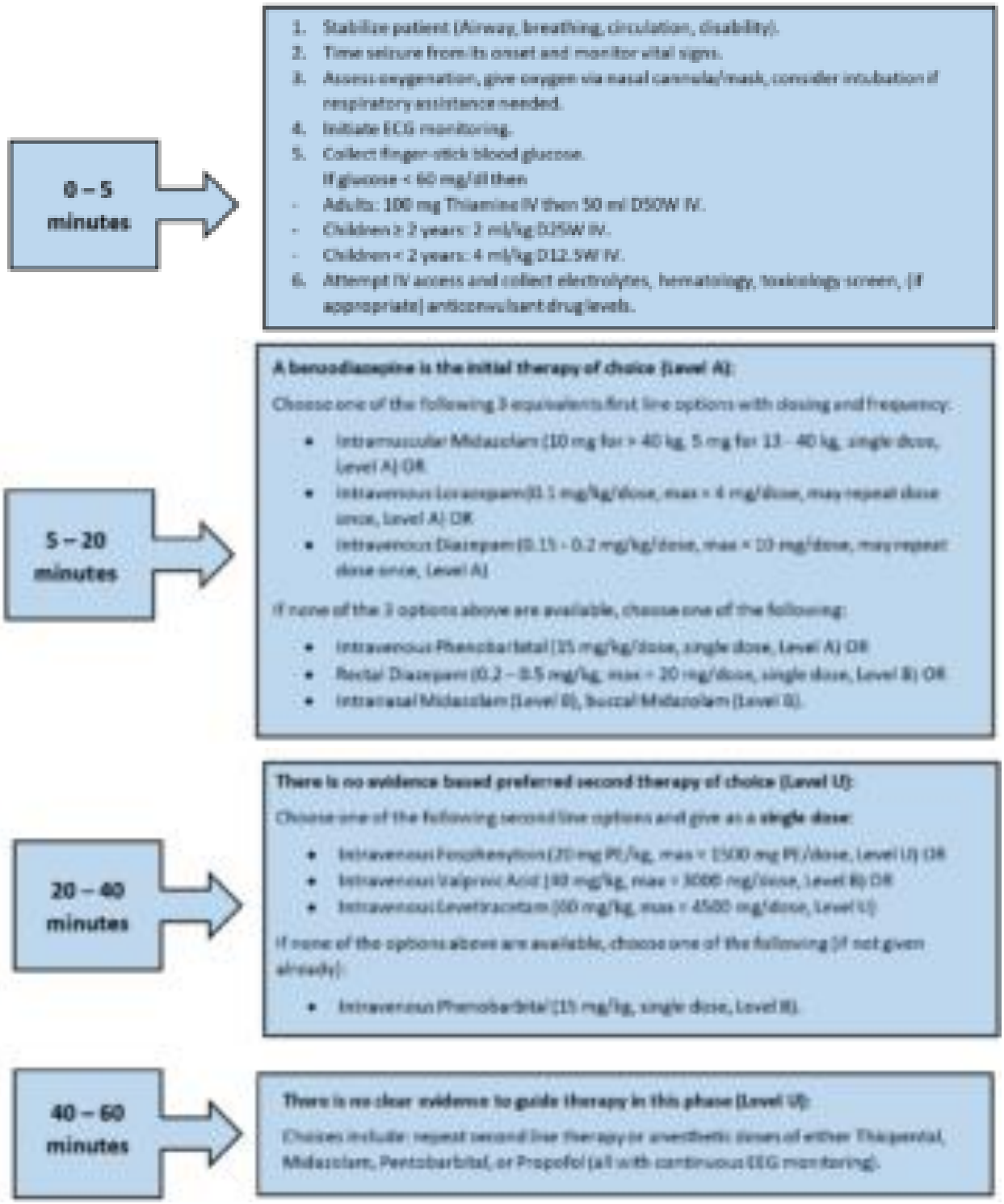


Figure (3) American Epilepsy Society Treatment Guidelines [14].

References

[1] G. M. Brophy *et al.*, “Guidelines for the evaluation and management of status epilepticus.,” *Neurocrit. Care*, vol. 17, no. 1, pp. 3–23, Aug. 2012, doi: 10.1007/s12028-012-9695-z.
[2] P. W. Kaplan, “The clinical features, diagnosis, and prognosis of nonconvulsive status epilepticus.,” *Neurologist*, vol. 11, no. 6, pp. 348–361, Nov. 2005, doi: 10.1097/01.nrl.0000162954.76053.d2.
[3] A. O. Rossetti and D. H. Lowenstein, “Management of refractory status epilepticus in adults: still more questions than answers.,” *Lancet. Neurol.*, vol. 10, no. 10, pp. 922–930, Oct. 2011, doi: 10.1016/S1474-4422(11)70187-9.
[4] D. Dubey, J. Kalita, and U. K. Misra, “Status epilepticus: Refractory and super-refractory.,” *Neurol. India*, vol. 65, no. Supplement, pp. S12–S17, 2017, doi: 10.4103/neuroindia.NI_958_16.
[5] et al. DeLorenzo RJ, Hauser WA, Towne AR, “A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia.,” *Neurology*, vol. 46, no. 4, pp. 1029–1035, 1996.
[6] R. Alroughani, M. Javidan, A. Qasem, and N. Alotaibi, “Non-convulsive status epilepticus; the rate of occurrence in a general hospital.,” *Seizure*, vol. 18, no. 1, pp. 38–42, Jan. 2009, doi: 10.1016/j.seizure.2008.06.013.
[7] D. C. Hesdorffer, G. Logroscino, G. D. Cascino, and W. A. Hauser, “Recurrence of afebrile status epilepticus in a population-based study in Rochester, Minnesota.,” *Neurology*, vol. 69, no. 1, pp. 73–78, Jul. 2007, doi: 10.1212/01.wnl.0000265056.31752.ff.
[8] S. E. Hocker, “Status Epilepticus.,” *Continuum (Minneap. Minn).*, vol. 21, no. 5 Neurocritical Care, pp. 1362–1383, Oct. 2015, doi: 10.1212/CON.0000000000000225.
[9] M. C. Walker, “Pathophysiology of status epilepticus.,” *Neurosci. Lett.*, vol. 667, pp. 84–91, Feb. 2018, doi: 10.1016/j.neulet.2016.12.044.
[10] C. Camello-Almaraz, P. J. Gomez-Pinilla, M. J. Pozo, and P. J. Camello, “Mitochondrial reactive oxygen species and Ca2+ signaling.,” *Am. J. Physiol. Cell Physiol.*, vol. 291, no. 5, pp. C1082-8, Nov. 2006, doi: 10.1152/ajpcell.00217.2006.
[11] D. C. Hesdorffer, G. Logroscino, G. Cascino, J. F. Annegers, and W. A. Hauser, “Incidence of status epilepticus in Rochester, Minnesota, 1965-1984.,” *Neurology*, vol. 50, no. 3, pp. 735–741, Mar. 1998, doi: 10.1212/wnl.50.3.735.
[12] A. Coeytaux, P. Jallon, B. Galobardes, and A. Morabia, “Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR).,” *Neurology*, vol. 55, no. 5, pp. 693–697, Sep. 2000, doi: 10.1212/wnl.55.5.693.
[13] T. Lawson and S. Yeager, “Status Epilepticus in Adults: A Review of Diagnosis and Treatment.,” *Crit. Care Nurse*, vol. 36, no. 2, pp. 62–73, Apr. 2016, doi: 10.4037/ccn2016892.
[14] T. Glauser *et al.*, “Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society.,” *Epilepsy Curr.*, vol. 16, no. 1, pp. 48–61, 2016, doi: 10.5698/1535-7597-16.1.48.

Article Topic: History of Epilepsy.

Author: Tasneem Ishaq Khallad.

Editor: Noor Qasem.

Reviwer: Ethar Hazimeh

Keywords: Seizures, epilepsy, Babylonia, Greek, stigma, history.

Overview

Epilepsy – derived from the Greek word epilambanein meaning “to seize,” in which the body and mind are seized from the individual (1) - is a disease that could occur in all mammals, but more frequently, in species with more complex brain anatomy. (2) Scientists traced epilepsy in humans back to as far as the existence of medical records: about 3000 years ago, where Babylonian clay tablets were seen to include medical texts mentioning and classifying epilepsy. (3)

Social stigmas have always been associated with epilepsy. Patients with epileptic seizures faced discrimination ranging from lack of health insurance, jobs, marriage equality to forced sterilization (4). This is due to the misconceptions about epilepsy, in which the patients were regarded as being ‘chosen’ or ‘possessed’ by gods or demons causing them to be isolated. (5) Therefore, magical and theological treatments were prescribed, and such practices can still be seen till now. (6) Also, in antiquity, people believed for so long that epilepsy is contagious, resulting in the mistreatment of epileptic patients, spitting on them, and refusing to use the same utensils. (5) Historically, the hypotheses of epilepsy started with demonic possession, passing through many theories, until the British neurologist, John Hughlings Jackson, correctly theorized that seizure results from the excessive electrical activity of the brain. (7)

Ancient History of Epilepsy

The oldest description of a seizure was included in an Akkadian clay tablet found in Mesopotamia (see figure 1); mentioned a patient with "his neck turning left, hands and feet are tense, and his eyes wide open, and from his mouth froth is flowing without him having any consciousness." (8) An Akkadian medical diagnostic series known as the Sakikku or “All Diseases” - found in Mesopotamia, written around 1067-1046 BC (9), included 40 tablets arranged in 6 chapters (10) – included chapter on epilepsy. Tablet 26, the first tablet in the said chapter, described signs and symptoms, characteristics of different seizure types, treatment, and outcomes. Also, it described terms relating to epilepsy, such as miqtu (fall), hayyatu (fit), and sibtu (seizure). (10)

Babylonians had no concept of pathology. They classified the types of seizures according to the evil spirit that invaded the body during it. Therefore, the role of the physicians was to drive out the demon or appease the god; spiritual treatment not a medical one. (11) Seizures, in general, were described to start with an aura, continue to the falling, and then reach a peak of a tonic stage which then shifts to a clonic stage that was represented as the starting of the release and departure of the demon from the body. In the end, the demon will “let (the patient) go.” (3)

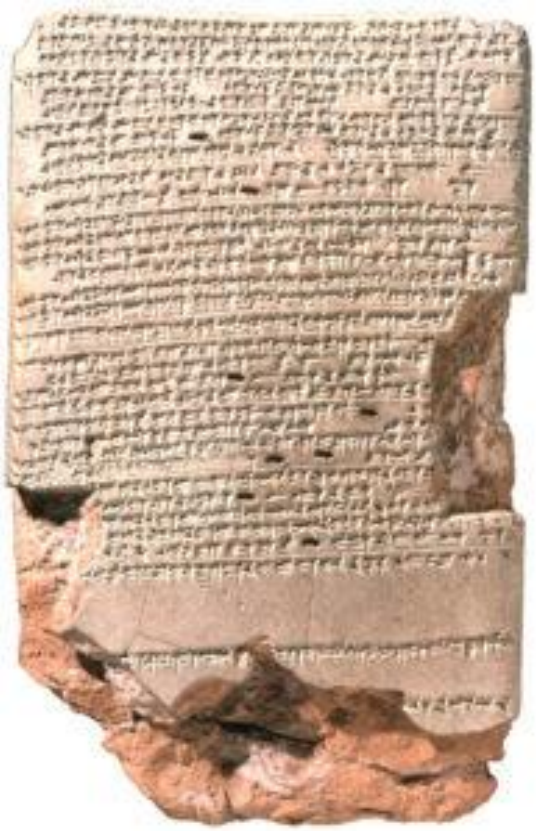


Figure 1: A tablet on epilepsy. Tablet BM 47753. Courtesy of the British Museum, London. Neo-Babylonian Period (ca. 626-539 BC) (10)

Epilepsy was also known during ancient Egypt. This is proved by the Edwin Smith Surgical Papyrus (medical text, named after Edwin Smith, who brought it in 1862) written circa 1700 BC. (4) Egyptians were distinguished from Mesopotamians in that they believed that the underlying cause of epilepsy could be cortical disruption. This is obvious in a case documented by Egyptians describing a man with "a gaping wound in his head" and when palpated, he would "shudder exceedingly." (8)

Chinese texts also reported epilepsy, from 770 to around 221 BC. Its description first appeared in a Chinese medicine book known as Yellow Emperor’s Classic of Internal Medicine which outlined generalized seizures. (12) The book mentioned that the underlying cause is congenital: “Epilepsy is a congenital illness. The baby contracts epilepsy inside its mother’s womb when the mother experiences an emotional shock.”

(12) The treatment was by herbs, massages, and acupuncture. The first attempt to classify epileptic seizures was by Cao Yuan Fang (a Chinese physician and medical author) in 610 AD. (12)

During the Roman times, people were considered as 'free of the falling sickness' if they didn't fall when given a piece of jet stone to smell, which was a common procedure when buying a slave. (13) About a millennium earlier, the Hammurabi code (a code of laws, dated 1780 BC) also stigmatized epilepsy patients by preventing them from marriage, testifying in a court, as well as considering the purchase of a slave to be void if he suffered from a seizure within the first three months of purchase. (5) Until this day, epilepsy still carries social stigmas, distressing the patient even more.

Ancient Greeks referred to epilepsy as 'sacred' due to its divine origin. (8) Around the 5th century BC, Hippocrates was among the earliest to suggest that the brain is the root cause of the disease. (4) He suggested that it is hereditary but not contagious and described its signs as a unilateral motor with an aura (warning sign for the patient to leave the public). (4) Hippocrates believed that it can be cured just like other diseases unless it becomes chronic, emphasized by his quote: "Moreover, it can be cured no less than other diseases so long as it has not become inveterate and too powerful for the drugs which are given. When the malady becomes chronic, it becomes incurable." (2)

Hippocrates observed convulsions following head trauma which were contralateral to the site of the wound, leading him to be one of the first to introduce the concept of post-traumatic epilepsy. (8) He stated that the misconceptions about epilepsy are the result of the fear of the divine that the society had and believed that the disease was no more divine than others, but the 'sacred' name refers to its unique clinical presentations. (8) However, the non-spiritual basis for epilepsy that Hippocrates had hypothesized was not acceptable for centuries.

Aristotle (philosopher of the 4th century BC) had another concept for epilepsy. In his treatise, On Sleep and Waking, he stated that the process of epilepsy is similar to that of sleep: "sleep is similar to epilepsy and in some way, sleep is epilepsy." (14) He believed that sleep happens when the food produces evaporations into the veins which rises upward and descends again, and so happens for epilepsy. (15) Influenced by the Hippocratic theories and the new concepts of anatomy and physiology, Galen – Greek physician, surgeon, and philosopher during the Roman Empire – described two types of seizure: primary idiopathic and sympathetic. (1) The primary idiopathic is due to the accumulation of phlegm or black bile in the cerebral ventricles blocking the psychic pneuma – the soul. (1) Galen introduced the other type when he saw a case of a 13-year-old boy that had a passing feeling from legs to head before the seizure, characterized later as a "cool breeze", from which the word aura arose. (6) Thus, he considered the seizures that stem from other origins the stomach and extremities to be sympathetic. Despite the efforts that have been made, the dark ages (early Middle Ages) experienced

a regress in the theories back to antiquity. Also, with the rise of Christianity, epileptics were believed again to be either divine or demonic. (6)

Epilepsy during the Modern Era

During the Renaissance (15th-16th century), Paracelsus (1493-1541) believed in the presence of a living spirit in each creature which if suddenly and abnormally boiled up in the brain, causes epilepsy. (16) In the 17th and 18th centuries, the Hippocratic idea about epilepsy being a brain disorder, started to take root in Europe. (2) A Scottish physician called William Cullen (1710-1790) stated that seizures could occur in parts of the body and not necessarily be accompanied by loss of consciousness. (17)(18) During the same time, Maisonneuve (1745-1826), a French physician, highlighted how important is to hospitalize epileptic patients. (19) Therefore, in 1857, the first hospital for epileptic and crippled patients was founded in France. At the same time, the social distress that epileptics had, led to the foundation of care centers for them. Such institutions were also found in Norway, The Netherlands, Germany, Switzerland, England, and Denmark. (20)

Years later, Doctor Robert Bentley Todd (1809-1860) introduced an electrical theory of brain function and epilepsy (21), as he stated that an electrical discharge in the brain may be the cause of seizures. (2)(22) Todd later confirmed his theory by using the magnetoelectrical rotation machine of Michael Faraday on rabbits. (23) John Hughlings Jackson (1835-1911) put the basis for the science of epileptology and studied the localization of lesions that could produce seizures. (19)(20) His scientific findings were collected in a text he published called “Study of Convulsions”. In 1875, Richard Caton invented the first electroencephalogram (EEG) on cats, monkeys, and rabbits. (24) In 1929, Hans Berger, a German physician, recorded the first human EEG. (25) The discovery of EEG made revolutionary advancements in the fields of neurology, neurosurgery, and neuroscience, especially seizures. (25)

Once the concept of epilepsy being a brain disorder was established between the 17th and 19th centuries, its etiology was then attributed to vascular abnormalities, such as acute anemia or acute congestion in the brain. (2) During the early 1920, psychoanalysts considered epilepsy as a result of Id – Latin for “it”, is being detached from the external world and unaware of time. William Lennox (1884-1960) disagreed with this hypothesis. (26) He believed that epilepsy is due to intrinsic cerebral factors. Lennox tried to confirm the vascular etiology of epilepsy. After many unsuccessful attempts to do so, he joined Erna Leonhardt and Dr. Frederic Gibbs to explore cerebral activity recording with the nascent EEG. In 1935, Lennox concluded that epilepsy results from cerebral dysrhythmia. (26) He also frustrated the vascular effect on epilepsy and stated that there is no change in the cerebral blood flow during a seizure. (27)

In 2014, The International League Against Epilepsy (ILAE) defined epilepsy as a brain disease with any of the following conditions: (28)

- At least two unprovoked (or reflex) seizures occurring more than twenty-four hours apart.
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years; or
- Diagnosis of the epilepsy syndrome.

References

1. Khalil N, Benbadis S, Robertson D. Ceasing Antiquated Conceptions: A Telling of the Early and Evolving History of Epilepsy. Eur Neurol. 2020;83(3):341–4.
2. WHO, ILAE, IBE, editors. Atlas: Epilepsy Care in the World . Geneva: World Health Organization Press; 2005. 18–20 p.
3. Wilson J V, Reynolds EH. Texts and documents. Translation and analysis of a cuneiform text forming part of a Babylonian treatise on epilepsy. Med Hist. 1990 Apr;34(2):185–98.
4. Kaculini CM, Tate-Looney AJ, Seifi A. The History of Epilepsy: From Ancient Mystery to Modern Misconception. Cureus. 2021 Mar;13(3):e13953.
5. The History and Stigma of Epilepsy. Epilepsia [Internet]. 2003 Sep 1;44(s6):12–4. Available from: https://doi.org/10.1046/j.1528-1157.44.s.6.2.x
6. Gross RA. A brief history of epilepsy and its therapy in the Western Hemisphere. Epilepsy Res. 1992 Jul;12(2):65–74.
7. The West-Riding Lunatic Asylum Medical Reports. Glasgow Med J [Internet]. 1877 Jul;9(3):401–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5899571/
8. Magiorkinis E, Sidiropoulou K, Diamantis A. Hallmarks in the history of epilepsy: epilepsy in antiquity. Epilepsy Behav. 2010 Jan;17(1):103–8.
9. Eadie MJ. Epilepsy—from the Sakikku to hughlings Jackson. J Clin Neurosci [Internet]. 1995;2(2):156–62. Available from: https://www.sciencedirect.com/science/article/pii/0967586895900101
10. A Tablet on Epilepsy [Internet]. Available from: https://cdli.ox.ac.uk/wiki/doku.php?id=tablet_on_epilepsy
11. Longrigg J. Epilepsy in ancient Greek medicine--the vital step. Seizure. 2000 Jan;9(1):12–21.
12. Lai CW, Lai YH. History of epilepsy in Chinese traditional medicine. Epilepsia. 1991;32(3):299–302.
13. Pierce JMS. A DISEASE ONCE SACRED. A HISTORY OF THE MEDICAL UNDERSTANDING OF EPILEPSY. Brain [Internet]. 2002 Feb 1;125(2):441–2. Available from: https://doi.org/10.1093/brain/awf038
14. Aristotle. On sleep and waking. In: On the Soul Parva Naturalia On Breath. p. 8–9.
15. Aristotle. On sleep and waking. In: On the Soul Parva Naturalia On Breath. p. 334–6.
16. Mora G. Paracelsus' psychiatry: on the occasion of the 400th anniversary of his book "Diseases that deprive man of his reason" (1567). Am J Psychiatry. 1967 Dec;124(6):803–14.
17. Patel P, Moshé SL. The evolution of the concepts of seizures and epilepsy: What's in a name? Epilepsia open. 2020 Mar;5(1):22–35.
18. Cullen W. First lines of the practice of physic. A new edit.
19. Magiorkinis E, Diamantis A, Sidiropoulou K, Panteliadis C. Highights in the history of epilepsy: the last 200 years. Epilepsy Res Treat. 2014;2014:582039.
20. Sidiropoulou K, Diamantis A, Magiorkinis E. Hallmarks in 18th- and 19th-century epilepsy research. Epilepsy Behav. 2010 Jul;18(3):151–61.
21. Todd RB. The Lumleian Lectures for 1849. On the pathology and treatment of convulsive diseases. Epilepsia. 2005 Jul;46(7):995–1009.
22. Binder DK, Rajneesh KF, Lee DJ, Reynolds EH. Robert Bentley Todd's contribution to cell theory and the neuron doctrine. J Hist Neurosci. 2011 Apr;20(2):123–34.
23. From the London Medical Gazette. London 1849: Printed by Wilson and Ogilvy Skinner Street, Snowhill. 57, Todd RB. Delivered at the Royal College of Pysicians, London. By Robert Bentley Todd, M.D., F.R.S. ON THE PATHOLOGY AND TREATMENT OF CONVULSIVE DISEASES. Epilepsia [Internet]. 2005 Jul 1;46(7):995–1009. Available from: https://doi.org/10.1111/j.1528-1167.2005.10205.x
24. Caton R. IV.—Interim Report on Investigation of the Electric Currents of the Brain. Am J EEG Technol [Internet]. 1971 Mar 1;11(1):23–4. Available from: https://doi.org/10.1080/00029238.1971.11080813
25. Tudor M, Tudor L, Tudor KI. [Hans Berger (1873-1941)--the history of electroencephalography]. Acta Med Croatica. 2005;59(4):307–13.
26. Rosso M, Chu D, Santoro JD. William Gordon Lennox (1884–1960). J Neurol [Internet]. 2021; Available from: https://doi.org/10.1007/s00415-020-10338-z

27. Berger H. Über das Elektrenkephalogramm des Menschen. Arch Psychiatr Nervenkr [Internet]. 1929;87(1):527–70. Available from: https://doi.org/10.1007/BF01797193
28. Definition of Epilepsy 2014 [Internet]. Available from: https://www.ilae.org/guidelines/definition-and-classification/definition-of-epilepsy-2014

Article Topic: Trigeminal Neuralgia.

Author: Hashem Mohammad Jameel Bani Ata.

Editor: Yaman B. Ahmed.

Reviwer: Ethar hazaimeh

Keywords: Headache, Migraine, Cranial nerves, Pain.

Introduction[1,2]

The International Classification of Headache Disorders ICHD-3 defines neuralgia as "pain in the distribution(s) of a nerve or nerves, presumed to be due to dysfunction or injury of those neural structures. Common usage has implied a paroxysmal or lancinating quality, but the term neuralgia should not be reserved for paroxysmal pains."

The most common neuralgias are trigeminal neuralgia, occipital neuralgia, glossopharyngeal neuralgia, and Nervus intermedius neuralgia.

The International Classification of Headache Disorders defines trigeminal neuralgia (TN) as "A disorder characterized by recurrent unilateral brief electric shock-like pain, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli." trigeminal neuralgia is the most common form of craniofacial pain.

Epidemiology[5]

TN is a rare condition; however, it is the most common neuralgia with an incidence of 5/100,000 annually and is usually seen in the middle or elderly ages with female to male ratio equal (3:1). (2 - 5) % of patients with multiple sclerosis suffer from trigeminal neuralgia. The incidence increases with age: it is rare below the age of 40 so in 90% of the cases, symptoms appear after age 40. Familial cases of TN are reported in (1-2%) of all cases. Racial or geographic differences in trigeminal neuralgia are not reported.

Pathogenesis[5,12]

It is proposed that the trigeminal nerve roots into the pons are compressed by an aberrant loop of the vessel (usually by a superior cerebellar artery), so demyelination of nerve fibers occurs, which makes nerve fibers hyperexcitable. This hypothesis is supported by that microvascular decompression relieves pain in most cases.

compression causes could be by:

- Brain tumors: meningiomas and vestibular schwannomas
- Aneurysms
- Arteriovenous malformations
- Cysts

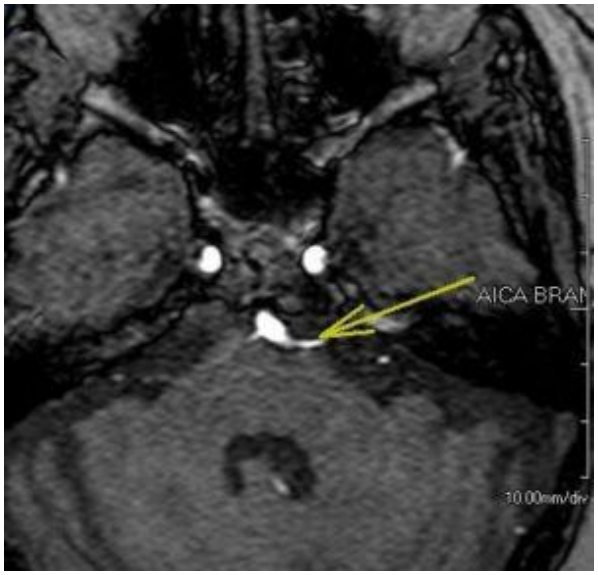


Figure 1: Enlarged vascular loop of anterior inferior cerebellar artery pressing upon trigeminal nerve.[13]

Etiology[1,3,4]

The pathology of these cranial neuralgias can be due to almost any type of lesion: compressive, metabolic, or infectious. According to ICHD-3, It is classified too classical, secondary, and idiopathic. Table 1.

Classical	Secondary	Idiopathic
Pain occurs along the distribution of TN without any obvious reasons other than neurovascular compression. Recurrent paroxysms of unilateral facial pain and involves pain-free periods or concomitant background facial pain.	Caused by underlining pathology. Unilateral facial pain in paroxysmal fashion and may have background continuous or near continuous pain. Multiple sclerosis is the most common cause.	Classical symptoms of TN. No significant abnormalities is diagnosed.

Table 1, classification of trigemnial neuralgia

Clinical features[5,6]

TN is characterized by short paroxysms of high-intensity sharp, stabbing facial pain in the distribution of the fifth cranial nerve, lasting from second to two minutes, each attack is followed by a refractory period during it no other attack is provoked.

The most trigeminal branch affected is maxillary and the least one is ophthalmic. Low probability of three branches being affected.

Triggers are described as minimal, seemingly harmless touches to the critical areas. Among the commonly described triggers are chewing, talking, touching, cold or hot sensations, shaving, or wind, usually over the division of cranial nerve V affected. These triggers reflect negatively on the quality of life because patients avoid feeding and communication due to fear to stimulate the pain.

Autonomic symptoms: such as conjunctival injection or tearing, miosis, ptosis, sweating, and clogged nose may also occur with pain unilaterally in the affected side. Episodes of pain interval may last for weeks or months followed by intervals with no pain.

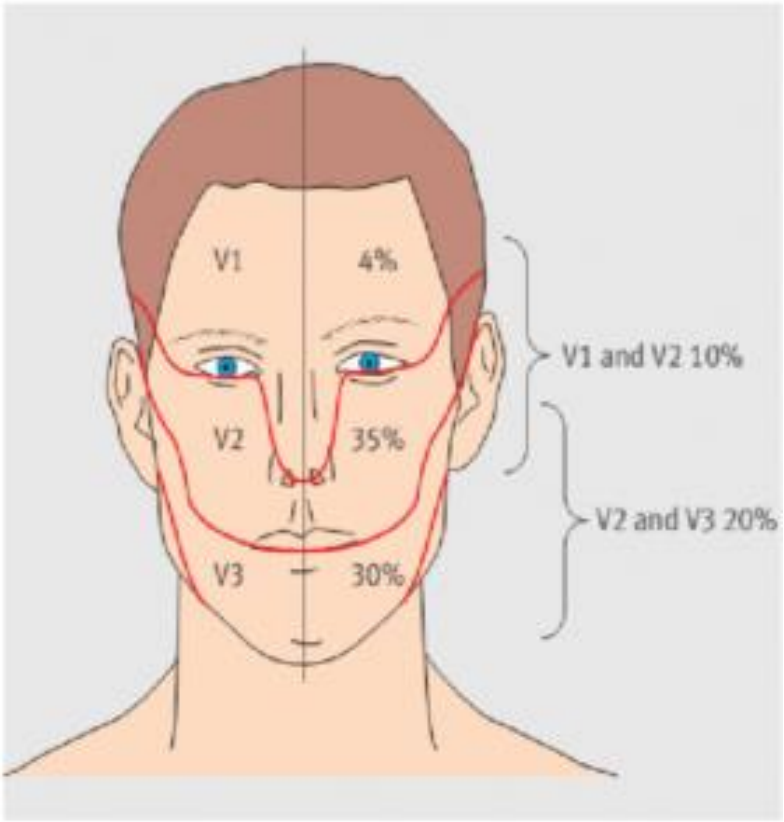


Figure 2: distribution of trigeminal neurolagia 7.

Painful trigeminal neuropathies[1,8,9]

The painful trigeminal neuropathies listed by the ICHD-3 include:

Acute herpes zoster

Diagnosis is got by the history of chickenpox and dermatologic lesion of a division of trigeminal nerve, and it is most common in V1, unlike classical trigeminal neuralgia. It is more common in females. Immunosuppression is a risk factor for acute herpetic infection.

Postherpetic trigeminal neuropathy

is caused by the reactivation of varicella-zoster virus in the dorsal root ganglia neural cells. It causes unilateral stabbing radiating pain, confined to a dermatome. Risk factors associated with a higher risk to develop PHN are old age and Immunosuppression. It resolves spontaneously over weeks or months after the rash resolutes in most cases.

Painful posttraumatic trigeminal neuropathy

is a complication of oral and maxillofacial procedures such as implant surgery and the removal of impacted lower third molars. It is characterized by sensation disturbance and neuropathic pain.

Trigeminal neuralgia secondary to Multiple sclerosis[10]

Multiple sclerosis: is a chronic, demyelinating disease of axons in the central nervous system, it increases the risk of developing trigeminal neuralgia by 20-fold, which is characterized by a sudden, more frequently bilateral, brief, stabbing recurrent pain with a distribution of one or more branches of the fifth cranial nerve. Attacks last from parts of a second to two minutes with frequency possibility through (1-50) days. trigeminal neuralgia secondary to multiple sclerosis is more common in females than in males and characterized earlier age of onset with a range (40-50) year.

Diagnosis of trigeminal neuralgia secondary to multiple sclerosis is done by:

1. Trigeminal reflex (blink reflex and the masseter inhibitory reflex): structural lesion caused by multiple sclerosis results in abnormal reflex,89% of patients with trigeminal neuralgia due to multiple sclerosis have the abnormal reflex. This technique provides specificity and sensitivity reach to 90%.
2. MRI: it is useful in identifying any linear plaques in the ventrolateral pons located between the trigeminal root entry zone and the trigeminal nuclei, and to identify compression of the trigeminal nerve root by vessels.

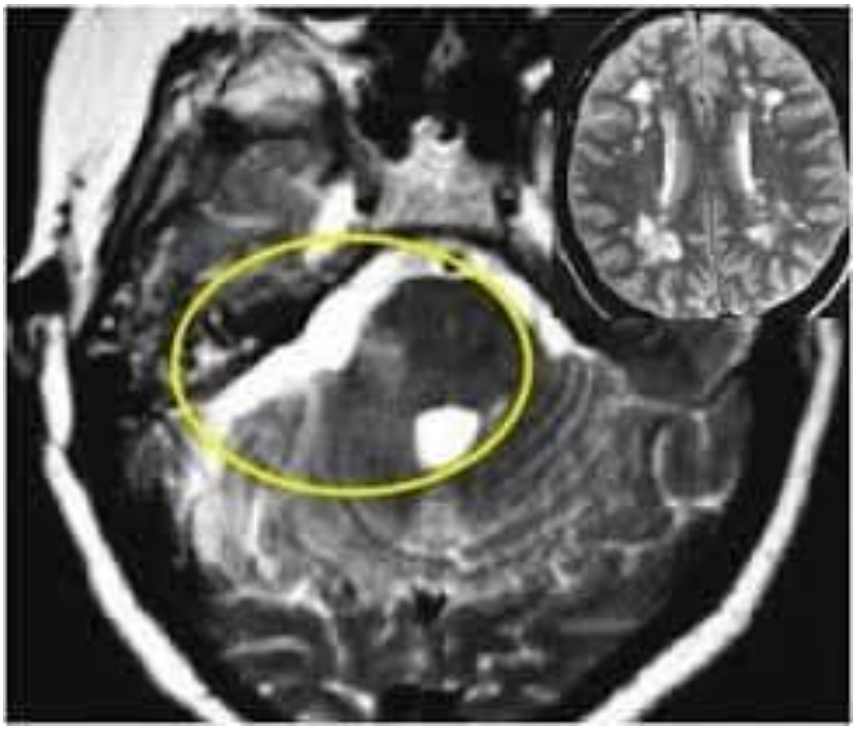


Figure 3: trigeminal neuralgia secondary to MS11.

Risk Factors[14]

The risk of trigeminal neuralgia increases with age, so most cases are above the age of 40 with women predominance. Multiple sclerosis and hypertension are the most common risk factors for trigeminal neuralgia. Diabetes and chronic sinusitis are reported in rare cases.

Diagnosis[4,15,16]

Trigeminal neuralgia is diagnosed clinically depending on the Diagnostic criteria for classic TN from The International Classification of Headache Disorders:

1. Pain has all of the following characteristics:
    1. lasting from a fraction of a second to 2 minutes
    2. severe intensity
    3. electric shock-like, shooting, stabbing, or sharp in quality
2. Precipitated by innocuous stimuli within the affected trigeminal distribution
3. Not better accounted for by another ICHD-3 diagnosis.

Neuroimaging with MRI and CT is considered when suspecting with trigeminal neuralgia, but without symptoms of trigeminal neuralgia, also to identify vascular compression.

Electrophysiologic trigeminal reflex assessment is normal in classic TN, so it is useful to differentiate classic TN from painful trigeminal neuropathy.

Differential diagnoses[6]

- Glossopharyngeal neuralgia
- Cluster headache
- Chronic paroxysmal hemicrania
- Tolosa-Hunt syndrome
- HZ involving the trigeminal ganglion
- Short-lasting unilateral neuralgiform headache with autonomic symptoms (SUNA).

Treatment[2,12,17–19]

Pharmacological therapy

Carbamazepine

It is the drug of choice in the treatment of trigeminal neuralgia. at the beginning of treatment, the dose is 100 - 200 mg twice /day with an increase of 100 mg every other day until the pain is relieved. The maximum dose is 1200 mg/d. However long-term treatment with Carbamazepine is associated with bad side effects as the following:

- **Hyponatremia**: in many cases is mild hyponatremia that results in drowsiness, diplopia, vertigo, and Some cases have severe hyponatremia which results in coma.
- **Development of resistance and intolerance**.
- **Hemopoietic depression.**
- **Aplastic anemia.**
- **Abnormalities in liver functions.**

Oxcarbazepine

It is often used as an initial drug for trigeminal neuralgia, its side effects are the same as Carbamazepine except for hyponatremia, with lower frequency than with carbamazepine. The dose is 150 mg twice/day, The dose can be increased as tolerated in 300 mg increments every third day until pain relief occurs. The largest dose is 1800 mg/d.

Anticonvulsant drugs

gabapentin, lamotrigine, and baclofen may improve the case:

- Gabapentin: 300 mg/d with increase 300mg/ 2-3 days. maximum dose is 1800 mg/d.
- Lamotrigine: dose 25 mg twice/day, with a gradual increase to 200-400 mg/d. Lamotrigine is associated with some side effects like sleepiness, dizziness, headache, vertigo, ataxia, and skin rash in the first 1-2 months of treatment, most often resolves during the therapy and it occurs in 7–10% of patients, Stevens-Johnson syndrome: once it occurs the medication should be stopped. It develops in 1 from 10,000 patients.
- baclofen: dose is 10 mg/d for 3 days with the possibility to increase the dose to 10-20 /d every 3 days if there is a need.
- Phenytoin: less effective but is used in cases of refractory pain and carbamazepine intolerance.

Peripheral alcohol injections

it may relieve the pain; however, it has 3 negative points which are:

- tissue inflammation and fibrosis.
- temporary weakness the muscles of mastication
- burning alcohol neuritis

Surgery

Surgical intervention is considered to patients of trigeminal neuralgia refractory to pharmacological treatments, these surgeries are:

1. **Microvascular decompression:** release the pressure on the trigeminal nerve by vessels. this procedure requires craniotomy to get the posterior fossa. However, this surgery has some complications at different rates as the following:

- Aseptic meningitis (11%): is the most common complication.
- hearing loss (10%): ipsilateral, major long-term complication
- Diplopia: damage of the 4th or 6th nerve, often transient.
- Sensory loss (7%)
- 7th nerve palsy: rare
- Cerebrospinal fluid leak
- Infarction
- hematomas

2. **Percutaneous procedures on the Gasserian ganglion (percutaneous rhizotomies):**

This procedure is done by inserting cannula through foramen ovale to reach the lesion of the trigeminal ganglion or root, and treat this lesion by:

- Thermal: radiofrequency thermocoagulation.
- Chemical: injection of glycerol.
- Mechanical: compression by an inflation balloon in Meckel's cave.

This technique is recommended for patients with multiple sclerosis complications are:

- Sensory loss happens in half of the patients.
- Postoperatively sensation of burning, heavy or aching (12%)
- Dysesthesias (6%).
- Anesthesia dolorosa (4%).
- Corneal numbness (4%): there is risk to develop keratitis
- Meningitis: a major complication
- temporary chronic masticatory problems: half of the patients with balloon compression suffer from it.

3. Gamma knife surgery: a non-invasive procedure which is done by focus beam of radiation to the trigeminal root in the posterior fossa. Complications are facial numbness, sensory loss, or paresthesia in some patients.
4. Peripheral neurectomy: is done by block or damage of trigeminal nerve outside the cranium.

- Recurrence of pain after surgery reaches up to 50% of patients after 5 years. Microvascular decompression has the longest duration of pain freedom in comparison with other interventions.

References

1. Tepper SJ. Cranial Neuralgias. *Continuum (Minneap Minn)*. 2018;24(4, Headache):1157-1178. doi:10.1212/CON.0000000000000637
2. Nova CV, Zakrzewska JM, Baker SR, Riordain RN. Treatment Outcomes in Trigeminal Neuralgia-A Systematic Review of Domains, Dimensions and Measures. *World Neurosurg X*. 2020;6:100070. doi:10.1016/j.wnsx.2020.100070
3. Cruccu G, Di Stefano G, Truini A. Trigeminal Neuralgia. *N Engl J Med*. 2020;383(8):754-762. doi:10.1056/NEJMra1914484
4. Majeed MH, Arooj S, Khokhar MA, Mirza T, Ali AA, Bajwa ZH. Trigeminal Neuralgia: A Clinical Review for the General Physician. *Cureus*. 2018;10(12):e3750. doi:10.7759/cureus.3750
5. Araya EI, Claudino RF, Piovesan EJ, Chichorro JG. Trigeminal Neuralgia: Basic and Clinical Aspects. *Curr Neuropharmacol*. 2020;18(2):109-119. doi:10.2174/1570159X17666191010094350
6. Jones MR, Urits I, Ehrhardt KP, et al. A Comprehensive Review of Trigeminal Neuralgia. *Curr Pain Headache Rep*. 2019;23(10):74. doi:10.1007/s11916-019-0810-0
7. trigeminal neurolagia. https://www.researchgate.net/figure/Distribution-of-trigeminal-neuralgia-11_fig1_349251166
8. Feller L, Khammissa RAG, Fourie J, Bouckaert M, Lemmer J. Postherpetic Neuralgia and Trigeminal Neuralgia. *Pain Res Treat*. 2017;2017:1681765. doi:10.1155/2017/1681765
9. De Poortere A, Van der Cruyssen F, Politis C. The benefit of surgical management in post-traumatic trigeminal neuropathy: a retrospective analysis. *Int J Oral Maxillofac Surg*. 2021;50(1):132-138. doi:10.1016/j.ijom.2020.05.004
10. Di Stefano G, Maarbjerg S, Truini A. Trigeminal neuralgia secondary to multiple sclerosis: from the clinical picture to the treatment options. *J Headache Pain*. 2019;20(1):20. doi:10.1186/s10194-019-0969-0
11. ms. https://biomedscis.com/pdf/OAJBS.ID.000145.pdf
12. Gambeta E, Chichorro JG, Zamponi GW. Trigeminal neuralgia: An overview from pathophysiology to pharmacological treatments. *Mol Pain*. 2020;16:1744806920901890. doi:10.1177/1744806920901890
13. trigeminal pict. https://radiology-information.blogspot.com/2011/08/trigeminal-neuralgia-mra.html
14. Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. *Ann Neurol*. 1990;27(1):89-95. doi:10.1002/ana.410270114
15. Cruccu G, Gronseth G, Alksne J, et al. AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol*. 2008;15(10):1013-1028. doi:10.1111/j.1468-1331.2008.02185.x
16. Bašić Kes V, Zadro Matovina L. Accommodation to Diagnosis of Trigeminal Neuralgia. *Acta Clin Croat*. 2017;56(1):157-161. doi:10.20471/acc.2017.56.01.21
17. Fields HL. Treatment of trigeminal neuralgia. *N Engl J Med*. 1996;334(17):1125-1126. doi:10.1056/NEJM199604253341709
18. Ali FM, Prasant M, Pai D, Aher VA, Kar S, Safiya T. Peripheral neurectomies: A treatment option for trigeminal neuralgia in rural practice. *J Neurosci Rural Pract*. 2012;3(2):152-157. doi:10.4103/0976-3147.98218
19. Al-Quliti KW. Update on neuropathic pain treatment for trigeminal neuralgia. The pharmacological and surgical options. *Neurosciences (Riyadh)*. 2015;20(2):107-114. doi:10.17712/nsj.2015.2.20140501

Article topic: Management of Acute Ischemic Stroke.

Author: Zain Alsaddi.

Reviwer: Omar Jbarah.

Editor: Ethar Hazaimeh.

Keywords: Acute ischemic stroke, Revascularization, rTPA, IV thrombolysis, Endovascular Therapy.

Overview

A multidisciplinary approach that involves the critical care of specialists has been established to treat an acute ischemic stroke (AIS) attack. Before the 1990s, treatment options for AIS were limited and they mainly focused on managing the patient's symptoms, secondary prevention as well as rehabilitation. [2]

However, since then, two major innovations were introduced into the field that lead to a dramatic transformation of the care of an acute stroke attack. In 1995, the use of IV tissue plasminogen (IV-tPA) was approved by the Federal Drug Administration (FDA) based on a landmark study conducted by the National Institutes of Neurological Disease and Stroke (NINDS). [3]

For almost 2 decades, IV-tPA remained the mainstay of treatment. In 2015, more sophisticated clinical trials were conducted and showed robust outcomes for the use of endovascular therapy (EVT). [4]

Early detection

Stroke is a clinical diagnosis; therefore, the first key step is the early identification of an acute stroke attack. As it may occur in a hospital setting or anywhere else in the community, it is important that bystanders are able to recognize it and act as fast as possible in order to deliver the appropriate treatment for the patient.

Starting with the prehospital setting, the BEFAST acronym is the algorithm that was made popular by the American Heart Association/American Stroke Association to diagnose stroke easily. To achieve a diagnosis, all these symptoms must be present.

The BEFAST acronym stands for:

- Balance: sudden onset of losing of balance or coordination
- Eyes: blurry or unclear vision, double vision

- Facial droopiness, weakness, or asymmetry
- Arm and/or weakness
- Speech difficulty or slurring
- Time of onset of the symptoms.

Another way to identify signs of an acute stroke attack is the presence of the 6S:[1]

1. Sudden onset of symptoms
2. Slurred Speech (The patients' words become unclear and hard to understand.)
3. Side Weak (weakness is seen on one side of the body like the face, arm, or leg or all three can get weak)
4. Spinning (vertigo)
5. Severe headache
6. Seconds (take note of the time the patient was last seen normal and the time the symptoms appeared)

Early recognition activates a stroke-specific chain of survival known as the 8Ds of stroke care chain:[2]

- Detection: involves recognition of the signs and symptoms of an acute stroke attack.
- Dispatch: usually includes calling 911 to activate Emergency medical services.
- Delivery: refers to prompt delivery of the patient to the hospital for further evaluation by specialists.
- Door: refers to the patient's arrival at the emergency department. The patient must be assessed with 10 minutes of arrival by an ED physician, according to the recommendations from the National Institute of Neurological Disorders and stroke.
- Data collection includes both physical and neurological exams as well as laboratory tests.
- Decision of the proper treatment method is made once the data has been assessed.
- Drug/device involves the administration of fibrinolytic therapy with 4.5 hours of the onset of symptoms.
- Disposition: it is recommended to admit the patient to the ICU or stroke unit within 3 hours of his arrival.

It is recommended to use the NIH stroke scale to completely assess a patient presenting with stroke symptoms. The patient should be examined by a trained physician or a neurologist within 10 minutes of arrival at the emergency room.

PRINCIPLES OF ACUTE STROKE CARE

There are three main principles of acute stroke:

(1) Achieve timely recanalization of the occluded artery and reperfusion of the ischemic tissue

(2) Optimize collateral flow

(3) Avoid secondary brain injury.

The mainstays of acute stroke treatment are recanalization and reperfusion, which can reduce the size of the infarct and reverse neurologic deficits. Recanalization is defined by the degree at which an occluded artery can be reopened. Without recanalization, the ischemic penumbra is surely destined to progress to infarction. Reperfusion is measured by the degree of flow reaching the previously hypo-perfused brain region.

Collateral flow is responsible for maintaining the viability of the ischemic penumbra. It provides enough flow to prevent critical ischemia and infarction, but the flow isn't sufficient to maintain normal cellular function. It can be protected by monitoring and avoiding blood pressure drops and is also supported by IV fluids administration.

In the emergency department. The initial evaluation of a patient with a possible acute stroke presentation mainly focuses on establishing whether the patient is eligible for reperfusion therapy. Necessary information is collected about the patient. This includes the time the patient was last seen or known to be well, his medical condition, and any recent surgery that could contraindicate thrombolysis. A neurologic examination is performed in order to calculate the National Institutes of Health Stroke Scale (NIHSS) score, a capillary glucose level, blood pressure as well as brain imaging are done.

Revascularization

The main and primary goal of managing advanced stroke is revascularization and limiting the possibility of a secondary neuronal injury. For selected patients, IV thrombolysis and EVT are now available.

IV thrombolysis

In 1995, the transition in the treatment for AIS from being purely and completely symptomatic to a highly time-sensitive matter was proven in the first landmark clinical trial which proved the use of IV-tPA to be safe and efficient. It shows that, on the 90-day mark, if IV-tPA is administered within the first 3 hours of symptoms onset, patients are at least 30% more likely to have only minimal or no disability.

in 2009, the American Heart Association/American Stroke Association (AHA/ASA) extended the IV-tPA window from 3 to 4.5 hours. Based on the European study Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke (ECASS-3). This extension led to an increase in the utilization of IV-tPA by up to 20%. [5,6,7]

In recent clinical trials, it was suggested that imaging rather than the known time of onset, which is the last time the patient was seen normal, can guide clinicians to treat patients using the time discrepancies of acute stroke showing. Data obtained from a clinical trial conducted by the European multicenter, MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset (WAKE-UP) suggested that almost 50% of wake-up strokes and strokes that occur during the daytime and have an unknown onset are IV-tPA candidates when MRI criteria are used. However, due to its cost, time spent in metal screening as well as the often far distance to the scanner, its implementation is limited. In another clinical trial where Thrombolysis- Guided-by Perfusion Imaging was performed up to 9 Hours after Onset of Stroke (EXTEND). CT-P imaging was used to assess the eligibility for IV-tPA and suggested that the efficacy and safety of IV-tPA can extend up to 9 hours and that revascularization can extend up to 24 hours. [8,9]

The US Food and Drug Administration (FDA) has only approved rtPA for use within 3 hours of stroke onset, but regulatory agencies in most other countries, those in the European Union are included, have approved its administration within 4.5 hours of stroke onset. However, according to the American Heart Association (AHA)/American Stroke Association, 4.5 hours is the recommended time window.[18]

The narrow therapeutic window and the fact that it is less effective in cases of large-vessel occlusions (internal carotid, initial segment of the medial cerebral artery, basilar artery) or large thrombi are considered as a limitation of this treatment. [15,17]

The indications and contraindications for IV rtPA have been revisited in the most recent version of the AHA guideline for the management of acute stroke and modified by the FDA in the package insert for the drug. [14, 18]

American Heart Association Guideline 2019	US Food and Drug Administration (FDA) Package Insert 2015
Indications	
Diagnosis of ischemic stroke with disabling neurologic deficit (regardless of severity)	Same
Symptom onset within 4.5 hours	Within 3 hours

Wake-up stroke with a diffusion-weighted imaging-FLAIR mismatch on MRI	Not mentioned
Age ≥18 years	Warning for age >77 years with risk factors for intracranial hemorrhage
Contraindications	
Severe head trauma within 3 months	Contraindicated
Ischemic stroke within 3 months	Removed
Previous intracranial hemorrhage	Warning for recent intracranial hemorrhage (contraindicated if active intracranial hemorrhage)
Suspected subarachnoid hemorrhage	Contraindicated
Suspected infective endocarditis	Not listed
Suspected aortic arch dissection	Not listed
Recent intracranial or intra-spinal surgery (within 3 months)	Contraindicated
Intracranial intra-axial neoplasm	Not listed

Gastrointestinal malignancy or gastrointestinal bleeding within previous 21 days	Warning
Active internal bleeding	contraindicated
Systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg that cannot be lowered safely	Contraindicated for severe uncontrolled hypertension. Warning for BP >175/110 mmHg.
Bleeding diathesis International normalized ratio (INR) >1.7 Heparin within 48 hours with abnormal activated partial thromboplastin time (aPTT). Low-molecular-weight heparin full treatment dose within the previous 24 hours. Platelets <100,000/ mm^3 Current use of direct thrombin inhibitor or factor Xa inhibitor with abnormal coagulation tests.	Contraindicated for bleeding diathesis
CT showing acute hemorrhage	contraindicated

CT showing extensive hypo-density (e.g., >1/3 of the cerebral hemisphere)	Removed

Table 1

By far, the most effective treatment for acute ischemic stroke is Acute reperfusion. The treatment of acute stroke also includes adequate management of the hemodynamic state of the patient, monitoring and managing ischemic brain edema, as well as early recognition of and therapy for systemic complications such as infections, cardiac arrhythmias, heart failure, and venous thromboembolism in a stroke unit staffed by specially trained personnel.

IV thrombolysis' wide adoption that began 25 years ago has recently been followed with clear evidence that adding endovascular treatment along with mechanical thrombectomy to the treatment of acute stroke onset can further improve the outcomes in patients with severe neurologic deficits from a proximal intracranial vessel occlusion.

The standard dose of IV rtPA administered for acute ischemic stroke is 0.9 mg/kg, with 10% of the dose is administered as a bolus while the remainder is infused over 1 hour. The total dose should not exceed 90 mg. the drip-and-ship strategy is followed in the emergency departments of medical centers that have more limited capabilities, where the patients first receive the bolus of rtPA and then get transferred to a primary or a comprehensive stroke center while the rest of the dose of the drug gets infused.

In ischemic stroke, no other thrombolytic agent has been approved for use. however, there is growing information on the value and efficacy of Tenecteplase when used for treating patients with acute cerebral ischemia. Tenecteplase is a bioengineered variant of rtPA that has a longer half-life, greater fibrin specificity as well as increased resistance against tissue plasminogen inhibitor-1 compared to rtPA. Therefore, it is administered as a single IV bolus.

A clinical trial is known as the NOR-TEST (Norwegian Tenecteplase Stroke Trial) was conducted to test the safety and efficacy of Tenecteplase 0.4mg/kg (up to 40mg) versus the standard dose of rtPA within 4.5 hours of the onset of an acute ischemic stroke. The proportions of patients with serious adverse events, including symptomatic intracerebral hemorrhage (ICH), and functional independence at 3 months were similar in the Tenecteplase and rtPA groups. However, the authors could not conclude that the two treatments were equivalent because the trial had been designed to test only for superiority. [19]

Another clinical trial was conducted which assigned patients with acute ischemic stroke and a proximal intracranial artery occlusion eligible for mechanical thrombectomy randomly to receive Tenecteplase (0.25 mg/kg, up to 25 mg) or standard dose rtPA within 4.5 hours of symptom onset. In this trial, known as the EXTEND-IA TNK (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke) trial, the Patients who received treatment with Tenecteplase had higher rates of recanalization/reperfusion at the time of initial assessment by conventional angiography, 22%versus 10%with rtPA. At 3 months, they also had a better functional outcome with similarly low rates of symptomatic ICH (1% in both groups). Thus, if future studies confirm such promising results, Tenecteplase may become a preferred alternative to rtPA. [20]

Endovascular Therapy

Since 1996, the only standard care trusted for acute ischemia has been Intravenous tissue plasminogen activator (IV tPA) however, this treatment has been used in only a small portion of acute ischemic stroke patients due to many contraindications and the low rates of recanalization/reperfusion in large vessel occlusions.

Although the FDA approved the use of IV-tPA, up to 69% of stroke patients are ineligible to receive IV-tPA due to delayed hospital presentation. Thanks to Endovascular treatment (EVT) the time window for AIS treatment has expanded providing the physicians with a stronger therapeutic arsenal over the last 3 years. The interventions for stroke with Endovascular therapy offer theoretical advantages over intravenous fibrinolysis, which include speed and rate of recanalization, reduced risk of hemorrhage, and a longer time window for use. [22]

Substantial efforts have been made to explore other possible treatment modalities that could improve clinical outcomes, particularly endovascular therapy (EVT) using mechanical devices. The EVT devices, which were approved by the Food and Drug Administration (FDA) in the United States for the treatment of acute ischemic stroke in 2004, 2008, and 2012 were the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Retriever, the second-generation of mechanical device the Penumbra System and the third-generation stent retrievers, respectively. [23]

The degree or quality of revascularization indicates the success of EVT. The Thrombolysis in Cerebral Infarction scale, shown below, is a tool used to standardize the different degrees of reperfusion ranging from no perfusion (TICI 0) to complete perfusion (TICI 3). TICI scores of 2B to 3 are usually regarded as successful reperfusion. [10,11,12]

Grade	**Radiographic Features**
0	No perfusion beyond the point of occlusion.

1	Penetration with minimal perfusion. Contrast passes the obstruction but fails to visualize the entire cerebral bed beyond the point of obstruction.
2	Partial perfusion. Contrast passes the obstruction and visualizes the cerebral bed past the obstruction. However, the flow of contrast in the distal bed is slower than in other non-obstructed vessels.
2A	Only <2/3 of the entire vascular territory is visualized.
2B	Complete visualization of the vascular territory but with slower filling than normal.
3	Complete perfusion. The entire vascular territory is visualized with normal flow.

Table 2: Thrombolysis in Cerebral infarction scale. (TCIS)

Candidates for Acute Endovascular Stroke Therapy:

◆ Age ≥18 years

◆ National Institutes of Health Stroke Scale score ≥6

◆ Time from symptom onset to groin puncture <6 hours (up to 24 hours if evidence of sizable ischemic penumbra is seen on perfusion imaging)

◆ Good pre-stroke functional status

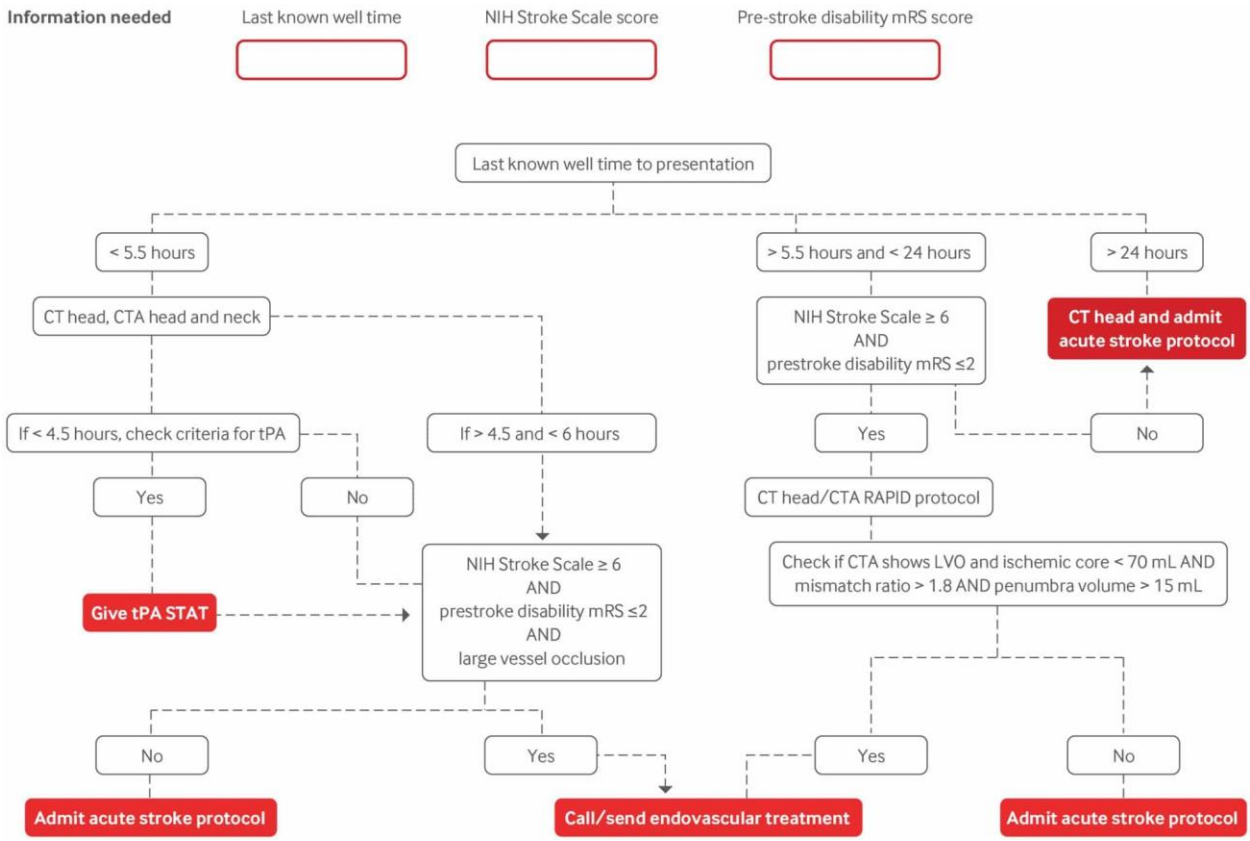
◆ Alberta Stroke Program Early CT Score ≥6 on baseline CT scan

◆ Presence of proximal intracranial artery occlusion

During endovascular therapy, the patient is usually put under General anesthesia (GA) and conscious sedation which allows a completely motionless procedure. This may however be associated with significant disadvantages including hemodynamic fluctuations in cerebral perfusion pressures and time delays. standardly, the common femoral artery is used as an access route for percutaneous neuro-interventions but in some patient subsets, including those with severe systemic atherosclerosis with bilateral iliofemoral artery occlusions, thoracic aortic dissection, extreme tortuosity, ostial stenosis of the proximal cervical vasculature, or unfavorable anatomy of the aortic arch pose a challenge during the procedure.[21]

The best imaging modality to select patients for acute endovascular intervention is yet to be determined. Evaluation of early ischemic changes on a non-contrast CT is indispensable, but the relative value of collateral flow assessment by non-invasive angiography and degree of perfusion deficit by CT or MRI perfusion scans continues to be debated for patients presenting within the first 6 hours after symptom onset.

Below is a diagram that illustrates the steps followed when handling a patient presenting with an acute ischemic stroke event. [24]



Acute Ischemic Stroke Protocol [24]

Conclusion

Acute ischemic stroke is a medical emergency in which every minute counts. The main target is to achieve reperfusion and reverse neurologic deficits to allow patients to regain function, even in severe cases. Two reperfusion strategies are now proven: IV rtPA and mechanical thrombectomy. for the right candidates, they are both safe and effective. Patient selection is crucial to optimize outcomes, but the attitude of the clinician should be that treatment should be given unless a solid contraindication exists. Efforts continue to expand indications for endovascular therapy, both within the early and extended time windows and those efforts should also be concentrated on refining systems of care to allow more patients to have access to reperfusion treatment.

References

- Chugh C. Acute Ischemic Stroke: Management Approach. *Indian J Crit Care Med*. 2019;23(Suppl 2):S140-S146. doi:10.5005/jp-journals-10071-23192
- Herpich F, Rincon F. Management of Acute Ischemic Stroke. *Crit Care Med*. 2020;48(11):1654-1663. doi:10.1097/CCM.0000000000004597

- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke.*N Engl J Med*. 1995; 333:1581–1587 [PubMed] [Google Scholar]
- Prabhakaran S, Ruff I, Bernstein RA. Acute stroke intervention: A systematic review.*JAMA*. 2015; 313:1451–1462 [PubMed] [Google Scholar]
- Del Zoppo GJ, Saver JL, Jauch EC, et al. ; American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: A science advisory from the American Heart Association/American Stroke Association.*Stroke*. 2009; 40:2945–2948 [PMC free article] [PubMed] [Google Scholar]
- Hacke W, Kaste M, Bluhmki E, et al. ; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke.*N Engl J Med*. 2008; 359:1317–1329 [PubMed] [Google Scholar]
- Lyerly MJ, Albright KC, Boehme AK, et al. The potential impact of maintaining a 3-hour IV thrombolysis window: How many more patients can we safely treat?.*J Neurol Disord Stroke*. 2013; 29:997–1003 [PMC free article] [PubMed] [Google Scholar]
- Ma H, Campbell BCV, Parsons MW, et al. ; EXTEND Investigators. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med*. 2019; 380:1795–1803 [PubMed] [Google Scholar]
- Campbell BCV, Ma H, Ringleb PA, et al. ; EXTEND, ECASS-4, and EPITHET Investigators. Extending thrombolysis to 4·5-9 h and wake-up stroke using perfusion imaging: A systematic review and meta-analysis of individual patient data.*Lancet*. 2019; 394:139–147 [PubMed] [Google Scholar]
- O'Connor RE, McGraw P, Edelsohn L. Thrombolytic therapy for acute ischemic stroke: Why the majority of patients remain ineligible for treatment.*Ann Emerg Med*. 1999; 33:9–14 [PubMed] [Google Scholar]
- De Los Ríos La Rosa F, Khoury J, Kissela BM, et al. Eligibility for intravenous recombinant tissue-type plasminogen activator within a population: The effect of the European Cooperative Acute Stroke Study (ECASS) III trial. *Stroke*. 2012; 43:1591–1595 [PMC free article] [PubMed] [Google Scholar]
- Higashida RT, Furlan AJ, Roberts H, et al. ; Technology Assessment Committee of the American Society of Interventional and Therapeutic Neuroradiology; Technology Assessment Committee of the Society of Interventional Radiology. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke*. 2003; 34:e109–e137 [PubMed] [Google Scholar]
- Jauch EC, Saver JL, Adams HP, Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870–947. [PubMed] [Google Scholar]
- ACTIVASE (alteplase). Prescribing information. gene.com/download/pdf/activase_prescribing. pdf. Accessed January 30, 2020.

- Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995;333(24):1581–1587. [PubMed] [Google Scholar]
- Guillan M, Alonso-Canovas A, Garcia-Caldentey J, et al. Off-label intravenous thrombolysis in acute stroke. Eur J Neurol. 2012;19(3):390–394. [PubMed] [Google Scholar]
- CONTINUUM (MINNEAP MINN) 2020;26 (2, CEREBROVASCULAR DISEASE):268–286.
- Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344–e418. doi:10.1161/STR.0000000000000211.
- Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol 2017;16(10):781n788. doi:10.1016/S1474-4422(17)30253-3.
- Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med 2018;378(17):1573–1582. doi:10.1056/NEJMoa1716405.
- Widimsky *et al.* Catheter-based interventions for acute ischaemic stroke Eur Heart J (2016)
- Khatri *et al.* Revascularization end points in stroke interventional trials: recanalization versus reperfusion in IMS-I Stroke (2005)
- Guo B, Moga C, Tjosvold L. Technological Safety and Effectiveness. In: Endovascular Therapy for Acute Ischemic Stroke [Internet]. Edmonton (AB): Institute of Health Economics; 2017 Aug. SECTION THREE.Available from: https://www.ncbi.nlm.nih.gov/books/NBK549072/
- Phipps M S, Cronin C A. Management of acute ischemic stroke BMJ 2020; 368 :l6983 doi:10.1136/bmj.l6983

Article topic: Phases and Phenotypes of Multiple Sclerosis.

Author: Bayan Khasawneh.

Editor: Omar Jbarah.

Reviewer: Ethar Hazaimeh.

Keywords: Multiple Sclerosis, Phases, Phenotypes, Relapsing, Remitting.

Overview

Multiple sclerosis (MS) is a chronic, non-traumatic, disabling inflammatory disease of the central nervous system that leads to demyelination and neurodegeneration. (1) MS usually affects young adults and the incidence of it is increasing worldwide. Multiple sclerosis has been classified as an organ-specific T-cell mediated autoimmune disease. It is considered a two-stage disease, with early inflammation responsible for relapsing-remitting disease and delayed neurodegeneration causing non-relapsing progression, i.e., secondary, and primary progressive MS.

Pathogenesis and Etiology

The underlying cause of Multiple Sclerosis remains uncertain. There are many factors that are believed to increase the susceptibility to have MS; including genetic factors (HLA-DRB1*15), and a few environmental factors, such as Vitamin D deficiency or ultraviolet B light (UVB) exposure, Epstein-Barr virus (EBV) infection, smoking and obesity. (2)

The characteristic pathological hallmark of MS is periventricular inflammatory lesions, forming demyelinating plaques. The inflammatory infiltrates contain T-lymphocytes, dominated by MHC class I restricted CD8+ T-cells; B-cells and plasma cells are also present but in smaller numbers. As a consequence of inflammation, Oligodendrocytes are damaged, and demyelination occurs. Axons are initially reasonably intact, but as the disease advances, irreversible axonal damage occurs.

Phases and disease course in Multiple Sclerosis

The disease course in MS is characterized by the interaction of two phenomena: relapses and progression. At different stages of the disease, these manifestations may

overlap. Approximately 80% of patients eventually evolve to the progressive phase of the disease, each phase of MS is further defined as active or inactive at any given time. (3)

Multiple sclerosis (MS) was classified as relapsing-remitting, primary progressive, secondary progressive, or progressive relapsing as of 1996. With a better understanding of MS and its pathology, several clinical characteristics have been re-examined and the main recommendations of the 2013 revisions were provided. After that, the Clinically isolated syndrome was added to the clinical course description, and progressive relapsing MS was eliminated.

All types of MS should be further subdivided into two groups: active and non-active, the occurrence of a clinical relapse or the presence of new T2 or gadolinium-enhancing lesions over a set length of time, is considered active MS (contrast-enhancing T1-hyperintense lesions, new T2-hyperintense lesions, or enlarging T2-hyperintense lesions). (4) The absence of active disease for a period of one year or more is referred to as "No evidence of disease activity" (NEDA). (5)

Relapses, Pseudo-relapses and Progression

Relapses suggest an acute inflammatory demyelination episode with or without axonal damage. The biological basis for why some MS presentations is asymptomatic is currently unknown. Asymptomatic relapse usually peaks over days to weeks, and then a recovery period begins, this phase of recovery is referred to as remission, and it includes some restoration of myelin and axonal integrity.

After a relapse, maximum clinical recovery usually occurs within the first three months and seldom lasts longer than six months. The majority of patients return to baseline clinically; some recover partially, and a small percentage of patients do not recover at all.

A recurrence of symptoms from a previous clinical relapse or a subclinical disease is known as a Pseudo-relapse. A pseudo-relapse means that the earlier CNS damage was not fully recovered. A pseudo-relapse can be triggered by any stress to the neurological system that exceeds a threshold that the damaged nervous system can withstand (e.g., heat, infection, exercise, fatigue).

If symptoms attributed to a pseudo-relapse last longer than 24 hours or do not improve within a few days despite identifying and treating a potential trigger (e.g., urinary tract infection), an MRI should be obtained to distinguish it from a symptomatic relapse recurrent in the same location or close vicinity on the same neural pathway.

Progression is the gradual and permanent deterioration of neurologic function over time. Progressive axonal damage or loss is the most common underlying pathology. Because imaging technology is improving, detecting subclinical progression will become a more essential part of the therapeutic decision-making process in MS in the future.

- ## Relapsing-Remitting Phase

The relapsing-remitting phase begins in many people as subclinical activity, usually long before they present with a clinically isolated syndrome. A relapse causes nerve signal disruption due to new injury in the brain or spinal cord. As a result, the patient may have new symptoms or the recurrence of previous ones. Relapses last at least 24 hours and it will be followed by a remission. During remission, symptoms partly or completely go away.

Multiple clinically distinct events affecting different areas of the CNS separated in time (at least 1 month apart) are required for the diagnosis of relapsing-remitting MS. The term "Dissemination in time and space" refers to this core operational diagnostic rule. However, in practice, typical lesions in location, shape, and orientation must be seen on MRI. Sequential lesions may develop in less than 1-month intervals in some patients with severe presentations.

Activity status is used to describe whether the patient is having active or inactive relapsing-remitting MS during a specific time.

- ## Progressive Phase

After one year of clinical progression, the progressive phase of MS is assumed to be established. Because of the temporal overlap between the relapsing and progressive phases, patients can still have an active disease with symptomatic relapses or asymptomatic MRI activity during this phase. After that, the patient is classified as having active progressive MS or inactive progressive MS.

The presence or absence of prior clinical relapses before the onset of a progressive disease course divides the progressive phase into subgroups. The term Primary progressive MS refers to a radiologically isolated syndrome that progresses. (6)

Secondary progressive MS refers to Relapsing-Remitting MS followed by the progressive phase. If solitary sclerosis leads to a progressive phase, it is described as progressive solitary sclerosis. (7)(8)

Understanding the primary progressive MS diagnosis should be given special consideration because, in most cases, patients have evidence of MRI activity compatible with a previous radiologically isolated syndrome at the time of primary progressive MS

presentation, even if a formal diagnosis of the radiologically isolated syndrome had not been established previously. However, it is reasonable to believe that if these patients had been imaged earlier, they would have been diagnosed with a radiologically isolated syndrome.

The differences between the progressive MS subtypes do not seem to be because of different progression mechanisms but rather because of why the disease activity remains subclinical in some individuals.

- **Clinically Isolated Syndrome**

Clinically isolated syndrome is used after a first-ever or single clinical incident. It becomes clinically definite relapsing-remitting MS when a patient has another clinical relapse (clinically active disease). (9)

MRI activity can meet "dissemination in time and space" criteria without the need for any further clinical relapse, according to the 2016 Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) and 2017 McDonald criteria updates. (10)(11)

The clinically isolated syndrome can be further subgrouped into two categories. Patients with solitary sclerosis have imaging results that do not meet the minimal MRI criterion for an MS diagnosis at the time of clinically isolated syndrome (at least three of the four imaging criteria), but the existing CNS lesions are unexplained by any other pathology and are typical of MS in location, orientation, and shape. When a patient with solitary sclerosis meets the MRI criteria for an MS diagnosis (at least three of the four imaging criteria) (12), the diagnosis of single-attack MS may be utilized.

Conclusion

Multiple sclerosis is a demyelinating disease of the Central Nervous System (CNS), including the brain and spinal cord. Every patient begins with a period of high risk, which is dictated by genetic and environmental factors. This is followed by the presymptomatic active phases of MS, the relapsing-remitting phase, and, eventually, the progressive phase of MS in most individuals.

Therefore, MS is a dynamic progression of phenotypic phases. Each phase is associated with a change in disability worsening caused by poorly recovered relapses, progression, and non-MS-related causes.

As a result, different types of interventions, such as currently existing disease-modifying therapies, future reparative or regeneration therapies, or even preventive methods, have ideal windows of opportunity. For existing disease-modifying therapies, the best time is earlier in life, when the disease is more likely to be active. However, our current

treatment strategy of escalating from lesser to stronger medications may not be the right thing to do.

References

1. Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: progress and challenges. Lancet 2017;389(10079):1336–1346. doi:10.1016/S0140-6736(16)30959-X.
2. Moutsianas L, Jostins L, Beecham AH, et al. Class II HLA interactions modulate genetic risk for multiple sclerosis. Nat Genet 2015;47(10):1107–1113. doi:10.1038/ng.3395.
3. Tutuncu M, Tang J, Zeid NA, et al. Onset of progressive phase is an age-dependent clinical milestone in multiple sclerosis. Mult Scler 2013; 19(2):188–198. doi:10.1177/1352458512451510.
4. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83(3):278–286. doi:10.1212/WNL.0000000000000560.
5. Rotstein DL, Healy BC, Malik MT, et al. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. JAMA Neurol 2015;72(2):152–158. doi:10.1001/jamaneurol. 2014.3537.
6. Kantarci OH, Lebrun C, Siva A, et al. Primary progressive multiple sclerosis evolving from radiologically isolated syndrome. Ann Neurol 2016;79(2):288–294. doi:10.1002/ana.24564.
7. Schmalstieg WF, Keegan BM, Weinshenker BG. Solitary sclerosis: progressive myelopathy from solitary demyelinating lesion. Neurology 2012; 78(8):540–544. doi:10.1212/WNL.0b013e318247cc8c.
8. Keegan BM, Kaufmann TJ, Weinshenker BG, et al. Progressive solitary sclerosis: gradual motor impairment from a single CNS demyelinating lesion. Neurology 2016;87(16):1713–1719. doi:10.1212/WNL.0000000000003235.
9. Brex PA, Ciccarelli O, O'Riordan JI, et al. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med 2002;346(3): 158–164. doi:10.1056/NEJMoa011341.
10. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol 2016;15(3):292–303. doi:10.1016/S1474-4422(15) 00393-2.
11. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69(2):292–302. doi:10.1002/ana.22366.
12. Tintoré M, Rovira A, Río J, et al. New diagnostic criteria for multiple sclerosis: application in first demyelinating episode. Neurology 2003;60(1): 27–30. doi:10.1212/WNL.60.1.27.

Article topic: Cerebral Venous Thrombosis (CVT).

Author: Mira Hasan.

Editor: Noor Qasem.

Reviewer: Ethar Hazaimeh.

Keywords: Stroke, emboli, anticoagulation, thrombophilia, antiphospholipid syndrome.

Introduction and epidemiology

Dural venous sinus thrombosis or thrombosis of cerebral veins is considered a special type of stroke [1], distinct from arterial strokes. Cerebral venous thrombosis (CVT) is less frequent than arterial stokes, and they target younger populations predominantly affecting females, rarely present as stroke syndrome, associated with a wider spectrum of clinical presentations which make the diagnosis even harder, and often delayed or missed, risk factors are also different from the ones known to be associated with arterial stokes, treatment options mainly parental heparin followed by oral anticoagulation, also associated with much less favorable factors [2] [3].

Low and middle-income countries have higher incidence due to higher pregnancy rates, increased infection rates, and nutritional deficiencies [4]. In some high-income countries, a study was conducted in the Netherlands showed an overall incidence of 1.32/100000/year and of 2.78/100000/year for women who are between 31 and 50 years [5]. Another study in Adelaide, Australia, using International Classification of Disease codes for CVT and neuroimaging reports, found the incidence to be of 1.57/100000/year, with a higher relative risk of 1.18 in females of reproductive ages [6]. A systematic review including 8829 CVT patients, from 74 case series including more than 40 subjects, found an average age of 32.9 years, along with a male to female ratio of (2:3).

This review showed a clear trend in the declining frequency of CVT patients who present with focal deficits or coma and a decrease in mortality over time. The decline in mortality can be owed to better management, and a decrease in septic CVT, but is mostly related to the recognition of less severe cases by MRI. Over time a shift in sex ratio was noted, with an increase in the proportion of women affected, associated with an increase in the use of oral contraceptives [7]. Another study confirmed that in elderly patients, the sex ratio is evenly distributed and is associated with a poorer prognosis than in younger CVT patients [8].

Risk factors and triggers

A condition associated with CVT can be classified into two groups, the first is predisposing like antiphospholipid syndrome, genetic prothrombotic diseases, the second is precipitant like oral contraceptive pills (OCPs) use, infections. They cannot be considered as causes of CVT because they do not fulfill the causality principles [4].

A multicenter case-control study compared women under 50 years of age, who suffered a CVT with historical controls to clarify the association between CVT and pregnancy along with puerperium, to revile no association with pregnancy but increased risk during postpartum especially during the first 6 weeks [9]. Using the same method, another study reported an increased risk of CVT in obese women reference. For women who are obese or overweight, the use of OCPs showed an increased risk of CVT in a dose-dependent manner [4]. Cancer is also a strong risk factor for CVT, specifically within the first year of diagnosis and hematological malignancies [10]. In leukemic patients treated with asparaginase, high dose steroid regimens, intrathecal methotrexate injections in acute lymphocytic leukemia (ALL), are considered risk factors for CVT in these patients [11] two references, also all-trans-retinoic acid use [12]. The world health organization also confirmed anemia as a risk factor [13]. They found that anemia itself is associated with unfavorable factors for CVT [4]. Patients found to have higher levels of VIII a few months following the acute period were more frequent in CVT patients, which indicates it might be a risk factor too [14]. VENOST study in turkey found that Behc¸et's disease handled CVT in 9.4% of the patients. Most of the patients had a subacute course along with an intracranial hypertension syndrome, associated with thrombosis of the transverse sinus [15].

Clinical features

Signs and symptoms of CVT can be grouped into presenting syndromes, the most frequent ones are isolated intracranial hypertension syndrome, focal syndrome, and encephalopathy [16]. Less frequent ones are cavernous sinus thrombosis syndromes, syndromes of multiple palsies of the lower CN. In the conducted VENOST study, a large Turkish multicenter retrospective study, they collected 1144 patients to find the onset was acute in 47%, subacute in 34%, and chronic in 19%. Most frequently seen clinical symptoms and signs were headache (87%), which was isolated in 25%, nausea, and vomiting in 28%, seizures in 24%, visual field defects in 27%, other focal neurological deficits in 18%, altered consciousness in 18% and cranial nerve palsies in 18% [17].

So, the clinical picture varies according to patients' age. In elderlies, encephalopathy was more frequent, with fewer reporting headaches [8][16]. Another factor affecting the presentation of CVT is cerebral venous topography of thrombosis. A systemic review of

116 patients with cortical venous thrombosis [18] complained mostly of headache, seizures, and focal neurological deficits.

Few patients presented with non-aneurysmal subarachnoid hemorrhage, either generalized or localized to a single or few cortical sulci of the hemisphere [19][20], or to perimesencephalic cisterns [21]. In a retrospective review of 138 patients with CVT [22], a subarachnoid hemorrhage in the absence of venous infarct happened only in 3 patients (2.2%). While in CVT patients with generalized subarachnoid hemorrhage presented with headache and neck stiffness, those with convexity subarachnoid hemorrhage have more complex symptomatology. In a series of 10 cases of convexity subarachnoid hemorrhage associated with CVT, all were related to superior sagittal sinus thrombosis. All patients complained of headache, 9 experienced seizures, 4 had papilledema, and only 4 complained of meningeal signs [19].

Seizures can also be focal or generalized from the onset and may progress to status epilepticus. In a large administrative US database, 16% of hospitalized CVT patients experienced seizures [23]. Acute symptomatic seizures are more frequently seen in CVT patients with supratentorial lesions, particularly if hemorrhagic, in those with motor and sensory deficits, and in cases with thrombosis of the superior sagittal sinus or cortical veins [24][25][26][27]. CVT patients can also present with status epilepticus, or status epilepticus may develop, particularly in patients with severe forms of CVT with supratentorial lesions, especially if multiple and hemorrhagic. Status may be refractory in about 1/6 of the patients, with refractoriness being related to the pretreatment duration of status [28]. At 6 months, 84% of CVT patients who had status epilepticus had a good recovery. Status epilepticus was not an independent predictor of poor outcome [4].

Few patients have experienced severe presentation such as encephalopathy or coma and may need intensive care [29][30]. These patients also have decreased consciousness, altered mental status, bilateral or multifocal signs, and/or seizures or status epilepticus. They usually have multiple sinus occlusion, specifically the superior sagittal sinus and the deep cerebral vein system, also bilateral parenchymal lesions were seen, diffuse brain edema, or large herniating lesions. In a German multicenter neurocritical unit study of 114 CVT comatose patients, 1/3 of them recovered fully (mRS 0–1), 10% were severely disabled, and 1/3 died [4]. Clinical deterioration after admission, midline shift, and age predicted poorer outcomes [29].

Clinical scores may be useful to predict the outcome after CVT [31]. Barboza et al. [32] derived a CVT grading scale from a large multicenter Mexican series. The score has is composed of the following points, parenchymal lesion size >6 cm (3 points), bilateral Babinski signs (3 points), male sex (2 points), parenchymal hemorrhage (2 points), and level of consciousness (3 points). The above-mentioned score does not include the

associated conditions in the prediction of outcome and needs validation in an independent sample.

Diagnosis

CVT diagnosis can be difficult to make [33], once suspected an emergent neuroimaging is required [34]. D dimer is a potentially useful diagnostic tool prior to imagining, false negative can occur especially in patients with isolated headache or prolonged duration of symptoms (>1 week) [40].

In one-quarter of patients, direct signs of CVT may be detected in plain CT, examples of finding are “dense triangle” a finding of a clot in the superior sagittal sinus, “ empty delta sign” (Fig. 1) for a no opacified thrombus surrounded by a collateral vein of the sinus wall after contrast injection, another sign is the “cord sign” (Fig. 2) indicated thrombosis of cortical or deep veins. Increased attenuation of the occluded sinus [41]. Nevertheless, these signs are less common in subacute/chronic cases and nonspecific. CT venography is a sensitive technique for the detection of low flow, and demonstrating filling defects in the dural sinuses and veins can confirm the diagnosis of CVT. This is particularly useful in patients with contraindication to perform MRI or with limited access to MRI. However, the diagnostic yield of CT venography alone is limited by the presence of several anatomic variants that may mimic sinus thrombosis like sinus atresia or hypoplasia, asymmetrical sinus drainage, normal sinus filling defects related to prominent arachnoid granulations, or intrasinus septa, and the difficulties in detecting cortical veins thrombosis [18], [35].

Figure. 1 “Empty Delta sign” Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 4408 [36]

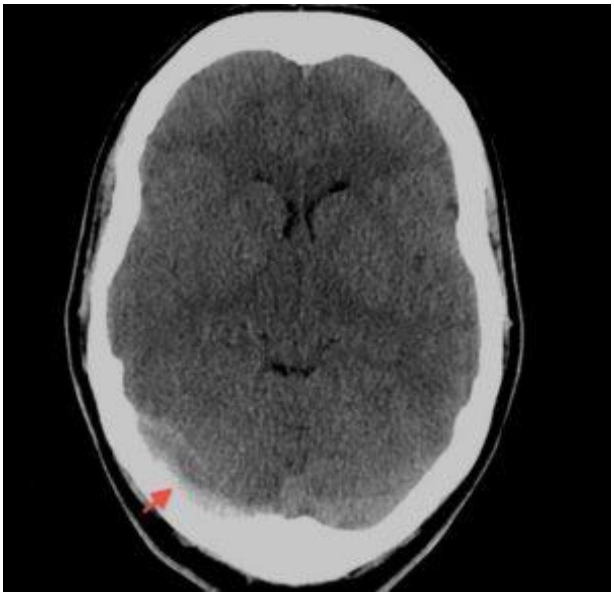


Figure. 2 “cord sign” Case courtesy of Dr Hani Makky Al Salam, Radiopaedia.org, rID: 13621 [37]

Concerning MRI, signals in T1 and T2 can appear falsely reassuring in the acute phase and the diagnosis of isolated cortical vein thrombosis is therefore challenging. Therefore, the use of T2*- weighted gradient recalled echo (T2*GRE) or susceptibility-weighted imaging (SWI) is recommended to improve the accuracy of diagnosis, allowing the identification of intraluminal thrombus as a hypointense region [38]. The use of 3D T1 weighted black blood sequences also has shown promising results [39][40]. MR venography alone has many limitations, particularly in patients with hypoplastic sinus, cortical vein thrombosis or partial sinus occlusions. Contrast-enhanced MR venography is more sensitive than time-of-flight MR venography because artifacts may be produced when there is flow in the plane of image acquisition [41]. Intraarterial angiography should be preserved for cases with inconclusive or contradictory findings in the other imaging modalities, to exclude dural arteriovenous fistula or when an endovascular therapeutic intervention is planned [35], 47

Small nontraumatic juxtacortical hemorrhages account for up to one fourth of intracerebral hemorrhages in patients with CVT and are associated with superior sagittal sinus occlusion. The brush sign (Fig. 3), an abnormally accentuated signal drop of subependymal and deep medullary veins in paramagnetic sensitive MR sequences, is occasionally found in CVT, especially in patients with thrombosis of the deep venous system or straight sinus, this sign likely represents increased deoxyhemoglobin and congestion of the deep veins and is associated with a clinical presentation with focal signs, more extensive thrombosis, and ipsilateral parenchymal brain lesion [42].

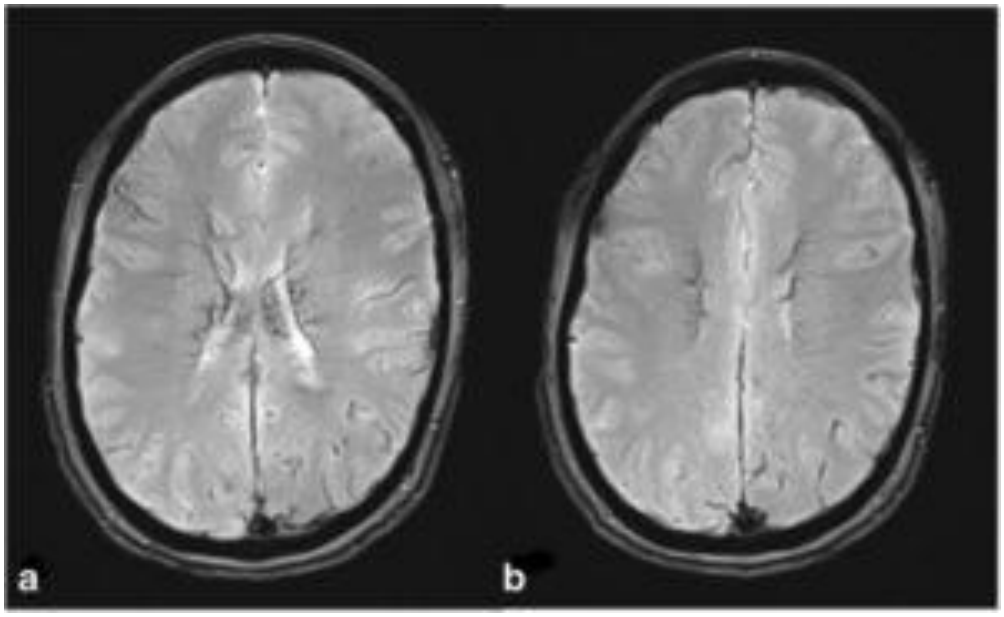


figure. 3 “Brush sign” (a, b, T2*-weighted imaging) in a patient with thrombosis of the superior sagittal sinus, torcula, straight sinus, deep venous system, and left lateral sinus [4].

Treatment

The European Stroke Organization along with the European Academy of Neurology issued a comprehensive guideline for the management of CVT [34]. The guidelines followed the GRADE system, which increases objectivity, decreases bias, and makes the recommendations simpler and clearer. The recommendations are viewed in Table 2.

Treatment	Recommendations
Heparin in the acute phase	For, strong
Low molecular weight heparin preferable to unfractionated heparin	For, weak
Endovascular treatment	No recommendation
Duration of oral anticoagulation 3-12 months	For, weak
Direct oral anticoagulation	Against, weak
Therapeutic lumbar puncture	No recommendation
Acetazolamide to improve outcome	Against, weak
Acetazolamide to improve headache or visual disturbances	No recommendations
Steroids to improve outcome	Against, weak
Steroids to treat associated Behcet's disease or other inflammatory diseases	For, weak
Shunting to improve outcome in patients with parenchymal lesions with impending herniation	Against, weak
Decompressive surgery to improve outcome in patients with parenchymal lesions with impending herniation	For, strong
Antiepileptics in patients with acute seizures and supratentorial lesions	For, weak
Antiepileptic drugs in patients with remote seizures	No recommendation
Low molecular weight heparin in CVT during pregnancy or puerperium	For, weak
Not contraindicating further pregnancies	For, weak
Low molecular weight heparin during subsequent pregnancies	For, weak

Table 2. Recommendation of management of cerebral venous thrombosis [34].

In the acute phase, all CVT patients should be started on parenteral anticoagulants either unfractionated IV heparin or SC low molecular weight heparin (LMWH). LMWH is preferable, unless the patient is clinically unstable, or lumbar puncture or surgery is planned. A systematic review and meta-analysis proved the evidence gathered by the European CVT Guidelines group, who reported a trend in favor of LMWH in relation to mortality and functional outcomes, with similar rates of systemic bleedings [43]. Observational studies described reassurance towards low rates of new or enlarging intracranial bleeding in cases of CVT with specific associated conditions (head trauma [44] head and neck infections [45]) or clinical features (posterior fossa lesions [46]), where anticoagulation can potentially be considered unsafe.

Patients with large hemispheric lesions, hemorrhagic, and impending herniation should be offered decompressive neurosurgery, or in general hemicraniectomy. No randomized controlled trial (RCT) of decompressive hemicraniectomy was specifically performed in CVT, but such a trial is unlikely to be feasible and will be considered unethical. In

retrospective series, the vital and functional outcomes of decompressive craniectomy in CVT are much better than in ischemic or hemorrhagic stroke [47].

Endovascular acute treatment of CVT yet remains unproven as a therapy option. The US Guidelines state that endovascular treatment may be considered for patients who are comatose or who deteriorate despite starting them on anticoagulation and have no parenchymal lesions [48][49]. Due to the very low quality of available evidence, the European guidelines do not make any recommendations for using endovascular treatment in acute CVT patients with a pretreatment low risk of poor outcome [34]. A systematic review of case series of more than 3 CVT cases treated with mechanical thrombectomy, 40% of whom had encephalopathy of coma, reported mortality of 14%, worsening or new intracranial hemorrhage in 9%, complete recanalization in 69%, and complete recovery in 35%. Chemical thrombolysis with mechanical thrombectomy did not result in additional harm nor benefit, in comparison with other techniques [50]. However, without a control group, no solid conclusions on the efficacy and safety of thrombectomy can be inferred. Two studies provided important evidence against the usage of endovascular thrombectomy or thrombolysis in acute CVT. The randomized controlled trial of thrombolysis or anticoagulation for severe acute CVT (TO-ACT) [51] was ended prematurely for futility. Of the 67 randomized patients, no difference was noted in clinical outcomes between those allocated to anticoagulation and endovascular treatment.

After initiating parenteral anticoagulation, oral anticoagulants like vitamin K antagonists should be used for at least 3–12 months, or for more prolonged periods in patients with genetic (e.g., protein C, S, and antithrombin deficiencies) or acquired (antiphospholipid syndrome, active cancer) prothrombotic conditions with a high risk of venous thrombosis recurrence [4]. The European Guidelines [34] recommend against the use of direct oral anticoagulants like factor Xa or thrombin inhibitors for the treatment of CVT, because of the low level of the available evidence, consisting of small case series without controls. Recently, a randomized controlled trial (RE- SPECT CVT) comparing the efficacy and safety of dabigatran 150 mg, bid, versus dose-adjusted warfarin (INR 2–3) for 6 months was completed, after allocating 60 CVT patients to each treatment arm. Results are waiting for publication [44]. The AHA/ASA guidelines recommend anticoagulation for 3–6 months in provoked CVT, 6–12 months in unprovoked CVT, and lifelong anticoagulation in recurrent CVT, CVT followed by venous thromboembolism or CVT associated with severe thrombophilia.[52]

Outcome

Large CVT series confirmed that nowadays, an acute CVT showed low death rates about (0 to 2%) [17][48]. An important cause of death in acute CVT but is much less frequent than seen after deep venous thrombosis of the limbs (1.4% vs. 6.6%, HR 0.26) [53]. In

the last years, there was interest in knowing the subtle consequences of CVT in patients who recovered completely. About 1/3 of CVT patients did not return to paid work this was more frequently seen in females and in patients with parenchymal lesions [54]. In CVT patients with bilateral vision 10/10 and normal fundoscopic finding and visual field tests, optical coherence tomography demonstrated major axonal loss [55]. Male gender, myeloproliferative disorders, factor V Leiden mutation but not persistent venous occlusion were confirmed as risk factors for the recurrence of venous thrombotic events after a CVT event [56][57][58]. In a South American cohort study [58], recurrence of venous thrombotic events after CVT was lower (1.6/100 patients-years) than in previous studies (~4/ 100), but the mean age was 30 years, and most CVT patients were females using oral contraceptives or pregnant, without associated prothrombotic conditions. Therefore, they recognized a lower risk of further venous thrombotic events.

Recanalization

In patients on anticoagulants, the rate of venous recanalization in the follow-up was found to be around 85% [59]. Analyzing the available cohort studies indicates that this process predominantly occurs in the first few months after CVT, although it can take up to 1 year. An association between the worse functional outcome and the lack of venous recanalization has been recently shown in a meta-analysis of CVT patients treated with anticoagulation [59]. More specifically, recanalization occurrence was related to a 3.3-fold increase in the odds of complete recovery. However, information on the temporal profile of recanalization was limited, hindering further conclusions on a possible critical time window for venous recanalization. Evidence on whether persistent occlusion increases the risk of recurrent CVT is even scanter, although an association has been shown in the pediatric population [51].

Follow-up imaging to establish the degree of recanalization can be useful to support or exclude the diagnosis of recurrent CVT in patients who must worsen complaints, such as headache, during follow-up. Previous documentation of recanalization facilitates the diagnostic workup if patients with suspected recurrence.

Conclusions

Case-control studies are required to establish the association between several risk factors and CVT. Ideally, these studies should be performed in countries and centers with diverse health care conditions, systems, and available resources. Given the low prevalence of CVT and the ubiquity of some of its presenting symptoms like headache, cost-effective diagnostic studies of different imaging modalities and their combinations to identify CVT are desirable. The appropriateness of screening for acute CVT with some rare predisposing conditions must consider not only to reach a diagnosis but also patient-centered outcomes whether performing screening prevents death, leads to a

better functional outcome, or decreases psychological distress. In the near future, results of the treatment trials on endovascular thrombolysis/thrombectomy (To- ACT), dabigatran (RE-SPECT CVT), and duration of anticoagulation (Extending oral anticoagulation treatment after acute Cerebral Vein Thrombosis) will significantly increase the level of evidence that currently supports the management of CVT. [4]

References

[1] W. Ageno, J. Beyer-Westendorf, D. A. Garcia, A. Lazo-Langner, R. D. McBane, and M. Paciaroni, "Guidance for the management of venous thrombosis in unusual sites," *J. Thromb. Thrombolysis*, vol. 41, no. 1, pp. 129–143, 2016, doi: 10.1007/s11239-015-1308-1.

[2] J. M. Ferro, P. Canhão, and D. Aguiar de Sousa, "Cerebral venous thrombosis," *Presse Med.*, vol. 45, no. 12, Part 2, pp. e429–e450, 2016, doi: https://doi.org/10.1016/j.lpm.2016.10.007.

[3] S. M. Silvis, D. A. de Sousa, J. M. Ferro, and J. M. Coutinho, "Cerebral venous thrombosis," *Nat. Rev. Neurol.*, vol. 13, no. 9, pp. 555–565, 2017, doi: 10.1038/nrneurol.2017.104.

[4] J. M. Ferro and D. Aguiar de Sousa, "Cerebral Venous Thrombosis: an Update," *Curr. Neurol. Neurosci. Rep.*, vol. 19, no. 10, pp. 1–9, 2019, doi: 10.1007/s11910-019-0988-x.

[5] J. M. Coutinho, S. M. Zuurbier, M. Aramideh, and J. Stam, "The incidence of cerebral venous thrombosis: A cross-sectional study," *Stroke*, vol. 43, no. 12, pp. 3375–3377, 2012, doi: 10.1161/STROKEAHA.112.671453.

[6] S. Devasagayam, B. Wyatt, J. Leyden, and T. Kleinig, "Cerebral Venous Sinus Thrombosis Incidence is Higher Than Previously Thought: A Retrospective Population-Based Study," *Stroke*, vol. 47, no. 9, pp. 2180–2182, 2016, doi: 10.1161/STROKEAHA.116.013617.

[7] S. M. Zuurbier, S. Middeldorp, J. Stam, and J. M. Coutinho, "Sex differences in cerebral venous thrombosis: A systematic analysis of a shift over time," *Int. J. Stroke*, vol. 11, no. 2, pp. 164–170, Jan. 2016, doi: 10.1177/1747493015620708.

[8] S. M. Zuurbier *et al.*, "Cerebral venous thrombosis in older patients," *Stroke*, vol. 49, no. 1, pp. 197–200, 2018, doi: 10.1161/STROKEAHA.117.019483.

[9] S. M. Silvis *et al.*, "Postpartum period is a risk factor for cerebral venous thrombosis: A case-control study," *Stroke*, vol. 50, no. 2, pp. 501–503, 2019, doi: 10.1161/STROKEAHA.118.023017.

[10] S. M. Silvis *et al.*, "Cancer and risk of cerebral venous thrombosis: a case–control study," *J. Thromb. Haemost.*, vol. 16, no. 1, pp. 90–95, 2018, doi: 10.1111/jth.13903.

[11] S. Ranta *et al.*, "Cerebral sinus venous thromboses in children with acute lymphoblastic leukaemia - a multicentre study from the Nordic Society of Paediatric Haematology and Oncology," *Br. J. Haematol.*, vol. 168, no. 4, pp. 547–552, 2015, doi: 10.1111/bjh.13162.

[12] K. R. Lee, V. Subrayan, M. M. Win, N. Fadhilah Mohamad, and D. Patel, "ATRA-induced cerebral sinus thrombosis," *J. Thromb. Thrombolysis*, vol. 38, no. 1, pp. 87–89, 2014, doi: 10.1007/s11239-013-0988-7.

[13] J. M. Coutinho *et al.*, "Association between anemia and cerebral venous thrombosis: Case-control study," *Stroke*, vol. 46, no. 10, pp. 2735–2740, 2015, doi: 10.1161/STROKEAHA.115.009843.

[14] L. Vecht, S. M. Zuurbier, J. C. M. Meijers, and J. M. Coutinho, "Elevated factor VIII increases the risk of cerebral venous thrombosis: a case–control study," *J. Neurol.*, vol. 265, no. 7, pp. 1612–1617, 2018, doi: 10.1007/s00415-018-8887-7.

[15] D. Uluduz *et al.*, "Behçet's disease as a causative factor of cerebral venous sinus thrombosis: subgroup analysis of data from the VENOST study," *Rheumatology*, vol. 58, no. 4, pp. 600–608, Apr. 2019, doi: 10.1093/rheumatology/key153.

[16] J. M. Ferro, P. Canhão, J. Stam, M. G. Bousser, and F. Barinagarrementeria, "Prognosis of Cerebral Vein and Dural Sinus Thrombosis: Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)," *Stroke*, vol. 35, no. 3, pp. 664–670, 2004, doi: 10.1161/01.STR.0000117571.76197.26.

[17] T. Duman *et al.*, "A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study," *J. Stroke Cerebrovasc. Dis.*, vol. 26, no. 8, pp. 1848–1857, Aug. 2017, doi: 10.1016/j.jstrokecerebrovasdis.2017.04.020.

[18] A. Batra, R. Rathakrishnan, and V. K. Sharma, "Isolated Cortical Vein Thrombosis," *Venous Thromb. Risk Factors, Manag. Complicat.*, pp. 141–156, 2014, doi: 10.1161/strokeaha.113.004414.

[19] S. Panda, D. K. Prashantha, S. Ravi Shankar, and D. Nagaraja, "Localized convexity subarachnoid haemorrhage-a sign of early cerebral venous sinus thrombosis," *Eur. J. Neurol.*, vol. 17, no. 10, pp. 1249–1258, 2010, doi: 10.1111/j.1468-1331.2010.03001.x.

[20] R. Geraldes, P. R. Sousa, A. C. Fonseca, F. Falcão, P. Canhão, and T. Pinho e Melo, "Nontraumatic Convexity Subarachnoid Hemorrhage: Different Etiologies and Outcomes," *J. Stroke Cerebrovasc. Dis.*, vol. 23, no. 1, pp. e23–e30, Jan. 2014, doi: 10.1016/j.jstrokecerebrovasdis.2013.08.005.

[21] F. W. Fu *et al.*, "Perimesencephalic nonaneurysmal subarachnoid hemorrhage caused by transverse sinus thrombosis: A case report and review of literature," *Med. (United States)*, vol. 96, no. 33, 2017, doi: 10.1097/MD.0000000000007374.

[22] M. Azeemuddin, M. Awais, F. Mubarak, A. Rehman, and N. U.-A. Baloch, "Prevalence of subarachnoid haemorrhage among patients with cranial venous sinus thrombosis in the presence and absence of venous infarcts," *Neuroradiol. J.*, vol. 31, no. 5, pp. 496–503, Jun. 2018, doi: 10.1177/1971400918783060.

[23] Y. Leavell, M. Khalid, S. Tuhrim, and M. S. Dhamoon, “Baseline Characteristics and Readmissions after Cerebral Venous Sinus Thrombosis in a Nationally Representative Database,” *Cerebrovasc. Dis.*, vol. 46, no. 5–6, pp. 249–256, 2018, doi: 10.1159/000495420.
[24] J. M. Ferro, P. Canhão, M. G. Bousser, J. Stam, and F. Barinagarrementeria, “Early seizures in cerebral vein and dural sinus thrombosis: Risk factors and role of antiepileptics,” *Stroke*, vol. 39, no. 4, pp. 1152–1158, 2008, doi: 10.1161/STROKEAHA.107.487363.
[25] F. Masuhr *et al.*, “Risk and predictors of early epileptic seizures in acute cerebral venous and sinus thrombosis,” *Eur. J. Neurol.*, vol. 13, no. 8, pp. 852–856, 2006, doi: 10.1111/j.1468-1331.2006.01371.x.
[26] R. Mahale *et al.*, “Acute seizures in cerebral venous sinus thrombosis: What predicts it?,” *Epilepsy Res.*, vol. 123, no. January 2011, pp. 1–5, 2016, doi: 10.1016/j.eplepsyres.2016.01.011.
[27] H. Ding *et al.*, “Clinical features of seizures after cerebral venous sinus thrombosis and its effect on outcome among Chinese Han population,” *Stroke Vasc. Neurol.*, vol. 2, no. 4, pp. 184 LP – 188, Dec. 2017, doi: 10.1136/svn-2017-000095.
[28] J. Kalita, U. K. Misra, V. K. Singh, and D. Dubey, “Predictors and outcome of status epilepticus in cerebral venous thrombosis,” *J. Neurol.*, vol. 266, no. 2, pp. 417–425, 2019, doi: 10.1007/s00415-018-9145-8.
[29] C. M. Kowoll *et al.*, “Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis,” *Neurocrit. Care*, vol. 25, no. 3, pp. 392–399, 2016, doi: 10.1007/s12028-016-0256-8.
[30] B. Soyer *et al.*, “Outcome of a cohort of severe cerebral venous thrombosis in intensive care,” *Ann. Intensive Care*, vol. 6, no. 1, pp. 4–11, 2016, doi: 10.1186/s13613-016-0135-7.
[31] J. M. Ferro *et al.*, “Risk Score to Predict the Outcome of Patients with Cerebral Vein and Dural Sinus Thrombosis,” *Cerebrovasc. Dis.*, vol. 28, no. 1, pp. 39–44, 2009, doi: 10.1159/000215942.
[32] M. A. Barboza *et al.*, “A practical score for prediction of outcome after cerebral venous thrombosis,” *Front. Neurol.*, vol. 9, no. OCT, pp. 1–8, 2018, doi: 10.3389/fneur.2018.00882.
[33] A. L. Liberman, G. Gialdini, E. Bakradze, A. Chatterjee, H. Kamel, and A. E. Merkler, “Misdiagnosis of cerebral vein thrombosis in the emergency department,” *Stroke*, vol. 49, no. 6, pp. 1504–1506, 2018, doi: 10.1161/STROKEAHA.118.021058.
[34] J. M. Ferro *et al.*, “European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis – Endorsed by the European Academy of Neurology,” *Eur. Stroke J.*, vol. 2, no. 3, pp. 195–221, Jul. 2017, doi: 10.1177/2396987317719364.
[35] R. M. H *et al.*, “Thrombosis and Multidetector CT Angiography : Tips and Tricks,” *Radiogr. a Rev. Publ. Radiol. Soc. North Am. Inc*, vol. 26, pp. 5–18, 2006.
[36] “empty delta sign radiopaedia.” https://radiopaedia.org/cases/4408/studies/6629?lang=gb&source_of=https%3A%2F%2Fradiopaedia.org%2Farticles%2Fempty-delta-sign-dural-venous-sinus-thrombosis.
[37] Radiopedia, “cord sign.” https://radiopaedia.org/cases/13621/studies/19472?lang=gb&source_of=https%3A%2F%2Fradiopaedia.org%2Farticles%2Fcord-sign-dural-sinus-thrombosis.
[38] A. Idbaih, M. Boukobza, I. Crassard, R. Porcher, M. G. Bousser, and H. Chabriat, “MRI of clot in cerebral venous thrombosis: High diagnostic value of susceptibility-weighted images,” *Stroke*, vol. 37, no. 4, pp. 991–995, 2006, doi: 10.1161/01.STR.0000206282.85610.ae.
[39] P. P. Niu *et al.*, “Diagnosis of non-acute cerebral venous thrombosis with 3D T1-weighted black blood sequence at 3 T,” *J. Neurol. Sci.*, vol. 367, no. February, pp. 46–50, 2016, doi: 10.1016/j.jns.2016.05.052.
[40] Q. Yang *et al.*, “Early Detection and Quantification of Cerebral Venous Thrombosis by Magnetic Resonance Black-Blood Thrombus Imaging,” *Stroke*, vol. 47, no. 2, pp. 404–409, 2016, doi: 10.1161/STROKEAHA.115.011369.
[41] N. Rollins, C. Ison, T. Reyes, and J. Chia, “Cerebral MR venography in children: Comparison of 2D time-of-flight and gadolinium-enhanced 3D gradient-echo techniques,” *Radiology*, vol. 235, no. 3, pp. 1011–1017, 2005, doi: 10.1148/radiol.2353041427.
[42] D. Aguiar De Sousa *et al.*, “Brush Sign Is Associated with Increased Severity in Cerebral Venous Thrombosis,” *Stroke*, vol. 50, no. 6, pp. 1574–1577, 2019, doi: 10.1161/STROKEAHA.119.025342.
[43] A. Qureshi and A. Perera, “Low molecular weight heparin versus unfractionated heparin in the management of cerebral venous thrombosis: A systematic review and meta-analysis,” *Ann. Med. Surg.*, vol. 17, pp. 22–26, 2017, doi: 10.1016/j.amsu.2017.03.016.
[44] D. S. Hersh *et al.*, “Pediatric cerebral venous sinus thrombosis or compression in the setting of skull fractures from blunt head trauma,” *J. Neurosurg. Pediatr.*, vol. 21, no. 3, pp. 258–269, 2018, doi: 10.3171/2017.9.PEDS17311.
[45] S. M. Zuurbier *et al.*, “Clinical Outcome of Anticoagulant Treatment in Head or Neck Infection-Associated Cerebral Venous Thrombosis,” *Stroke*, vol. 47, no. 5, pp. 1271–1277, 2016, doi: 10.1161/STROKEAHA.115.011875.
[46] D. A. De Sousa *et al.*, “Cerebral venous thrombosis causing posterior fossa lesions: Description of a case series and assessment of safety of anticoagulation,” *Cerebrovasc. Dis.*, vol. 38, no. 5, pp. 384–388, 2014, doi: 10.1159/000368999.
[47] T. Goedemans *et al.*, “Neurologic Outcome After Decompressive Craniectomy: Predictors of Outcome in Different Pathologic Conditions,” *World Neurosurg.*, vol. 105, pp. 765–774, 2017, doi: 10.1016/j.wneu.2017.06.069.
[48] D. M. Nasr, W. Brinjikji, H. J. Cloft, G. Saposnik, and A. A. Rabinstein, “Mortality in Cerebral Venous Thrombosis: Results from the National Inpatient Sample Database,” *Cerebrovasc. Dis.*, vol. 35, no. 1, pp. 40–44, 2013, doi: 10.1159/000343653.
[49] S. K. Lee, M. Mokin, S. W. Hetts, J. T. Fifi, M. G. Bousser, and J. F. Fraser, “Current endovascular strategies for cerebral venous thrombosis: Report of the SNIS Standards and Guidelines Committee,” *J. Neurointerv. Surg.*, vol. 10, no. 8, pp. 803–810, 2018, doi: 10.1136/neurintsurg-2018-013973.
[50] F. M. Siddiqui *et al.*, “Mechanical Thrombectomy in Cerebral Venous Thrombosis,” *Stroke*, vol. 46, no. 5, pp. 1263–1268, 2015, doi: 10.1161/STROKEAHA.114.007465.

[51] J. M. Coutinho *et al.*, "Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis: Rationale and Design of the TO-ACT Trial," *Int. J. Stroke*, vol. 8, no. 2, pp. 135–140, Feb. 2012, doi: 10.1111/j.1747-4949.2011.00753.x.
[52] G. Saposnik *et al.*, "Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association.," *Stroke*, vol. 42, no. 4, pp. 1158–1192, Apr. 2011, doi: 10.1161/STR.0b013e31820a8364.
[53] A. L. Liberman *et al.*, "Risk of Pulmonary Embolism after Cerebral Venous Thrombosis," *Stroke*, vol. 48, no. 3, pp. 563–567, 2017, doi: 10.1161/STROKEAHA.116.016316.
[54] E. Lindgren, K. Jood, and T. Tatlisumak, "Vocational outcome in cerebral venous thrombosis: Long-term follow-up study," *Acta Neurol. Scand.*, vol. 137, no. 3, pp. 299–307, 2018, doi: 10.1111/ane.12875.
[55] Y. Koban, H. Ozlece, S. Karayol, and N. Huseyinoglu, "Decreased retinal nerve fiber layer thickness in patients with cerebral venous thrombosis," *BMC Ophthalmol.*, vol. 19, no. 1, pp. 1–6, 2019, doi: 10.1186/s12886-019-1046-9.
[56] H. Y. Lim, C. Ng, G. Donnan, H. Nandurkar, and P. Ho, "Ten years of cerebral venous thrombosis: male gender and myeloproliferative neoplasm is associated with thrombotic recurrence in unprovoked events," *J. Thromb. Thrombolysis*, vol. 42, no. 3, pp. 423–431, 2016, doi: 10.1007/s11239-016-1362-3.
[57] I. Martinelli *et al.*, "Cerebral vein thrombosis in patients with Philadelphia-negative myeloproliferative neoplasms An European Leukemia Net study," *Am. J. Hematol.*, vol. 89, no. 11, pp. E200–E205, 2014, doi: 10.1002/ajh.23809.
[58] G. S. Pires *et al.*, "Risk factors associated with recurrent venous thromboembolism after a first cerebral venous thrombosis event: A cohort study," *Thromb. Res.*, vol. 178, no. April, pp. 85–90, 2019, doi: 10.1016/j.thromres.2019.04.008.
[59] D. A. De Sousa, L. L. Neto, P. Canhão, and J. M. Ferro, "Recanalization in cerebral venous thrombosis a systematic review and meta-analysis," *Stroke*, vol. 49, no. 8, pp. 1828–1835, 2018, doi: 10.1161/STROKEAHA.118.022129.

Article topic: Rehabilitation for Patients with Multiple Sclerosis.

Author: Yara Abu Al Halaweh.

Editor: Omar Jbarah.

Reviewer: Ethar Hazaimeh.

Keyword: Multiple sclerosis, Demyelinating, physiotherapy.

Overview

Multiple sclerosis (MS) is a long-lasting inflammatory demyelinating illness of the central nervous system (CNS) the reasons of which are not fully clear yet and whose course is tough to predict. [1] It is well recognized that the progress of demyelinating lesions might be caused by autoimmune processes as well as geographical and genetic factors. The pathophysiology of MS suspects that demyelination changes are harmful to the gray matter and cerebral cortex. As well as basal ganglia and cerebellar cortex. The inflammatory process is parallel to the existence of two main sub-types of immune cells and pro-inflammatory cytokines influences on the brain-blood barrier. Which is linked to swelling and neuronal dysfunction, which can lead to a relapse of the disease.[2]

Involvement of the myelin sheath and neurodegenerative processes result in a decrease in the number of synapses and axons, which eventually to the loss of nerve cells.[3] Viral infections, insufficiency of vitamin D, and the action of sex hormones are recorded as some of many causes of the disease. Sex hormones consider an important factor influencing the development of (MS), which is reflected in the increase of (MS) cases in women. Literature has shown that women suffering from MS who have higher levels of estradiol and decreased levels of progesterone experience greater severity of the disease.[4,5] The highest rate is between the twenties and forties years of age. MS is also found in children as a childhood form of MS. People over 50 may be diagnosed with the late form of MS.[6]

Four main types of MS have been described[9, 10]; relapsing-remitting MS (RRMS), which considers 85% of cases. This type shows periods of symptom attacks and periods of complete remission; secondary progressive MS (SPMS) is described by an initial relapsing-remitting course and is marked by disability progression. The possibility of having SPMS is close to 2% each year and 50% will develop SPMS within 10 years[11]; primary progressive MS (PPMS) contain a worsening progression of disability, patients do not experience symptom relapses in fact there is a constant decrease of functional level from the time of disease onset, almost 10-15% of cases are this form of MS[11];

progressive relapsing MS (PRMS) is characterized by periods when symptoms gradually worsen and periods of symptom attacks. This type is the least frequent, affecting around 5% of patients with MS[11]. (Fig.1)

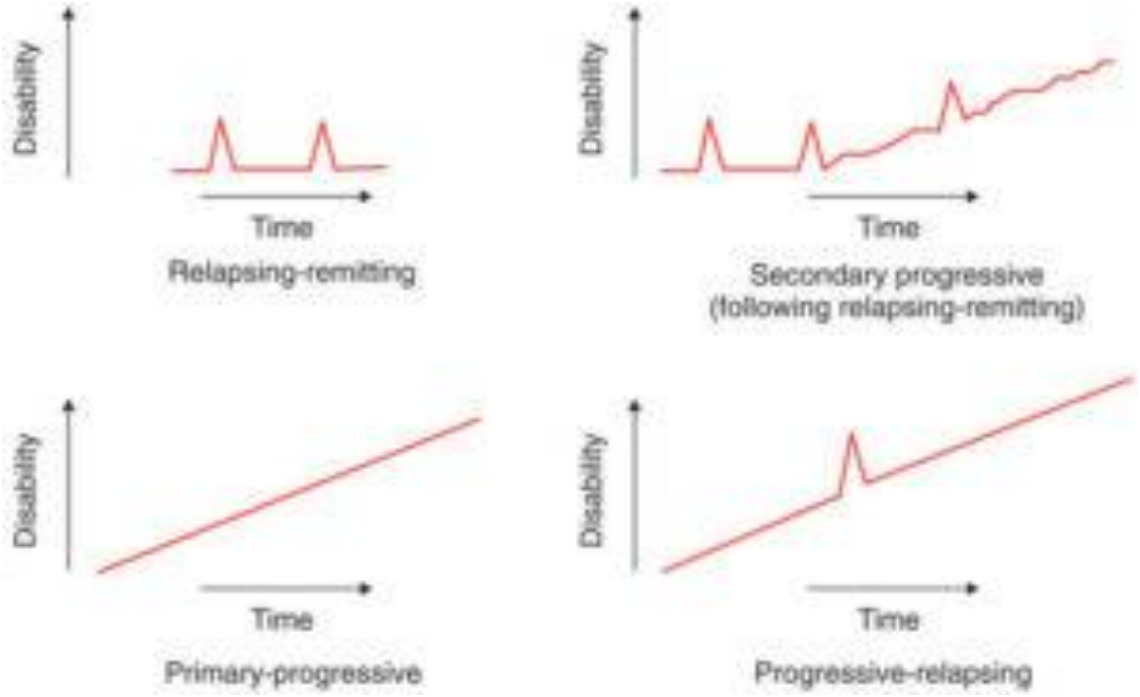


Fig.1 Main types of multiple sclerosis70

Rehabilitation and Multiple Sclerosis

Physiotherapy in multiple sclerosis's main goal is to improve mobility through compensation mechanisms that work on the activation of capabilities of effectors and behavior, which gain in the patient regaining functioning, not a movement. The introduction of physical activity, regardless of the progression of the disease, will decrease the negative effects of akinesia, and thus improve the functional capabilities of all body systems[7].

The severity of the disease, degree of impairment, and neurological deficiencies must all be considered in the rehabilitation program. The therapy at the time of remissions is therefore based on the level of impairment and the goals of treatment. The patient's mental state, neurological status, and cognitive function state should all be considered in the process.[8].

The continuousness of the rehabilitation should include exercises that target the problems caused by disease. Therefore, daily rehabilitation would be a mix of balance and coordination exercises. Also, breathing, stretching, and relaxation exercises. Additionally, it would include aerobic training, hydrotherapy, exercises that strengthen specific groups of muscles and get better proprioception. The intensity level of load and

exercise should not cause overheating and fatigue of the body, which may result in an elevation in muscle tension. Kinesitherapy, physical therapy, massage, and hydrotherapy are all examples of physiotherapy, which is an important aspect of any rehabilitation program.

Hydrotherapy

In 1890, Professor Wilhelm Uhthoff reported that an elevation in body temperature due to physical effort could cause transient vision blindness in patients with MS due to retrobulbar optic neuritis. This effect was later described as the Uhthoff's sign '' Uhthoff's phenomenon (also known as Uhthoff sign or Uhthoff syndrome) is described as non-permanent, short-lived (less than 24 hours), and stereotyped worsening of neurological function among multiple sclerosis patients in response to an elevation in core body temperature."- S Panginikkod, A Rayi, LA Rukmangadachar – 2017 (20), and up until 1983, the hot bath test was used as a diagnostic tool for MS. Heat and physical efforts were limited for the fear of flaring up the disease and hydrotherapy were restricted to a water temperature of 30 °C.12, 23[21,22]. These contain mainly resistance training and suggest an overall improvement in disability and movement with aerobic training.

Magnificent results have also been achieved with rehabilitation programs containing treatment in swimming pools at temperatures around 30°C or higher. Rehabilitation approaches have to be designed specifically for the needs of each patient[23, 24] Rehabilitation and active lifestyle have been beneficial to keep the quality of life of patients with MS[25, 26]. Aquatic therapy has become an essential element of the rehabilitation process of MS patients.

Cold baths along with cooling devices elevate local and systemic hypothermia in MS patients. Also, mobility in water focusing on trunk movement, postural stability exercises, and body position changes have provided benefits for rehabilitating gait in these patients[27, 28]. The hydrostatic, hydrodynamic, and thermal impacts of aquatic activities in inpatients with multiple sclerosis are based on the physical characteristics of water (viscosity, surface tension, density, specific heat, and heat conductivity).[29]. In MS patients, hydrotherapy is well tolerated and helps in decreasing fatigue, pain, gait speed, motor actions, and endurance level [30] (Fig. 2). Although hydrotherapy has been well used in the rehabilitation program of patients with MS[13-19], the possible harmful effects of heat in these patients have been long known.

Fig. 2 [71] hydrotherapy for people with MS.

Balance intervention for MS patients

The maintenance of balance or upright stance needs collaboration between multiple sensorimotor systems (visual, vestibular, proprioception) to provide coordinated movements that keep the center of mass within the limits of stability[31, 32]. Balance is a comprehensive part of physical function, and a product of the task is taken and the environment in where it is performed[33]. The elements of balance rehabilitation include multisensory and motor strategy training, strengthening and endurance training and a lot of neurotherapeutic approaches in individual targeted or group sessions therapy[32, 33]. Impairments in balance and the underlying physical functions are common in people with MS[34-40].

Patients with MS have balance impairments characterized by increased sway in quiet stance, delayed responses to postural perturbations, and decreased ability to move towards their limits of stability[41]. Many people with MS fall over and over[41–43], are afraid of falling[44,] and the risk of fall-related injuries is high [45, 46]. Elevated risk of fall has also been found in connection with various gait assessments[41] and with the use of an assisted walking aid[47]. Recognition of the biomechanical and information processing demands affected by the task and by the environmental context allows us to assess this model[33].

The manner of movement for the lower extremities, upper extremities, neck, and head have been improved. One of using techniques that both methods employ is a manual technique of facilitation of movement (PNF). The aim of this technique is to help the patient to perform a movement correctly in a specific activity, so we prevent a pathological position of the body and assist in the beginning and end of the movement. The PNF technique also has gait training and exercises of facial muscles. Decrease the

impairment of chewing, swallowing, and breathing. The prober muscle tension and active movements can be gained by preventing abnormal patterns of posture. These exercises improve stability during gait, decrease falls, and improve posture control.

Coordination exercises enhance the coherence of movement and decrease energy consumption which is caused by deficiency of coordination[1]. Balance and proprioceptive exercises in people with stability in standing positions are executed using stabilometric and posturemetric platforms depending on the biofeedback.

Hippotherapy is another type of exercise that enhances balance and stability in people with MS. Promoted gait and balance were seen in patients who take hippotherapy when compared to the control group in which traditional physiotherapy was taken[49]. Other studies may provide a better sight of the effects of physiotherapy interventions on the balance if the interventions were designed in more detail (e.g., type of exercise, term of intervention, weekly frequency of exercise, number of exercises per session).

Spasticity in people with MS

Spasticity is a common sign in MS. Spastic paresis affects both limbs with higher severity of pathological tension in the lower extremities seen while higher physical efforts can increase muscle tension[50]. The physical application which is used pre kinesiotherapy is cooling the targeted parts of the body, as the spinal cord is treated with decreased temperatures also, this is to get the effect of topical anesthesia in peripheral sensory receptors, using of cold decrease responses to active stretching. Passive stretching is a contraindication, as it decreases the excitability of the motor neurons and keeps the elasticity properties of muscles and joints in 40–60% of patients with multiple sclerosis[1]. Mild spasticity is beneficial as it enhances blood circulation in the limbs and decreases muscular wasting. The high degree of spasticity (3 or 4 on the Ashworth scale) leads to contractures, joint deformity, and bed ulcers which cause infections[50]. The plan of the rehabilitation program should take into consideration the fact that the use of physical applications before kinesiotherapy has positive effects.

Physical techniques used in dealing with spasticity are electrotherapy and magnetic therapy. Electrical stimulation of transcutaneous electrical nerve stimulation (TENS), neuromuscular system (NMES). Electrical stimulation is the best technique because harm to the upper motor neuron does not reverse the excitability of the muscles to electrical stimulation so that the affected bioelectrical function of muscles can be replaced.

The treatment parameters are set based on Electromyography (EMG) or chosen according to the commonly accepted standards. Using implant electrodes may cause complications such as displacement of electrodes and this will lead to an adverse reaction of the body to implant[51]. Transcutaneous electrical nerve stimulation (TENS) is

a technique that has been widely used in the treating of pain in people with MS. Pads are placed along the nerves or in sites of pain. The frequency varies from 1 to 100 Hz, and the intensity depends on the patients according to their individual feelings. Hufschmidt procedure is also used to decrease muscle tension through the stimulation of spastic muscles and their antagonists.

Double square-wave impulses are used to get a functional balance between agonists and antagonists. This procedure helps in proprioceptive facilitation and affects alpha motor neurons[52] Functional electrical stimulation (FES) runs mini stimulators that are placed to paretic muscles behind the control of the central nervous system. Magnetic fields of low and high frequencies are also used in people with multiple sclerosis. The benefit of using magnetic fields is the fact that they are painless, thermal, and porous through the patient's tissue. In magnetotherapy, the frequency varies from 2 Hz to 60Hz, the induction can be up to 20. The application of impulses can be triangular, rectangular, sinusoidal, and trapezoidal shapes[53]. This application in people with MS is used to limit pain and reduce muscle tension. In the case of spasticity, the intermittent mission of magnetic fields beginning with a 3 s break and then in each subsequent application, the break is gradually decreased by 0.5 s till it reaches continuous emission. This results in the decrease of muscular tension, relaxation, which helps in the reduction of fatigue syndrome[54]. The research of magneto stimulation has proven the efficacy of this treatment for the exertion of hormones such as melatonin is correlated to an analgesic effect and serotonin the increase of which enhance well-being and mood[55].

Transcranial stimulation is a technique that involves stimulating specific areas of the cerebral cortex. This operation is used to improve the conductivity of the optic tract in the treatment of retrobulbar optic neuritis. The use of repeated transcranial magnetic stimulation in persons with MS resulted in a decrease in lower-limb stiffness and an improvement in neurogenic bladder dysfunction[56]. Laser radiation's regeneration impact is significant for persons with MS because it promotes demyelination regeneration in the central nervous system, which reduces nerve conduction. Biostimulation laser light affects neuron regeneration by stimulating the development of Schwann cells, which improves nerve conduction. Because cold is utilized in combination with laser radiation, cool lasers are also used to alleviate muscular tension and offer analgesia[57].

Resistance exercise for MS patients

Strengthening is considered one of the essential elements of exercise programs and physical activity for people with MS[61.] It might for strengthening training to improve function such as gait, it possible to need to be applied using parameters that different from what is wanted to what is commonly used to improve force production. A final and important explanation is that strengthening training studies to facilitate gait in patients with MS may not include exercises with the proper intervention approach in order of

modes, positions, or muscle targets[62]. Strength training using modes or positions that are not functional or are not focused on muscle groups that are important for gait, may not be beneficial for walking even if strength gets stronger[63]. In older adults, strengthening training has been found to be the only beneficial exercise intervention to improve gait speed, intensity varies between 70% and 80% 1RM (or up to 7- to 8-repetition maximum)[64].

Neurogenic bladder dysfunction

The rehabilitation plan should also contain pelvic diaphragm muscle exercises because of the neurogenic bladder dysfunction, which has been seen in 78% of people with MS[1]. Sphincter disorders caused by the form of urinary incontinence or retention led to discomfort for patients and restrict their involvement in activities of daily living and social participation. Kegel isometric exercises, which involve tightening and relaxation of specific groups of muscles, are executed to exercise the pelvic diaphragm, which results in an improvement in muscle mass and strengthening and the growth of the resting tension of these muscles. The exercises help in long-term contraction of the muscles, enhancing control of neuromuscular and connective tissue to stabilize the pelvis, which, in turn, enhances the mechanism of urination. Pelvic diaphragm muscle training should be mixed with the enhancement of deep muscles like transversus abdominis mostly because of the synergistic action of these structures. Co-activation of these muscles is decreased or seated aside in patients with urinary incontinence[65]. Also, the training must include gluteal muscles, the adductor muscle, and the ischio-crural muscle group. The parallel use of Kegel exercises, EMG biofeedback, and electrical stimulation (NMES) provide very well results[66].

Gait and endurance training

An overall analysis should precede gait training, with the goal of evaluating the impairment in many stages of gait in comparison to the normal gait style. Walking on a treadmill with a non-weight-bearing foot is one of the most commonly utilized training procedures. This contributes to the improvement of gait characteristics. The World Health Organization (WHO) recommends 30 minutes of moderate-intensity physical exercise five days a week, or 20 minutes of high-intensity physical activity three days a week.

Regulated physical activity in the type of sport or refreshment results in well health benefits, they prove the effectiveness of aerobic training in people with MS. The rehabilitation must be for several weeks or even months, mostly using a treadmill or a cycloergometer in this type of exercise[8]. Physical activities enhance their physical ability and their mood and attitude to the exercises. Best cardiorespiratory efficiency has been confirmed to improve cerebrovascular function, which proposes that movement can also

significantly enhance brain function in people with multiple sclerosis[67]. Aerobic training improves muscle strength of the lower limbs, which results in decreasing spasticity without the risk of relapse or the symptoms of fatigue[68].

Figure 3[72] gait training for people with MS

Updated recommendations for people with MS propose doing physical activities two to three times per week at an intensity of 50–70% of VO2max up to 60–80% of maximum heart rate. The span of the exercise should not exceed the initial period of 40 min. The intensity should elevate gradually depending on the degree of disability. Studies showed that patients who do not practice physical activities got a significantly reduced quality of life, and a major degree of disability compared to the group that practices regularly[69] (Fig 3).

References

1. AM Kubsik-Gidlewska, P Klimkiewicz, R Klimkiewicz... - Advances in clinical and ..., 2017
2. Stadelmann C, Albert M, Wegner C, Bruck W. Cortical pathology in

multiple sclerosis. Curr Opin Neurol. 2008;21:229–234.

3. Filippi M, Bozzali M, Rovaris M, et al. Evidence for widespread axonal

damage at the earliest clinical stage of multipl sclerosis.Brain.2003;126:433–437.

4. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology. 2004;62:60–65
5. Bansil S, Lee HJ, Jindal S, Holtz CR, Cook SD. Correlation between sex hormones and magnetic resonance imaging lesions in multiple sclerosis. Acta Neurol Scand. 1999;99:91–94.
6. Selmaj K. Multiple Sclerosis – diagnostic criteria, the natural course

of the disease. Pol Prz Neurol. 2005;1(3):99–105.

7. Kwolek A, Podgórska J, Rykała J. Own experience in the rehabilitation of multiple sclerosis patients. Przegląd Medyczny Uniwersytetu Rzeszowskiego. 2010;2:213–220.
8. Opara J. Physiotherapy in multiple sclerosis. Wydawnictwo AW, Katowice. 2012:16–70.
9. H auser SL, Goodin DS. Multiple sclerosis and other demyelinating.
10. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J.Harrison's principles of internal medicine. New York: McGraw Hill Education; 2015. p. 2661-74. Khan F, Amatya B, Kesselring J, Galea MP. Telerehabilitation for persons with multiple sclerosis. A Cochrane review. Eur J Phys RehabilMed 2015;51:311-25.
11. EM MEDICA - European Journal of Physical and Rehabilitation ..., 2017
12. I Corvillo, E Varela, F Armijo, A Alvarez-Badillo... - European journal of ..., 2017
13. Gehlsen GM, Grigsby SA, Winant DM. Effects of an aquatic fitnessprogram on the muscular strength and endurance of patients with multiple sclerosis. Phys Ther 1984;64:653-7.
14. B roach E, Dattilo J. Effect of aquatic therapy on adults with multiple sclerosis. Ther Recreation J 2001;35:141-54.
15. B roach E, Dattilo J. The effect of aquatic therapy on strength of adults with multiple sclerosis. Ther Recreation J 2003;37:224-39.
16. R oehrs TG, Karst GM. Effects of an aquatics exercise program on quality of life measures for individuals with progressive multiple sclerosis. J Neurol Phys Ther 2004;28:63-71.
17. P ariser G, Madras D, Weiss E. Outcomes of an aquatic exercise program including aerobic capacity, lactate threshold, and fatigue in two individuals with multiple sclerosis. J Neurol Phys Ther 2006;30:82-90.
18. B roach E, Dattilo J, McKenny A. Effects of aquatic therapy on perceived fun or enjoyment experiences of participants with multiple sclerosis. Ther Recreation J 2007;41:179-200.
19. Morris DM. Aquatic rehabilitation for the treatment of neurological disorders. In: Becker BE, Cole AJ, editors. Comprehensive aquatic therapy. Third edition. Pullman, WA: Washington State University Publishing; 2010. p. 193-218.
20. S Panginikkod, A Rayi, LA Rukmangadachar – 2017
21. Becker BE. Aquatic therapy: scientific foundations and clinical rehabilitation applications. PM R 2009;1:859-72.
22. O para J, Szwejkowski W, Pidsudko Z. Did the description of the Uhthoff phenomenon complicate rehabilitation in multiple sclerosis? Rehabilitacja medyczna 2009;13:25-8.
23. P eterson C. Exercise in 94 degrees F water for a patient with multiple sclerosis. Phys Ther 2001;81:1049-58.
24. Wonneberger M, Schmidt S. Changes of gait parameters following long-term aerobic endurance exercise in mildly disabled multiple sclerosis patients: an exploratory study. Eur J Phys Rehabil Med 2015;51:755-62.
25. P alacios-Ceña D, Ortiz-Gutierrez RM, Buesa-Estellez A, Galán-Del-Río F, Cachon Perez JM, Martínez-Piedrola R, et al. Multiple sclerosis patients' experiences in relation to the impact of the kinect virtualhome-exercise programme: a qualitative study. Eur J Phys RehabilMed 2016;52:347-55.
26. Garopoulou V, Tsimaras V, Orologas A, Mavromatis I, Taskos N, Christoulas K. The effect of an aquatic training program on walking ability and quality of life of patients with multiple sclerosis. Journal of Physical Education and Sport 2014;14:106-14.
27. Edlich RF, Buschbacher RM, Cox MJ, Long WB, Winters KL, Beck-er DG. Strategies to reduce hyperthermia in ambulatory multiple sclerosis patients. J Long Term Eff Med Implants 2004;14:467-79.
28. Kalron A, Nitzani D, Magalashvili D, Dolev M, Menascu S, SternY, et al A personalized, intense physical rehabilitation program improves walking in people with multiple sclerosis presenting with different levels of disability: a retrospective cohort. BMC Neurol2015;15:21.
29. B ecker BE. Biophysiologic aspects of hydrotherapy. In: Becker BE,Cole AJ, editors. Comprehensive aquatic therapy. Third edition. Pullman,WA: Washington State University Publishing; 2010. p. 23-75.
30. B ecker B. Options in improving respiratory function in multiple sclerosis.Arch Phys Med Rehabil 2014;95:406.
31. Shumway-Cook A, Woollacott MH. Normal postural control. In:Shumway-Cook A, Woollacott MH, editors. Motor control: theory and practical applications. 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001, p. 163–191.
32. Rose DJ. FallProof: a comprehensive balance and mobility training program. 2nd edn. Champaign, IL: Human Kinetics; 2010,p. 3–10.
33. Huxham FE, Goldie PA, Patla AE. Theoretical considerations in balance assessment. Aust J Physiother 2001; 47: 89–100.
34. Jackson RT, Epstein CM, De l'Aune WR. Abnormalities in posturography
35. and estimations of visual and horizontal in multiple sclerosis. Am J Otol 1995; 16: 88–93.
36. Corradini ML, Fioretti S, Leo T, Piperno R. Early recognition of postural disorders in multiple sclerosis through movement analysis: a modeling study. IEEE Trans Biomed Eng 1997; 44: 1029–1038.
37. Karst GM, Venema DM, Roehrs TG, Tyler AE. Center of pressure measures during standing tasks in minimally impaired persons with multiple sclerosis. J Neurol Phys Ther 2005; 29: 170–180.
38. Sosnoff JJ, Shin S, Motl RW. Multiple sclerosis and postural control: the role of spasticity. Arch Phys Med Rehabil 2010; 91: 93–99.

39. Soyuer F, Mirza M, Erkorkmaz U. Balance performance in three forms of multiple sclerosis. Neurol Res 2006; 28: 555–562.
40. Frzovic D, Morris ME, Vowels L. Clinical tests of standing balance: performance of persons with multiple sclerosis. Arch Phys Med Rehabil 2000; 81: 215–221.
41. Cameron MH and Lord S. Postural control in multiple sclerosis: implications for fall prevention. Curr Neurol Neurosci Rep 2010;10: 407–412.
42. Cattaneo D, De Nuzzo C, Fascia T, Macalli M, Pisoni I, Cardini R. Risk of falls in subjects with multiple sclerosis. Arch Phys MedRehabil 2002; 83: 864–867.
43. Finlayson ML, Peterson EW, Cho CC. Risk factors for falling among people aged 45 to 90 years with multiple sclerosis. Arch Phys Med Rehabil 2006; 87: 1274–1279.
44. Peterson EW, Cho CC, Finlayson ML. Fear of falling and associated activity curtailment among middle aged and older adults with multiple sclerosis. Arch Phys Med Rehabil 2008; 89:1031–1037.
45. Peterson EW, Cho CC, von Koch L, Finlayson ML. Injurious falls among middle aged and older adults with multiple sclerosis. Arch Phys Med Rehabil 2008; 89: 1031–1037.
46. Cameron MH, Poel AJ, Haselkorn JK, Linke A, Bourdette D. Falls requiring medical attention among veterans with multiple sclerosis: a cohort study. J Rehabil Res Dev 2011; 48: 13–20.
47. Nilsagård Y, Lundholm C, Denison E, Gunnarsson L-G. Predict-treatment approaches to improve walking in multiple sclerosis: a pilot randomized controlled study. Clin Rehabil 1998; 12:477–486.
48. Klimkiewicz P, Kubsik A, Woldańska-Okońska M. NDT-Bobath method used in the rehabilitation of patients with a history of ischemic stroke. Wiad Lek. 2012;65:102–107.
49. Munoz-Lasa S, Ferriero G, Valero R, Gomez-Muniz F, Rabini A, Varela E. Effect of therapeutic horseback riding on balance and gait of people with multiple sclerosis. G Ital Med Lav Ergon. 2011;33:462–467.
50. Steiborn B, Łuczak-Piechowiak A. Kinesytherapeutic methods in the treatment of spasticity. Polski Przegląd Nauk o Zdrowiu.2006;1:95–103.
51. Taradaj J. Electrical treatment of muscular spasticity. Ogólnopol PrzMed. 2002;12:15–18.
52. Miller L, Mattison P, Paul L, Wood L. The effects of transcutaneous electrical nerve stimulation (TENS) on spasticity in multiple sclerosis. Mult Scler. 2007;13:527–533.
53. Straburzyńska-Lupa A, Straburzyński G. Physiotherapy. Wydawnictwo Lekarskie PZWL, Warszawa, 2007.
54. Marz-Loose H, Siemes H. Repetitive peripheral magnetic stimulation. Treatment option for spasticity? Nervenarz. 2009;80:1489–1495.
55. Czernicki J, Woldańska-Okońska M, Karasek M, Żylińska K, Plucińska M. Influence of magnetostimulation on the levels of melatonin and serotonin in serum of patients with back pain syndrome. KwartOrtop. 2006;1:13–17
56. Centonze D, Koch G, Versace V, et al. Repetitive transcranial magnetic stimulation of the motor cortex ameliorates spasticity in multiple sclerosis. Neurology. 2007;68:1045–1050.
57. Marovino T. Cold lasers in pain management. Practical Pain Management. 2004;9:21–25.
58. Mañago MM, Hebert JR, Schenkman M. Psychometric properties of a clinical strength assessment protocol in people with multiple sclerosis. Int J MS Care. 2017;19:253-262.
59. Hoang PD, Gandevia SC, Herbert RD. Prevalence of joint contractures and muscle weakness in people with multiple sclerosis. Disabil Rehabil. 2014;36:1588-1593.
60. Jørgensen M, Dalgas U, Wens I, Hvid LG. Muscle strength and power in persons with multiple sclerosis: a systematic review and meta-analysis.J Neurol Sci. 2017;376:225-241.
61. Latimer-Cheung AE, Martin Ginis KA, Hicks AL, et al. Development of evidence-informed physical activity guidelines for adults with multiple sclerosis. Arch Phys Med Rehabil. 2013;94:1829-1836.e7.
62. Williams G, Kahn M, Randall A. Strength training for walking in neurologicrehabilitation is not task specific: a focused review. Am J PhysMed Rehabil. 2014;93:511-522.
63. MM Mañago, S Glick, JR Hebert, S Coote... - International journal of MS ..., 2019
64. Van Abbema R, De Greef M, Craje C, Krijnen W, Hobbelen H, Van Der Schans C. What type, or combination of exercise can improve preferred gait speed in older adults? a meta-analysis. BMC Geriatr.2015;15:72.
65. Lucio AD, Perissinoto MC, Natalin RA, Prudente A, Damasceno BA, Levi D'ancona CA. A comparative study of pelvic floor muscle training in women with multiple sclerosis: Its impact on lower urinary tract symptoms and quality of life. Clinics. 2011;66:1563–1568.
66. Opara J, Socha T, Prajsner A, Poświata A. Physiotherapy in stress urinary incontinence in females. Part I. Contemporary recommendations for Kegel exercises (PFME). Fizjoterapia. 2011;19:41–49.
67. Prakash RS, Snook EM, Erickson KI, et al. Cardiorespiratory fitness:A predictor of cortical plasticity in multiple sclerosis. Neuroimage. 2007;34:1238–1244
68. Fragoso YD, Santana DLB, Pinto RC. The positive effects of a physical activity program for multiple sclerosis patients with fatigue. Neurorehabilitation. 2008;23:153–157.
69. Rietberg M, Brooks D, Uitdehaag B, Kwakkel G. Exercise therapy for multiple sclerosis. Cochrane Database Syst Rev. 2005;CD003980.
70. https://epomedicine.com/medical-students/multiple-sclerosis-mnemonic/
71. https://www.chilternsmscentre.org/what-we-do/hydrotherapy-for-multiple-sclerosis/
72. https://www.physio.co.uk/what-we-treat/neurological/conditions/multiple-sclerosis.php

Article topic: Transverse Myelitis.

Author: Rua'a Nader Abd Al-Qader.

Editors: Nicola Al-Madani.

Reviewer: Ethar Hazaimeh.

Keywords: Transverse Myelitis, Immune-mediated myelopathy, inflammatory, demyelinating, neurology, spinal cord.

Overview and epidemiology

Myelopathy is a broad, generic condition that does not have a particular etiology, while myelitis is an inflammatory disease, and both affect the spinal cord [1].
Transverse Myelitis (TM) is characterized by acute or subacute spinal cord dysfunction, leading to paresis, decreased sensations, or autonomic impairment (bladder, bowel, or sexual) below the level of the lesion [2][3]. It is considered as inflammation across the entire transverse section of the spinal cord, which is called complete transverse myelitis, and there are many cases referred to as partial transverse myelitis, the clinical presentation of these two conditions can overlap [4]. This inflammation results from infectious, immune-mediated, or non-inflammatory myelopathies, such as compressive, vascular, neoplastic, metabolic, nutritional, toxic, and inherited causes [5].

Transverse myelitis is classified as disease-associated that is related to infectious or immune-mediated etiology, and idiopathic cause, which should be a diagnosis of exclusion [4]. That has made great progress in the autoimmune neurology field for discovering neural autoantibodies (e.g., AQP4-IgG and myelin oligodendrocyte glycoprotein IgG), and this helped to know a specific cause for patients previously diagnosed with Idiopathic TM [6][7].

When we talk about the epidemiology of this disease, we should focus on race when evaluating patients with immune-mediated myelopathies. Neuro-sarcoidosis is common in African Americans [8], Multiple Sclerosis (MS) is numerous in whites and regions away from the equator, while the incidence of idiopathic transverse myelitis in 2019 was 8.6 per million, and the prevalence was 7.9 per 100,000 [7]. In general, the annual incidence of TM ranges from 1.34 to 4.60 cases per million [9][10][11] but increases to 24.6 cases per million with demyelinating diseases like MS [12].

Pathogenesis and etiology

1- Acquired demyelinating disorders

a. Multiple Sclerosis (MS)

MS is a progressive, demyelinating neurologic illness characterized by an immune-mediated inflammatory response. The first attack of MS, which is called Clinically Isolated Syndrome (CIS), might present with acute optic neuritis (AON), or acute partial transverse myelitis (APTM). The chance of APTM developing into Clinically Defined Multiple Sclerosis (CDMS) varies between 10% and 62 percent [13]. The most prevalent symptom of TM in MS is sensory impairment.

The MRI is the most crucial test for determining the likelihood of transitioning to CDMS. Only 10% of individuals with APTM will develop CDMS at 61 months if it is normal [13], but this increases to a 21% risk of progression to CDMS at 20 years follow-up, according to another study [14].

Another important factor that predicts the risk of progression to CDMS is CSF Oligoclonal bands (OCBs). In the case of TM, OCBs have been revealed to predict conversion to MS [15]. The presence of OCBs and/or an increased IgG in individuals with TM who have normal MRIs indicates a greater risk of developing MS [16]. With a normal brain MRI and CSF results, the probability of transitioning to MS is less than 10% [15].

b. Neuromyelitis Optica (NMO)

Patients with NMO usually coexist with autoimmune diseases, such as Systemic Sclerosis (SS), Systemic Lupus Erythematosus (SLE), Autoimmune Thyroid Disease, Type 1 Diabetes Mellitus, Ulcerative Colitis (UC), and Myasthenia Gravis [17][18]. All patients with known autoimmune diseases, who present with TM, undergo serologic testing for NMO-IgG. The high specificity of positive NMO-IgG will work up the additional diagnosis of NMO coexisting with the systemic autoimmune disorder [19][20].

c. Acute Disseminated Encephalomyelitis (ADEM)

ADEM is a monophasic disease that happens following infections or vaccinations. It is linked with multifocal demyelinating lesions and may compromise encephalopathy, coma, or seizures [21]. TM takes place in about 24% of patients [22]. Unlike MS and NMO, ADEM is possibly associated with demyelinating peripheral neuropathies [23]. ADEM is likely to occur at any age, but most commonly, in pediatric patients (mean age is 5.7 years) [24]. Post-vaccination ADEM incidence is changeable, and the most frequently involved vaccine is the non-neural measles, mumps, and rubella vaccine [25][26].

Typically, the spinal cord lesion is swollen, and mostly affects the thoracic cord [22]. CSF in ADEM shows marked pleocytosis, raised protein, normal IgG index, and no Oligoclonal bands (OCBs) [26].

2- Systemic inflammatory autoimmune disorders

a. Sjogren Syndrome (SS)

SS is a chronic, progressive, inflammatory autoimmune disease that occurs mainly in middle-aged to elderly women, as the immune system mainly attacks lacrimal and salivary glands, leading to keratoconjunctivitis sicca or sicca syndrome. SS may occur alone (primary SS) or exist with underlying autoimmune disease (secondary SS) [27][28][29].

A wide range of CNS symptoms may occur, including acute optic neuritis (AON) and transverse myelitis (TM) [28][30][31]. Neurological manifestation may be the initial presentation in 57% of patients with SS [29]. Involvement of spinal cord (either acute TM or progressive myelopathy) possibly happens in 20% to 35% of patients with SS and may compromise the initial presentation of the disease in up to 20% [27][29]. The lesions affect the cervical cord and may extend longitudinally [29][32].

Typically, CSF results in pleocytosis, mildly elevated protein, and a mildly increased IgG index [28][32]. Careful follow-up is important in SS, as recurrent attacks of TM or AON can end in substantial disability and may lead to a confirmed diagnosis of NMO or MS [1].

b. Systemic Lupus Erythematosus (SLE)

SLE is a chronic multisystem autoimmune disease. The most ruining complication of SLE is TM, which accounts for only 1% to 2% of patients [33], and it is considered to have a poor prognosis [25].

SLE-related TM occurs within the first 5 years from diagnosis. TM is the initial neurological manifestation in half of the patients and recurs in 21% to 55% of cases [34][35][36]. AON and brainstem manifestations may go along with TM in SLE [37].

In many cases of SLE-related TM, two different clinical patterns may present patients with gray or white matter myelitis. Gray matter myelitis presents with lower motor neuron (LMN) manifestations, urinary retention, and it happens in a monophasic, devastating course. White matter myelitis presents with UMN manifestations, it occurs in more indolent and recurrent courses [38].

c. Behcet Disease (BD)

BD is a relapsing systemic inflammatory disease of unclear cause, which presents with oral aphthous ulcers, genital ulcers, uveitis, cutaneous symptoms, and involvement of other systems [39].

Neurologic participation in BD (neuro-BD) occurs in the 3rd to 4th decade of life, and it is more common in men, often associated with ocular involvement [40][41][42].

Spinal cord involvement ranges between 2.5% and 30.0%, mainly the cervical and thoracic cord segments (specifically the posterolateral cord) and has a poor prognosis [40][41]. TM in neuro-BD alone is unusual [40][43]. Spinal cord lesions are longitudinally extensive and include multiple non-contiguous segments, or even the whole cord [44][45].

CSF shows normal glucose, elevated protein, and neutrophilic pleocytosis; IgG index may be increased, and OCBs are rare [41][46].

3- Parainfectious TM (PITM)

Parainfectious TM refers to TM associated with previous infection. It is hard to determine if PITM is caused by direct microbial invasion causing myelitis or a consequence of immune-mediated, inflammatory reaction induced by a distant infection. The previous infection was resolved before the onset of TM, and it is difficult to illustrate the offending organism in the spinal cord parenchyma [1].
The hepatitis viruses possibly cause TM by post-infectious, immune-mediated, inflammatory reaction [47]. Hepatitis A virus and Hepatitis B virus infection are associated with immune-mediated TM [47]. Hepatitis C virus (HCV) is the most commonly involved hepatitis virus in TM. HCV referred to recurrent, corticosteroid-responsive, demyelinating TM (even without hepatic association) [47][48]. There is a single report of hepatitis E–virus related to TM [49].

Regarding Mycoplasma Pneumoniae infection and its neurological symptoms that are considered the most common extra-pulmonary complication of this infection [26][50]. It was found that encephalitis is the most frequent complication [51], and TM is the most severe and serious manifestation [52]. Acute to subacute thoracic myelopathy usually appear 2 to 4 weeks after a previous respiratory infection and progresses to a severe condition in about 3 days; it may be associated with meningoencephalitis and/or polyradiculopathy [52].
These microbes most likely cause myelopathy by the direct pathogenic attack. A careful follow-up is needed, and more evaluation is to be held, because infections may trigger TM that precedes the diagnosis of MS or NMO [1].

4- Paraneoplastic TM

Collapsing response-mediator protein-5 (CRMP-5-IgG) antibody that has been appeared in small cell lung cancer, is the most commonly paraneoplastic antibody associated with TM [53][54].
Patients present with subacute, progressive motor myelopathy mainly as well as elevated CSF protein, increased IgG index, and mild pleocytosis [53][55].

5- Atopic Myelitis (AM)

Atopic myelitis (AM) is mainly present with the chronic, persistent, or fluctuating course of cervical myelitis. It is associated with hyper-IgEemia, allergen specific IgE (due to dust mites), and coexistent atopic diseases (e.g., atopic dermatitis, atopic rhinitis, or asthma) [56].
The majority of reported cases happen in Japanese patients, but there are few cases of AM in White patients [57]. Sensory impairment is a predominant symptom, with uncommon motor and bladder involvement [58]. CSF cells count and protein are mostly normal, and OCBs are not seen [59].

6- Drug-induced and Toxin-related TM

- TNF-alpha inhibitors cause CNS demyelination and TM [60].
- Sulfasalazine [61].
- Chemotherapeutic agents: Gemcitabine, cytarabine, and cisplatin [62].
- Heroin: most of the cases of myelopathy in heroin addicts are related to anterior spinal artery infarction, moreover, there are cases of TM [63].
- Benzene [64].
- Brown recluse spider bite: Incomplete TM (anterior spinal syndrome), responds to steroid therapy [65].

7- Idiopathic TM (ITM)

The proportion of patients with ITM differs widely, from 16% [66] to 60% [67]. The mean age of onset occurs between 35 and 40 years, mainly in females [66].
CSF shows elevated protein in most patients; pleocytosis and OCBs are seen occasionally [66][68]. Unlike other causes of TM, negative OCBs are related to recurrence [66].
ITM is monophasic, but it recurs in about 1/4 to 1/3 of patients (recurrence of primary insult, enlargement of prior lesion, or a new lesion) [66][69].
Risk factors for recurrence are male gender, age older than 50 years, severe motor weakness and sphincter dysfunction and negative CSF OCBs, normal IgG, and seronegative NMO-IgG [66][68][69]. If recurrences happen, they will lead to poor outcomes [69].
Generally, one-third of patients with ITM recover with little or no consequences, one-third have a moderate extent of permanent disability, and one-third have severe disabilities [66].

Clinical presentation and complications

Transverse Myelitis has an acute or subacute onset; with neurological dysfunction extending to very severe manifestations within a few weeks, and it may present as one of many syndromes of the spinal cord [1].
The typical clinical symptom of myelitis is to have sensorimotor deficits in one or more extremities. Sensory impairment, like ascending numbness is a characteristic presentation of TM. Some patients present with a rounded band of dysesthesia attributed to the dermatomes just rostral to the sensory level around their trunk, and this may be associated with constricting sensation (as the “MS hug”) that ranges from mild discomfort to severe burning pain [1]. The pain associated with TM can be central, deep aching, or radicular pain [3].
Autonomic dysfunction is common, and it presents as the neurogenic bladder (urinary retention), neurogenic bowel, or sexual dysfunction; these symptoms are common with

Myelin Oligodendrocyte Glycoprotein IgG (MOG-IgG)–associated disorder, also maybe reflect conus involvement radiologically [4]. Autonomic impairment also could be presented with temperature dysregulation or even bouts of hypertension [11][70].
Motor symptoms usually show weakness that can affect the flexors of the legs and extensors of the arms (pyramidal distribution) or can present with sphincter dysfunction [70]. Acutely, muscle tone and stretch reflexes could be reduced or absent, which is called “spinal shock syndrome” and that makes diagnostic confusion with Guillain-Barre syndrome (GBS). With time, spasticity, hyperreflexia, and extensor plantar responses (i.e., features of the upper motor neuron lesion) become apparent [1].
Clinical manifestations of a “demyelinating cause” involve the Lhermitte sign (an electrical sensation that spreads down the spine and extremities when the neck is flexed), and the Uhthoff sign (transient worsening of neurologic symptoms when the body is overheated). Also, tonic spasms (recurrent short events of involuntary painful contractions by flexors that last 30 seconds to a few minutes) may present [4].
In addition, we should ask about symptoms that are related to systemic autoimmune diseases (like oral or genital ulcers in Behçet disease) or sicca symptoms, also maybe the presence of arthritis or skin changes. Moreover, we should look for symptoms that suggest myelopathy related to connective tissue diseases [4].

Evaluation and diagnosis

MRI of the whole spinal cord is obligatory in any patient with myelopathic manifestations, in order to exclude structural lesions that are responsive for emergent neurosurgical intervention. The most sensitive MRI sequence to identify spinal cord lesions (particularly MS plaques) are short-tau inversion recovery (STIR) fast spin-echo and T2-weighted fast spin-echo [71][72]. The location and length of the lesion on MRI could give signs of the underlying disease (Fig 1), (Fig 2).

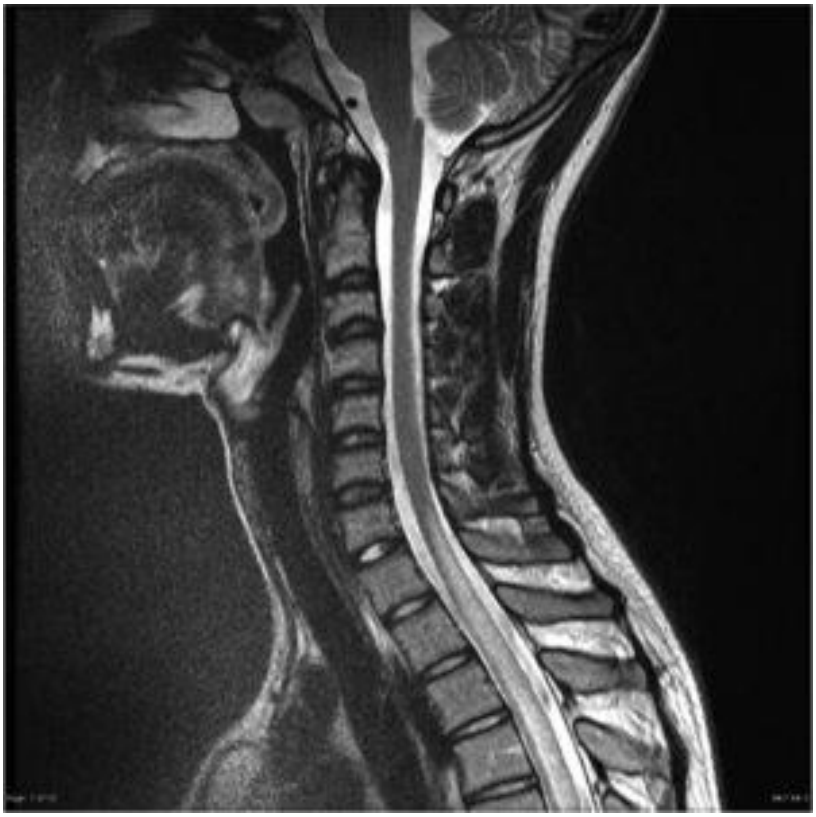


Fig 1. Extensive increased T2 signal and expansion of the cord is seen extending between C7 and T12. The T2 signal abnormality involves central grey matter and dorsal columns [85].

Fig 2. increased T2 signal and mild swelling (blue arrows) involves most of the conus, patchier towards the tip [86].

Brain MRI with and without gadolinium contrast should be established on all patients to find evidence of previous lesions that could give us clues about the etiology. The presence of MS-like brain lesions in patients with partial TM predicts an 80% risk of transformation to clinically definite MS at 3 to 5 years [73].
Vitamin B12 levels, thyroid function tests, syphilis, and HIV serology are acquired for evaluation of treatable causes of myelopathy. Vitamin E, serum copper, and ceruloplasmin levels should be checked in patients at risk of deficiency. Serum aquaporin-4–specific autoantibodies (NMO-IgG) should be investigated on all patients with TM due to high specificity for NMO [19][74].
Inflammatory markers should be assessed if systemic autoimmune diseases are suspected. In suspected Parainfectious TM, serologic titers of recent infection should be requested. Paraneoplastic profiles should be done in cases of paraneoplastic TM; moreover, in these cases, proper investigations should be made to look for hidden malignancy [1].
Cerebrospinal fluid (CSF) analysis is necessary for the evaluation of TM. CSF cell count, protein, glucose, oligoclonal bands (OCBs), and IgG index should be assessed on all patients with TM [75]. OCBs are useful in portending transition to MS, because OCBs are present in 85% to 90% of patients with MS, in 20% to 30% with NMO, and rarely in other etiologies of TM [73].
A neuro-ophthalmological evaluation is required to look for ophthalmic symptoms that could give us important diagnostic clues, especially when radiologic and lab investigations are unclear [76]. Demyelinating diseases that attack the brainstem or cerebellum usually cause ocular motor manifestations [77].
Electro-physiologic tests also could be useful in evaluating patients with TM. Nerve conduction studies (NCS) and electromyography (EMG) could help to show any peripheral nervous pathology [1].

Treatment

For most autoimmune myelopathies, after exclusion of other etiologies such as compressive lesions, spinal cord infarction, and infections, it is recommended to administer high-dose IV corticosteroids with 1 g IV methylprednisolone once daily for 5 days duration [4].
In patients with myelitis as a symptom of CNS demyelinating disease (e.g., MS, MOG-IgG–associated disorder, ADEM, idiopathic transverse myelitis) with severe neurological manifestations, plasma exchange (plasmapheresis) should be considered [78][79].
Early starting of plasmapheresis (within 15 days of onset) gives a favorable acute response and improvement at 6 months [80]. Typically, the regimen is to exchange 1.5 plasma volumes for five treatments within 10 days [81].
In children with MOG-IgG–an associated disorder of TM, IV immunoglobulin (IVIg) is used acutely, and it was shown an improvement of the outcome, also using steroids over

6 to 12 weeks could be considered after an acute attack to prevent early relapse [4]. Supportive care should be considered to prevent complications; it could be an implementation of bladder scans or temporary catheter placement, and prevention of deep venous thrombosis and ulcers. Depending on the cause of the TM, chronic immunomodulatory therapies will help to prevent future relapses and attacks [4].

Prognosis

The prognosis of acute transverse myelitis predicts a poor outcome, involving rapid progression of neurological manifestations, back pain, spinal shock, and absent central somatosensory conduction [66], but early initiation of plasma exchange has a better outcome [80]. Some cases revealed that 1/3 of patients recover with a few or no lasting symptoms, another 1/3 have a moderate disability, and 1/3 have a severe disability [82]. Furthermore, the long-term prognosis is highly influenced by determining the underlying etiology of transverse myelitis [83].

Does COVID-19 cause Transverse Myelitis?

Recently, it was shown an association between COVID-19 infection and the development of different types of CNS demyelination such as Transverse Myelitis. Some patients had isolated TM, and others were part of diffuse demyelinating disorders. Longitudinal Extensive Transverse Myelitis (LETM) was the most frequently reported spinal involvement in 72.5% of cases. There are several mechanisms by which SARS-CoV-2 can cause myelitis: acute viral myelitis, post-COVID-19 immune-mediated myelitis, and inflammatory demyelinating disorders that could be triggered by COVID-19 infection (ADEM, MS, and NMO). However, this association should be clarified in future literature [84].

References

[1] S. C. Beh, B. M. Greenberg, T. Frohman, and E. M. Frohman, "Transverse myelitis.," *Neurol. Clin.*, vol. 31, no. 1, pp. 79–138, Feb. 2013, doi: 10.1016/j.ncl.2012.09.008.

[2] B. A. C. Cree and D. M. Wingerchuk, "Acute transverse myelitis: is the 'idiopathic' form vanishing?," *Neurology*, vol. 65, no. 12. United States, pp. 1857–1858, Dec. 2005, doi: 10.1212/01.wnl.0000194615.51750.f8.

[3] E. M. Frohman and D. M. Wingerchuk, "Clinical practice. Transverse myelitis.," *N. Engl. J. Med.*, vol. 363, no. 6, pp. 564–572, Aug. 2010, doi: 10.1056/NEJMcp1001112.

[4] S. Lopez Chiriboga and E. P. Flanagan, "Myelitis and Other Autoimmune Myelopathies.," *Continuum (Minneap. Minn).*, vol. 27, no. 1, pp. 62–92, Feb. 2021, doi: 10.1212/CON.0000000000000900.

[5] E. P. Flanagan, "Autoimmune myelopathies.," *Handb. Clin. Neurol.*, vol. 133, pp. 327–351, 2016, doi: 10.1016/B978-0-444-63432-0.00019-0.

[6] N. L. Zalewski, E. P. Flanagan, and B. M. Keegan, "Evaluation of idiopathic transverse myelitis revealing specific myelopathy diagnoses.," *Neurology*, vol. 90, no. 2, pp. e96–e102, Jan. 2018, doi: 10.1212/WNL.0000000000004796.

[7] E. Sechi *et al.*, "Aquaporin-4 and MOG autoantibody discovery in idiopathic transverse myelitis epidemiology.," *Neurology*, vol. 93, no. 4, pp. e414–e420, Jul. 2019, doi: 10.1212/WNL.0000000000007828.

[8] O. C. Murphy *et al.*, "Clinical and MRI phenotypes of sarcoidosis-associated myelopathy.," *Neurol. Neuroimmunol. neuroinflammation*, vol. 7, no. 4, Jul. 2020, doi: 10.1212/NXI.0000000000000722.

[9] M. Berman, S. Feldman, M. Alter, N. Zilber, and E. Kahana, "Acute transverse myelitis: incidence and etiologic considerations.," *Neurology*, vol. 31, no. 8, pp. 966–971, Aug. 1981, doi: 10.1212/wnl.31.8.966.

[10] D. R. Jeffery, R. N. Mandler, and L. E. Davis, "Transverse myelitis. Retrospective analysis of 33 cases, with differentiation of cases associated with multiple sclerosis and parainfectious events.," *Arch. Neurol.*, vol. 50, no. 5, pp. 532–535, May 1993, doi: 10.1001/archneur.1993.00540050074019.
[11] A. Bhat, S. Naguwa, G. Cheema, and M. E. Gershwin, "The epidemiology of transverse myelitis.," *Autoimmun. Rev.*, vol. 9, no. 5, pp. A395-9, Mar. 2010, doi: 10.1016/j.autrev.2009.12.007.
[12] S. Debette *et al.*, "Long-term outcome of acute and subacute myelopathies.," *J. Neurol.*, vol. 256, no. 6, pp. 980–988, Jun. 2009, doi: 10.1007/s00415-009-5058-x.
[13] T. F. Scott, S. L. Kassab, and S. Singh, "Acute partial transverse myelitis with normal cerebral magnetic resonance imaging: transition rate to clinically definite multiple sclerosis.," *Mult. Scler.*, vol. 11, no. 4, pp. 373–377, Aug. 2005, doi: 10.1191/1352458505ms1194oa.
[14] L. K. Fisniku *et al.*, "Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis.," *Brain*, vol. 131, no. Pt 3, pp. 808–817, Mar. 2008, doi: 10.1093/brain/awm329.
[15] B. Bourre *et al.*, "Long-term follow-up of acute partial transverse myelitis.," *Arch. Neurol.*, vol. 69, no. 3, pp. 357–362, Mar. 2012, doi: 10.1001/archneurol.2011.949.
[16] J. Perumal *et al.*, "Acute transverse myelitis with normal brain MRI : long-term risk of MS.," *J. Neurol.*, vol. 255, no. 1, pp. 89–93, Jan. 2008, doi: 10.1007/s00415-007-0686-5.
[17] S. J. Pittock *et al.*, "Neuromyelitis optica and non organ-specific autoimmunity.," *Arch. Neurol.*, vol. 65, no. 1, pp. 78–83, Jan. 2008, doi: 10.1001/archneurol.2007.17.
[18] D. M. Wingerchuk, V. A. Lennon, C. F. Lucchinetti, S. J. Pittock, and B. G. Weinshenker, "The spectrum of neuromyelitis optica.," *Lancet. Neurol.*, vol. 6, no. 9, pp. 805–815, Sep. 2007, doi: 10.1016/S1474-4422(07)70216-8.
[19] V. A. Lennon *et al.*, "A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis.," *Lancet (London, England)*, vol. 364, no. 9451, pp. 2106–2112, Dec. 2004, doi: 10.1016/S0140-6736(04)17551-X.
[20] S. Jarius *et al.*, "Frequency and syndrome specificity of antibodies to aquaporin-4 in neurological patients with rheumatic disorders.," *Mult. Scler.*, vol. 17, no. 9, pp. 1067–1073, Sep. 2011, doi: 10.1177/1352458511403958.
[21] D. H. Miller *et al.*, "Differential diagnosis of suspected multiple sclerosis: a consensus approach.," *Mult. Scler.*, vol. 14, no. 9, pp. 1157–1174, Nov. 2008, doi: 10.1177/1352458508096878.
[22] S. Tenembaum, T. Chitnis, J. Ness, and J. S. Hahn, "Acute disseminated encephalomyelitis.," *Neurology*, vol. 68, no. 16 Suppl 2, pp. S23-36, Apr. 2007, doi: 10.1212/01.wnl.0000259404.51352.7f.
[23] Y. Aimoto, F. Moriwaka, A. Matsumoto, K. Tashiro, and K. Abe, "[A case of acute disseminated encephalomyelitis (ADEM) associated with demyelinating peripheral neuropathy].," *No To Shinkei*, vol. 48, no. 9, pp. 857–860, Sep. 1996.
[24] H. Torisu *et al.*, "Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan.," *Brain Dev.*, vol. 32, no. 6, pp. 454–462, Jun. 2010, doi: 10.1016/j.braindev.2009.10.006.
[25] C. Eckstein, S. Saidha, and M. Levy, "A differential diagnosis of central nervous system demyelination: beyond multiple sclerosis.," *J. Neurol.*, vol. 259, no. 5, pp. 801–816, May 2012, doi: 10.1007/s00415-011-6240-5.
[26] W. Huynh, D. J. Cordato, E. Kehdi, L. T. Masters, and C. Dedousis, "Post-vaccination encephalomyelitis: literature review and illustrative case.," *J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas.*, vol. 15, no. 12, pp. 1315–1322, Dec. 2008, doi: 10.1016/j.jocn.2008.05.002.
[27] C. Vitali *et al.*, "Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group.," *Ann. Rheum. Dis.*, vol. 61, no. 6, pp. 554–558, Jun. 2002, doi: 10.1136/ard.61.6.554.
[28] M. Govoni, M. Padovan, N. Rizzo, and F. Trotta, "CNS involvement in primary Sjögren's syndrome: prevalence, clinical aspects, diagnostic assessment and therapeutic approach.," *CNS Drugs*, vol. 15, no. 8, pp. 597–607, 2001, doi: 10.2165/00023210-200115080-00003.
[29] S. Delalande *et al.*, "Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients.," *Medicine (Baltimore).*, vol. 83, no. 5, pp. 280–291, Sep. 2004, doi: 10.1097/01.md.0000141099.53742.16.
[30] E. L. Alexander, T. T. Provost, M. B. Stevens, and G. E. Alexander, "Neurologic complications of primary Sjögren's syndrome.," *Medicine (Baltimore).*, vol. 61, no. 4, pp. 247–257, Jul. 1982, doi: 10.1097/00005792-198207000-00004.
[31] D. Escudero, P. Latorre, M. Codina, J. Coll-Cantí, and J. Coll, "Central nervous system disease in Sjögren's syndrome.," *Ann. Med. Interne (Paris).*, vol. 146, no. 4, pp. 239–242, 1995.
[32] S. M. Kim *et al.*, "Sjogren's syndrome myelopathy: spinal cord involvement in Sjogren's syndrome might be a manifestation of neuromyelitis optica.," *Mult. Scler.*, vol. 15, no. 9, pp. 1062–1068, Sep. 2009, doi: 10.1177/1352458509106636.
[33] S. G. West, "Neuropsychiatric lupus.," *Rheum. Dis. Clin. North Am.*, vol. 20, no. 1, pp. 129–158, Feb. 1994.
[34] B. Kovacs, T. L. Lafferty, L. H. Brent, and R. J. DeHoratius, "Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature.," *Ann. Rheum. Dis.*, vol. 59, no. 2, pp. 120–124, Feb. 2000, doi: 10.1136/ard.59.2.120.
[35] S. W. Schulz, M. Shenin, A. Mehta, A. Kebede, M. Fluerant, and C. T. Derk, "Initial presentation of acute transverse myelitis in systemic lupus erythematosus: demographics, diagnosis, management and comparison to idiopathic cases.," *Rheumatol. Int.*, vol. 32, no. 9, pp. 2623–2627, Sep. 2012, doi: 10.1007/s00296-011-2053-1.
[36] C. G. Katsiari, I. Giavri, D. D. Mitsikostas, K. G. Yiannopoulou, and P. P. P. Sfikakis, "Acute transverse myelitis and antiphospholipid antibodies in lupus. No evidence for anticoagulation.," *Eur. J. Neurol.*, vol. 18, no. 4, pp. 556–563, Apr. 2011, doi: 10.1111/j.1468-1331.2010.03208.x.
[37] G. K. Bertsias *et al.*, "EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs.," *Ann. Rheum. Dis.*, vol. 69, no. 12, pp. 2074–2082, Dec. 2010, doi: 10.1136/ard.2010.130476.
[38] J. Birnbaum, M. Petri, R. Thompson, I. Izbudak, and D. Kerr, "Distinct subtypes of myelitis in systemic lupus erythematosus.," *Arthritis Rheum.*, vol. 60, no. 11, pp. 3378–3387, Nov. 2009, doi: 10.1002/art.24937.

[39] “Criteria for diagnosis of Behçet’s disease. International Study Group for Behçet’s Disease.,” *Lancet (London, England)*, vol. 335, no. 8697, pp. 1078–1080, May 1990.
[40] A. Al-Araji and D. P. Kidd, “Neuro-Behçet’s disease: epidemiology, clinical characteristics, and management.,” *Lancet. Neurol.*, vol. 8, no. 2, pp. 192–204, Feb. 2009, doi: 10.1016/S1474-4422(09)70015-8.
[41] N. Yesilot, M. Mutlu, O. Gungor, B. Baykal, P. Serdaroglu, and G. Akman-Demir, “Clinical characteristics and course of spinal cord involvement in Behçet’s disease.,” *Eur. J. Neurol.*, vol. 14, no. 7, pp. 729–737, Jul. 2007, doi: 10.1111/j.1468-1331.2007.01754.x.
[42] H. Ideguchi *et al.*, “Neurological manifestations of Behçet’s disease in Japan: a study of 54 patients.,” *J. Neurol.*, vol. 257, no. 6, pp. 1012–1020, Jun. 2010, doi: 10.1007/s00415-010-5454-2.
[43] G. Akman-Demir, P. Serdaroglu, and B. Tasçi, “Clinical patterns of neurological involvement in Behçet’s disease: evaluation of 200 patients. The Neuro-Behçet Study Group.,” *Brain*, vol. 122 (Pt 1, pp. 2171–2182, Nov. 1999, doi: 10.1093/brain/122.11.2171.
[44] S. Moskau, H. Urbach, A. Hartmann, and S. Schmidt, “Multifocal myelitis in Behçet’s disease.,” *Neurology*, vol. 60, no. 3, p. 517, Feb. 2003, doi: 10.1212/wnl.60.3.517.
[45] N. Koçer *et al.*, “CNS involvement in neuro-Behçet syndrome: an MR study.,” *AJNR. Am. J. Neuroradiol.*, vol. 20, no. 6, pp. 1015–1024, 1999.
[46] A. Lo Monaco, R. La Corte, L. Caniatti, M. Borrelli, and F. Trotta, “Neurological involvement in North Italian patients with Behçet disease.,” *Rheumatol. Int.*, vol. 26, no. 12, pp. 1113–1119, Oct. 2006, doi: 10.1007/s00296-006-0149-9.
[47] J.-P. Stübgen, “Immune-mediated myelitis associated with hepatitis virus infections.,” *J. Neuroimmunol.*, vol. 239, no. 1–2, pp. 21–27, Oct. 2011, doi: 10.1016/j.jneuroim.2011.09.001.
[48] K. M. Aktipi *et al.*, “Severe recurrent myelitis in patients with hepatitis C virus infection.,” *Neurology*, vol. 68, no. 6, pp. 468–469, Feb. 2007, doi: 10.1212/01.wnl.0000252931.77486.1a.
[49] K. Mandal and N. Chopra, “Acute transverse myelitis following hepatitis E virus infection.,” *Indian pediatrics*, vol. 43, no. 4. India, pp. 365–366, Apr. 2006.
[50] A. Pönkä, “Central nervous system manifestations associated with serologically verified Mycoplasma pneumoniae infection.,” *Scand. J. Infect. Dis.*, vol. 12, no. 3, pp. 175–184, 1980, doi: 10.3109/inf.1980.12.issue-3.04.
[51] M. Koskiniemi, “CNS manifestations associated with Mycoplasma pneumoniae infections: summary of cases at the University of Helsinki and review.,” *Clin. Infect. Dis. an Off. Publ. Infect. Dis. Soc. Am.*, vol. 17 Suppl 1, no. Suppl 1, pp. S52-7, Aug. 1993, doi: 10.1093/clinids/17.supplement_1. s52.
[52] S. Tsiodras, T. Kelesidis, I. Kelesidis, K. Voumbourakis, and H. Giamarellou, “Mycoplasma pneumoniae-associated myelitis: a comprehensive review.,” *Eur. J. Neurol.*, vol. 13, no. 2, pp. 112–124, Feb. 2006, doi: 10.1111/j.1468-1331.2006.01174. x.
[53] B. M. Keegan, S. J. Pittock, and V. A. Lennon, “Autoimmune myelopathy associated with collapsin response-mediator protein-5 immunoglobulin G.,” *Ann. Neurol.*, vol. 63, no. 4, pp. 531–534, Apr. 2008, doi: 10.1002/ana.21324.
[54] S. A. Cross *et al.*, “Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG.,” *Ann. Neurol.*, vol. 54, no. 1, pp. 38–50, Jul. 2003, doi: 10.1002/ana.10587.
[55] S. J. Pittock *et al.*, “Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction.,” *Mayo Clin. Proc.*, vol. 81, no. 9, pp. 1207–1214, Sep. 2006, doi: 10.4065/81.9.1207.
[56] M. Tanaka *et al.*, “Distinct CSF cytokine/chemokine profiles in atopic myelitis and other causes of myelitis.,” *Neurology*, vol. 71, no. 13, pp. 974–981, Sep. 2008, doi: 10.1212/01.wnl.0000326589.57128.c3.
[57] A. Zoli, M. Mariano, A. Fusari, F. Bonifazi, and L. Antonicelli, “Atopic myelitis: first case report outside Japan?,” *Allergy*, vol. 60, no. 3, pp. 410–411, Mar. 2005, doi: 10.1111/j.1398-9995.2004.00689.x.
[58] J. Kira *et al.*, “Clinical, immunological and MRI features of myelitis with atopic dermatitis (atopic myelitis).,” *J. Neurol. Sci.*, vol. 162, no. 1, pp. 56–61, Jan. 1999, doi: 10.1016/s0022-510x(98)00291-3.
[59] J. Kira, K. Yamasaki, Y. Kawano, and T. Kobayashi, “Acute myelitis associated with hyperIgEemia and atopic dermatitis.,” *J. Neurol. Sci.*, vol. 148, no. 2, pp. 199–203, May 1997, doi: 10.1016/s0022-510x(97)05369-0.
[60] H. F. Cay, H. A. Gungor, I. Sezer, C. Kacar, and N. Balci, “Adverse effect of TNF-alpha blocker? Demyelination in an ankylosing spondylitis patient: a case report.,” *J. Clin. Pharm. Ther.*, vol. 31, no. 6, pp. 645–648, Dec. 2006, doi: 10.1111/j.1365-2710.2006.00779.x.
[61] T. P. Olenginski, T. M. Harrington, and J. P. Carlson, “Transverse myelitis secondary to sulfasalazine.,” *The Journal of rheumatology*, vol. 18, no. 2. Canada, p. 304, Feb. 1991.
[62] M. Zhong, B. Li, and J. Li, “Acute transverse myelopathy probably related to intravenous gemcitabine plus cisplatin.,” *The Annals of pharmacotherapy*, vol. 45, no. 4. United States, pp. 544–545, Apr. 2011, doi: 10.1345/aph.1P674.
[63] R. W. Richter and R. N. Rosenberg, “Transverse myelitis associated with heroin addiction.,” *JAMA*, vol. 206, no. 6, pp. 1255–1257, Nov. 1968.
[64] P. Herregods, R. Chappel, and G. Mortier, “Benzene poisoning as a possible cause of transverse myelitis.,” *Paraplegia*, vol. 22, no. 5, pp. 305–310, Oct. 1984, doi: 10.1038/sc.1984.49.
[65] G. C. Sauer, “Transverse myelitis and paralysis from a brown recluse spider bite.,” *Mo. Med.*, vol. 72, no. 10, pp. 603–604, Oct. 1975.
[66] J. de Seze *et al.*, “Idiopathic acute transverse myelitis: application of the recent diagnostic criteria.,” *Neurology*, vol. 65, no. 12, pp. 1950–1953, Dec. 2005, doi: 10.1212/01.wnl.0000188896.48308.26.
[67] C. Krishnan, A. I. Kaplin, D. M. Deshpande, C. A. Pardo, and D. A. Kerr, “Transverse Myelitis: pathogenesis, diagnosis and treatment.,” *Front. Biosci.*, vol. 9, pp. 1483–1499, May 2004, doi: 10.2741/1351.
[68] S. H. Kim *et al.*, “Clinical characteristics, prognosis, and seropositivity to the anti-aquaporin-4 antibody in Korean patients with longitudinally extensive transverse myelitis.,” *J. Neurol.*, vol. 257, no. 6, pp. 920–925, Jun. 2010, doi: 10.1007/s00415-009-5438-2.
[69] S. Ravaglia *et al.*, “NMO-IgG-negative relapsing myelitis.,” *Spinal Cord*, vol. 47, no. 7, pp. 531–537, Jul. 2009, doi: 10.1038/sc.2008.157.

[70] M. J. Sá, “Acute transverse myelitis: a practical reappraisal.,” *Autoimmun. Rev.*, vol. 9, no. 2, pp. 128–131, Dec. 2009, doi: 10.1016/j.autrev.2009.04.005.
[71] J. C. Bot *et al.*, “Comparison of a conventional cardiac-triggered dual spin-echo and a fast STIR sequence in detection of spinal cord lesions in multiple sclerosis.,” *Eur. Radiol.*, vol. 10, no. 5, pp. 753–758, 2000, doi: 10.1007/s003300050998.
[72] A. Campi, S. Pontesilli, S. Gerevini, and G. Scotti, “Comparison of MRI pulse sequences for investigation of lesions of the cervical spinal cord.,” *Neuroradiology*, vol. 42, no. 9, pp. 669–675, Sep. 2000, doi: 10.1007/s002340000368.
[73] T. F. Scott, E. M. Frohman, J. De Seze, G. S. Gronseth, and B. G. Weinshenker, “Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.,” *Neurology*, vol. 77, no. 24, pp. 2128–2134, Dec. 2011, doi: 10.1212/WNL.0b013e31823dc535.
[74] B. G. Weinshenker *et al.*, “Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis.,” *Ann. Neurol.*, vol. 59, no. 3, pp. 566–569, Mar. 2006, doi: 10.1002/ana.20770.
[75] B. N. McLean, R. W. Luxton, and E. J. Thompson, “A study of immunoglobulin G in the cerebrospinal fluid of 1007 patients with suspected neurological disease using isoelectric focusing and the Log IgG-Index. A comparison and diagnostic applications.,” *Brain*, vol. 113 (Pt 5, pp. 1269–1289, Oct. 1990, doi: 10.1093/brain/113.5.1269.
[76] A. Rodriguez *et al.*, “Referral patterns of uveitis in a tertiary eye care center.,” *Arch. Ophthalmol. (Chicago, Ill. 1960)*, vol. 114, no. 5, pp. 593–599, May 1996, doi: 10.1001/archopht.1996.01100130585016.
[77] E. M. Frohman, T. C. Frohman, D. S. Zee, R. McColl, and S. Galetta, “The neuro-ophthalmology of multiple sclerosis.,” *Lancet. Neurol.*, vol. 4, no. 2, pp. 111–121, Feb. 2005, doi: 10.1016/S1474-4422(05)00992-0.
[78] B. G. Weinshenker *et al.*, “A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease.,” *Ann. Neurol.*, vol. 46, no. 6, pp. 878–886, Dec. 1999, doi: 10.1002/1531-8249(199912)46:6<878::aid-ana10>3.0.co;2-q.
[79] M. Bonnan *et al.*, “Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders.,” *J. Neurol. Neurosurg. Psychiatry*, vol. 89, no. 4, pp. 346–351, Apr. 2018, doi: 10.1136/jnnp-2017-316286.
[80] S. Llufriu *et al.*, “Plasma exchange for acute attacks of CNS demyelination: Predictors of improvement at 6 months.,” *Neurology*, vol. 73, no. 12, pp. 949–953, Sep. 2009, doi: 10.1212/WNL.0b013e3181b879be.
[81] K. Gwathmey, R. A. Balogun, and T. Burns, “Neurologic indications for therapeutic plasma exchange: an update.,” *J. Clin. Apher.*, vol. 26, no. 5, pp. 261–268, 2011, doi: 10.1002/jca.20298.
[82] “Proposed diagnostic criteria and nosology of acute transverse myelitis.,” *Neurology*, vol. 59, no. 4, pp. 499–505, Aug. 2002, doi: 10.1212/wnl.59.4.499.
[83] T. W. West, “Transverse myelitis--a review of the presentation, diagnosis, and initial management.,” *Discov. Med.*, vol. 16, no. 88, pp. 167–177, Oct. 2013.
[84] I. I. Ismail and S. Salama, “Association of CNS demyelination and COVID-19 infection: an updated systematic review.,” *J. Neurol.*, vol. 269, no. 2, pp. 541–576, Feb. 2022, doi: 10.1007/s00415-021-10752-x.
[85] Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org. From the case rID: 19649
[86]. Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org. From the case rID: 19648

Article topic: Neurological Manifestations of COVID-19

Author: Miramar Haddad.

Editor: Nicola Al-Madani.

Reviewer: Ethar Hazaimeh.

Keywords: Pandemic, covid-19, headache, CNS, nervous system, SARS-2.

Overview and epidemiology

Coronavirus is a single-stranded RNA genome with a positive sense and an envelope to protect its RNA. Corona in Latin means a crown that describes spikes like protein projection [1]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the coronavirus disease 2019 (COVID- 19), which is now a pandemic that has taken over the world since it started in December 2019 [5] that affected individuals in every country and of any age [11]. The median incubation period is usually 4 to 7 days, and symptoms will initially resemble influenza. Fever is present in 90% of cases [1].

As the number of patients grows as we go throw the pandemic the urgency to find a treatment for the patients, especially those who need aid ventilation and people with the neurological manifestation of COVID- 19 [7]. The clinical manifestation of COVID- 19 could happen as an asymptomatic infection or severe acute respiratory distress with multiorgan involvement and death. COVID- 19 can also cause extrapulmonary complications such as neurologic disorders, which are increasingly reported day by day. Understanding the nervous system involvement pathways and neurologic manifestations can be useful in improving the assessment and management of SARS-CoV-2 patients. These disorders can interfere with the prognosis or require treatment modification.

Pathogenesis and etiology

COVID- 19 binds to ACE2 (the angiotensin-converting enzyme 2) by the spikes that allow COVID-19 to enter and affect the cell. for the virus to have a complete entry the spikes have to be primed by an enzyme called protease (TMPRSS2) [12]. the virus enters the host cell and un coat. Then the genome is transcribed and then translated. The genome replication and transcription take a place at the cytoplasmic membrane [12]. COVID-19 is related to a severe innate immune response and continued raise of systemic cytokine levels. The innate immune response that started due to covid-19 infection is suggested to be an indication to predict mortality and severity[7].

Cardiovascular, cerebrovascular disease and several abnormalities also have been observed including cellular immune deficiency, coagulation activation myocardia injury, hepatic and kidney injury, and secondary bacterial infection rise the possibility of severe disease. It has been recorded that in these cases (severe disease and death) lymphopenia and sustained inflammation [12].

The majority of viral infection begins in the peripheral tissues. despite our body protective barrier and the immune system. viruses might invade the nervous system including covid-19 which either affect the CNS hematological (by the bloodstream) or by infecting the nerves connecting to peripheral tissue [11]. A lot has been investigated on the pathogenetic mechanisms involved in the acute phase of neuro-COVID in the past months and these studies hinted that SARS-CoV-2 is a neurotropic virus [6].

Clinical presentation and complications

COVID-19 can cause complications in the entire neuraxis [1], some of these complications might be a para-infection syndrome or postinfection syndrome, or both [1]. Fig (1) shows the mechanism of nervous system infections and neurological repercussions caused by SARS-CoV-2[9].

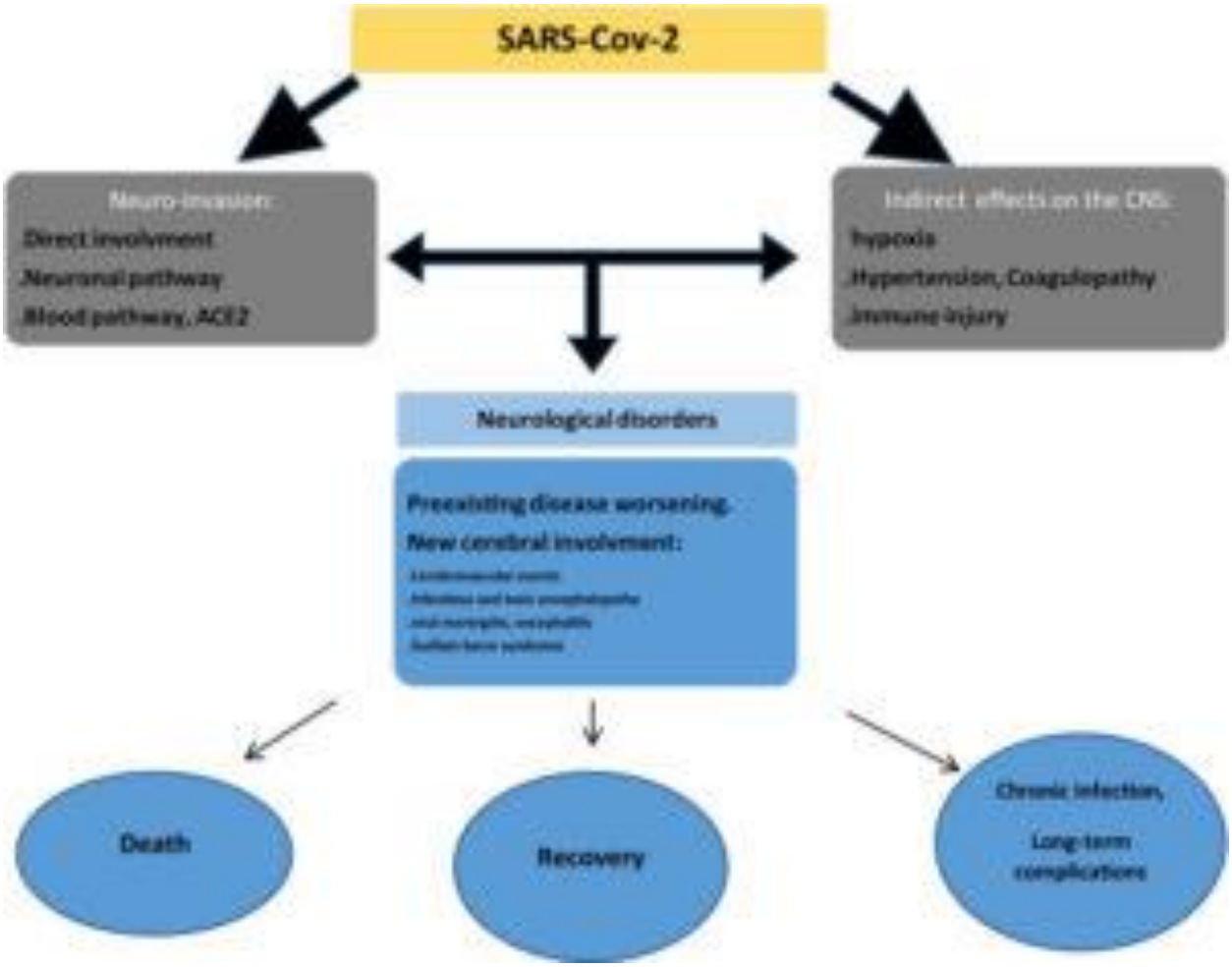


figure 1: The mechanism of nervous system infections.

Neurological symptoms and manifestations can affect three possible systems: the central nervous system CNS, the peripheral nervous system PNS, and the musculoskeletal system [10]. Around 26% of the acute phase of COVID-19 infection develop neurological symptoms and about 25% of them can be attributed to the direct involvement of the central nervous system [7].

Headache, confusion, and dizziness are the most common general but not specific neurological symptoms observed in COVID- 19 patients. Anosmia and ageusia are common manifestations also [1]. Some long-term complications that stay after the resolving of the infection include dysautonomia, exercise intolerance, malaise, sleep disturbances, cognitive impairment, and mood disorders [1]. Encephalopathy is the most common neurological manifestation in covid-19 hospitalized patients [1].

40% to 60% develop loss of smell and 90% alteration of smell [1]. The alteration of the sense of smell and/or taste in uncomplicated early-stage COVID-19 patients is suggestive of a movement of the virus to the brain via the olfactory bulb which allows the virus to reach and affect the brain [9]. The acute ischemic stroke incidence among COVID-19 patients is estimated at 2.3% with a pooled prevalence for an acute

cerebrovascular disease of 2.6%. the prevalence of acute cerebrovascular diseases in COVID-19 hospitalized patients with more severe infection almost reaches 6% [3,10].

These patients often have a prothrombotic problem and can develop occlusion of multiple arteries and the venous system simultaneously [1]. It has been recently reported several categories of cerebrovascular events (intracerebral hemorrhage, ischemic stroke, and cerebral venous thrombosis) in COVID- 19 patients [9]. All of this can generate severe and sometimes fatal outcomes for those who are affected [3].

Work up and diagnosis

Early detection of the possible neurological symptoms, manifestations, and complications is necessary to limit the long-term consequences of COVID- 19. The health care professional should be aware of the heterogeneous neurological manifestations of COVID- 19 when dealing with the patients during the current viral pandemic [10]. The patient who severely suffers from covid-19 and other clinical signs of seizures or encephalopathy could benefit from electroencephalography monitoring (EEG) to early diagnose and treat seizures [10].

We primarily diagnose the patient who dealing with cerebral venous sinus thrombosis based on clinical and radiological criteria with (MRI) and venography and computed tomographic venography being the non-invasive imaging modalities of choice [10].

Following a multidisciplinary approach for the treatment of neuro-PASC (post-acute sequelae of SARS-CoV-2) will be the best way to diagnose and address these symptoms. Tailored rehabilitation and novel cognitive therapy protocols are equally important as pharmacological treatments to treat neuro-PASC effectively [4].

Treatment and Management

Taking care of the patients who develop and suffer from COVID- 19 neurological manifestation will be the responsibility of the neurologist from early diagnosis and treatment to reach effective management to these patients [1]. The Management of COVID-19 patients has to include early clinical, radiologic, and laboratory neurologic assessment, with a close follow-up, especially in severe form [9].

The statistics that were collected during the pandemic highlight the careful and continuous follow-up of COVID- 19 patients, even if they are asymptomatic by regular screening for probable long-term persistent neurological sequelae. When several cases develop a neurological manifestation, they require rapid lines of communication to be established between primary care physicians and neurologists in many ways either via

direct emails or telephone communications through neurology registrars for at least once to properly document and study these cases that develop this kind of symptoms [3].

Patients who suffer from encephalopathy that can affect neurological function can benefit from exercises to stimulate neuroplasticity, these exercises might be music therapy, physical therapy, cognitive-behavioral therapy, gait training, telerehabilitation, among others. This is better achieved with the help of a multidisciplinary team that includes neurophysiology, biomechanics, biomedical engineering, physiotherapy, and clinical medicine [3].

For the patient who lost the sense of smell, most physicians have been administering empirical treatments for COVID-19-associated olfactory dysfunction, including topical or systemic steroid supplementation and olfactory training [2]. Sometimes knowing the pathogenesis helps in determining treatment modalities like attempting to rapidly neutralize the host cell binding S-protein of SARS-CoV-2 by infusion of monoclonal antibodies [6].

A couple of studies showed that there are a few recombinant compounds as IFN with ribavirin had only limited effects against COVID-19 infection [12]. Another study suggested the administration of immunomodulatory hormones, like melatonin, and curcumin to help the neurorehabilitation interventions, based on the demonstrated share pathobiology of the neurological impact in acute ischemic stroke and COVID-19, manifestations like fatigue, infection, dyspnea, muscle weakness, and neuropsychiatric manifestations as impaired thinking, depression, and anxiety. However, better quality studies are needed to support this intervention [3].

the prognosis of recovery from post-COVID neurological syndrome must be evaluated in a personalized way, taking into consideration the target organ damage, especially lungs and heart, which intervene in physical activity and maintenance of the patient daily living activities. It is necessary to design a specific protocol and to establish directed spaces for the neurorehabilitation process, that include personnel, infrastructure, and technological equipment that guarantee therapeutic success, especially in low and middle-income countries that do not have units of specialized rehabilitation [3].

Risk factors

The SARS-CoV-2 infection might affect the brain and influence it by different factors including genetic and environmental factors. Several patients who have COVID-19 infection also have chronic diseases, which might increase the probability of getting an infection and lower their immune-mediated response. Immune and neural cells serve as reservoirs of latent SARS-CoV-2, which may contribute to the delayed neurodegenerative events [11]. The blood-brain barrier in a healthy individual prevents the

breach by pathogens. However, if there is immunosuppression and inflammation, invasion of viruses could happen. (Mahalakshmi et al., 2021) [11]

Prognosis

Only a minority of patients with the usual risk factors develop severe neurological symptoms such as acute cerebrovascular disease which is associated with poor outcomes [9]. To provide a better prognosis early initiation of neurorehabilitation is crucial, it is not prudent to start until the patient's health status stabilizes, to avoid possible relapses during rehabilitation. It is essential to carry out a complete evaluation in stroke patients that eventually will go to the rehabilitation area since it must be determined the short-, medium-, and long-term prognosis [3].

Studies showing that patients who develop encephalopathy suggest that in general, these patients have a worse prognosis and a lower survival rate. This association could be mediated by ACE2 / SARS-Cov-2 interaction, which happens on capillary endothelium and neurons. Thus, neurotropism is directly affecting the entire brain territory [3].

References

1- Nath A. Neurologic Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *CONTINUUM: Lifelong Learning in Neurology*. 2021;27(4):1051-1065. doi:10.1212/con.0000000000000992

2- Seo MY, Lee SH. Treatment and Prognosis of COVID-19 Associated Olfactory and Gustatory Dysfunctions. *Journal of Personalized Medicine*. 2021;11(10):1037. doi:10.3390/jpm11101037

3- Camargo-Martínez W, Lozada-Martínez I, Escobar-Collazos A, et al. Post-COVID 19 neurological syndrome: Implications for sequelae's treatment. *Journal of Clinical Neuroscience*. 2021;88:219-225. doi:10.1016/j.jocn.2021.04.001

4- Moghimi N, Di Napoli M, Biller J, et al. The Neurological Manifestations of Post-Acute Sequelae of SARS-CoV-2 Infection. *Current Neurology and Neuroscience Reports*. 2021;21(9). doi:10.1007/s11910-021-01130-1

5- Lu L, Xiong W, Mu J, et al. The potential neurological effect of the COVID-19 vaccines: A review. *Acta Neurologica Scandinavica*. 2021;144(1):3-12. doi:10.1111/ane.13417

6- Baig AM. Deleterious Outcomes in Long-Hauler COVID-19: The Effects of SARS-CoV-2 on the CNS in Chronic COVID Syndrome. *ACS Chemical Neuroscience*. 2020;11(24):4017-4020. doi:10.1021/acschemneuro.0c00725

7- Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimer's Research & Therapy*. 2020;12(1). doi:10.1186/s13195-020-00640-3

8-Sharifian-Dorche M, Huot P, Osherov M, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. *Journal of the Neurological Sciences*. 2020;417:117085. doi:10.1016/j.jns.2020.117085

9- Abboud H, Abboud FZ, Kharbouch H, Arkha Y, El Abbadi N, El Ouahabi A. COVID-19 and SARS-Cov-2 Infection: Pathophysiology and Clinical Effects on the Nervous System. *World Neurosurgery*. 2020;140:49-53. doi:10.1016/j.wneu.2020.05.193

10- Harapan BN, Yoo HJ. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). *Journal of Neurology*. Published online January 23, 2021. doi:10.1007/s00415-021-10406-y

11-Mahalakshmi AM, Ray B, Tuladhar S, et al. Does COVID-19 contribute to development of neurological disease? *Immunity, Inflammation and Disease*. 2020;9(1):48-58. doi:10.1002/iid3.387

12- Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: Their roles in pathogenesis. *Journal of Microbiology, Immunology and Infection*. 2020;54(2). doi:10.1016/j.jmii.2020.03.022

Article topic: Cluster Headache.

Author: Tala Mohammad.

Editor: Nicola AL-Madani.

Reviewer: Ethar Hazaimeh.

Keywords: Unilateral, trigeminal, episodic, chronic, headache, sumatriptan.

Overview

Cluster headache is a primary headache disorder, part of the family of trigeminal autonomic cephalalgias (TCAs), characterized by excruciating unilateral pain, often involving the supraorbital, retro-orbital, or temporal regions[1]. All TACs share the common feature of unilateral pain, accompanied by prominent cranial parasympathetic autonomic features, which are usually ipsilateral to the headache[2]. Attacks of cluster headache may range between 15-180 minutes, occurring anywhere between once every other day to up to eight times per day[2]. Cluster headache has also been referred to as "suicide headache" due to the fact that some patients have taken their lives during an attack[3]. Moreover, cluster headache has also been portrayed as worse than childbirth [4] which further outlines the severity of attacks.

Epidemiology

Given the low prevalence of cluster headache when compared to migraine, it is challenging to assess accurately the abundance of cluster headache in community [5]. Based on surveys conducted in the USA and Europe, cluster headache is up to 0.1% of the population, with no evidence on whether the prevalence differs according to the region[6]. Cluster headache has been shown to have a significant male predominance, with an approximate male-to-female ratio of 2.5:1[5]. The mean age of onset has been shown to be between 20 and 40 years[7]. Epidemiologic studies regarding cluster headache have been mainly performed on Caucasians[5]. One study concluded that up to 80% of patients partaking in the study, who suffer from cluster headache, were smokers, suggesting strong evidence to the correlation between both factors.[8]

Pathogenesis and etiology

Many structures within both the peripheral and central nervous systems are involved in the pathophysiology of cluster headaches. Cluster headache is neurovascular in nature, with effects driven by the effects of the trigeminal-autonomic reflex activation[5]. The trigeminal-autonomic reflex is a pathway connecting the trigeminal nerve and facial nerve parasympathetic innervation, located in the brainstem[5]. Central activation can take place in the brainstem through the superior salivatory nucleus, which is a part of the facial nerve[9]. The superior salivatory nucleus is the origin of cranial parasympathetic autonomic vasodilator fibers, and its effects are mediated by several substances, including calcitonin gene-related peptide and nitric oxide[9]. This central activation is significant in the pathophysiology of cluster headache, mainly through the involvement of the posterior hypothalamus[9], Figure (1). In primary headaches, the activation of the trigeminal-autonomic reflex leads to typical symptoms which include rhinorrhea, miosis, ptosis, conjunctival injection, and facial sweating[4]. These autonomic symptoms are very prominent in cluster headaches, ipsilateral to the source of the headache. Conventionally, attacks due to cluster headache can be summarized as a combination of trigeminal activation and reactive parasympathetic increase[6].

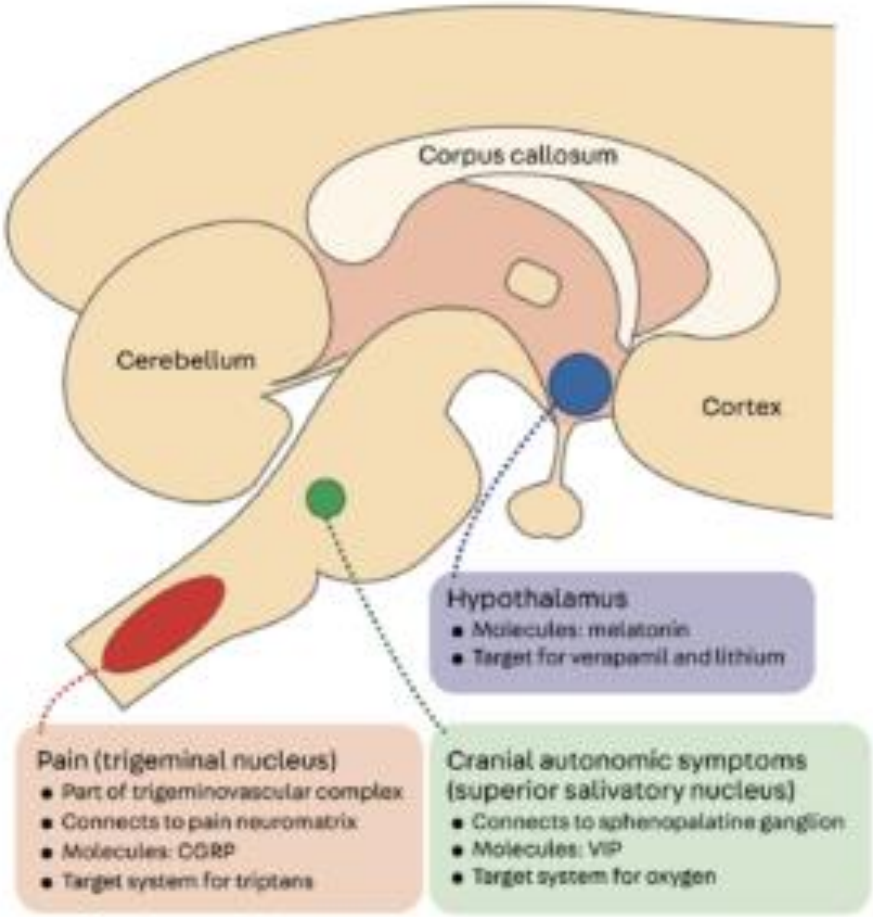


Fig (1) Overview of the structures involved in the pathophysiology of cluster headache [9]

Clinical presentation and complications

The clinical manifestations of cluster headache can be summarized into four keywords: side-locked, excruciating, agitating, and regularly recurring[9]. Cluster headache can be presented either episodically or chronically, depending on the duration between the attacks. The most common presentation among patients is the episodic form, forming up to 90% of all cases[6]. Episodic cluster headache typically refers to attacks that occur in periods ranging from seven days up to a year, with attack-free periods lasting at least three months[2]. However, chronic cluster headache presents with attacks occurring for one year either without pain-free periods, or pain-free periods of less than three months[2]. During the attacks, patients are typically agitated and restless[1], a key factor in distinguishing cluster headache from migraine.

Diagnosis

The diagnosis of cluster headache relies heavily on the accurate history of the patient[1]. According to the International Classification of Headache Disorders 3rd edition, the diagnostic criteria for cluster headache is as follows[2]:

A. Five or more attacks fulfilling criteria B-D
B. Severe or extremely severe unilateral orbital, supraorbital, and/or temporal pain, lasting anywhere between 15 minutes and three hours (when untreated)
C. Either or both of the following,
    - At least one of the following symptoms, ipsilateral to the headache
        - Conjunctival injection, may be accompanied by lacrimation
        - Nasal congestion with or without rhinorrhea
        - Eyelid oedema
        - Forehead and facial sweating
        - Miosis and/or ptosis
    - A sense of restlessness or agitation
D. Attack frequency between once every other day and eight times a day
E. Not better accounted for by other ICHD-3 diagnoses

Patients often have a delayed diagnosis or are simply misdiagnosed. A possible underlying reason can be the limited knowledge on cluster headache throughout many countries[10]. This lack of knowledge may also lead the physician to seek an alternative diagnosis for the patient, which increases the risk of misdiagnosis.[10]

Treatment and Management

Management of cluster headache is divided into acute and preventative management, both of which are further subdivided into several treatments. Acute treatment for cluster headaches can be achieved by sumatriptan, zolmitriptan, high-flow oxygen, and non-invasive vagus nerve stimulation[1]. The most effective treatment for cluster

headaches by far is subcutaneous sumatriptan[11]. Verapamil is often used as the first-line preventive treatment for cluster headaches[1]. However, side effects may arise, including cardiac arrhythmias and bradycardia[1]. Another medication used in preventive treatment is lithium. Evidence on the efficacy of lithium in the treatment of cluster headache is limited[1]. A review of literature suggests that lithium is most efficacious when used in treating chronic cluster headache[12]. Oral treatment is not recommended due to the short duration of the attacks[11]. One therapy that has been proven effective is oxygen therapy although the underlying pathophysiology remains unclear[11,13]. Compared to medications such as sumatriptan and zolmitriptan, oxygen implicates few side effects and is especially useful in patients suffering from more than two attacks per day [1,13]. Furthermore, studies have established the effectiveness of non-invasive vagus nerve stimulation when used in both acute and preventive treatments[14]. Not to mention, sphenopalatine ganglion stimulation elicits both acute and preventive responses, presenting as a reduction in the need for both acute and preventive treatments in a study population[15]. Serum levels of calcitonin gene-related peptide (CGRP) are elevated in cluster headache during cluster periods[11]. Thus, the administration of galcanezumab, a monoclonal antibody against CGRP, has been implicated in the treatment of episodic cluster headache by reducing the frequency of weekly attacks[1,16].

Risk factors

Many papers have outlined several risk factors that may be implicated with cluster headache. A systemic review outlined the major risk factors involved in cluster headache, including family history, smoking, alcohol consumption, and even head trauma[17]. Not to mention, according to the International Classification of Headache Disorders, 3rd edition, attacks are often triggered by alcohol, histamine, or nitroglycerin[2]. Tobacco smoking has been reported to be one of the leading risk factors in cluster headache, also playing a role in the transition between episodic and chronic forms.[17] According to a systematic review, cluster headache has been exhibited as an inherited disorder in certain families, with a female predominance towards familial cluster headache[18]. Thus, there are certain genetic patterns that may be supplementary with cluster headache.

Prognosis

Prognosis has been shown to be difficult to predict[5]. A study carried out to analyze the patterns in cluster headache over 10 years has shown that approximately 20% of episodic cluster headache shows a shift towards either chronic or “combined” forms[19]. Factors that support such shift include a disease ongoing for more than 20 years, late-onset age, and male patients[19]. Based on personal experience, patients have reported the amelioration of their cases with age, characterized by longer remission periods and decreased frequency of attacks[20]. Long remission periods do not fully indicate recovery[19].

Recent updates[21]

A recent retrospective study viewed the use of greater occipital nerve (GON) injection as a treatment. GON injection has been proven effective as a single injection in episodic cluster headache and chronic cluster headache, to a lesser extent. Moreover, similar results were seen with patients suffering from medically intractable chronic cluster headache (MICCH). The treatment used in the study was in the form of both single and repeated injections. As a summary, in the retrospective cohort, single GON injections were proven as an effective prophylactic treatment equally in episodic cluster headache, chronic cluster headache, and MICCH.

References

1. Wei DY, Khalil M, Goadsby PJ. Managing cluster headache. *Pract Neurol*. 2019;19(6):521-528. doi:10.1136/practneurol-2018-002124
2. Olesen J. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202
3. Buture A, Boland JW, Dikomitis L, Ahmed F. Update on the pathophysiology of cluster headache: Imaging and neuropeptide studies. *J Pain Res*. 2019;12:269-281. doi:10.2147/JPR.S175312
4. Möller M, May A. The unique role of the trigeminal autonomic reflex and its modulation in primary headache disorders. *Curr Opin Neurol*. 2019;32(3):438-442. doi:10.1097/WCO.0000000000000691
5. Wei DYT, Yuan Ong JJ, Goadsby PJ. Cluster headache: Epidemiology, pathophysiology, clinical features, and diagnosis. *Ann Indian Acad Neurol*. 2018;21(5):S3-S8. doi:10.4103/aian.AIAN_349_17
6. Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol*. 2018;17(1):75-83. doi:10.1016/S1474-4422(17)30405-2
7. Ekbom K, Svensson DA, Träff H, Waldenlind E. Age at onset and sex ratio in cluster headache: Observations over three decades. *Cephalalgia*. 2002;22(2):94-100. doi:10.1046/j.1468-2982.2002.00318.x
8. Manzoni GC. Cluster headache and lifestyle: Remarks on a population of 374 male patients. *Cephalalgia*. 1999;19(2):88-94. doi:10.1046/j.1468-2982.1999.019002088.x
9. Robbins MS, Nahas SJ. Cluster Headache and Other Trigeminal Autonomic Cephalalgias. *Contin Lifelong Learn Neurol*. 2021;27(3):633-651. doi:10.1212/CON.0000000000000965
10. Buture A, Ahmed F, Dikomitis L, Boland JW. Systematic literature review on the delays in the diagnosis and misdiagnosis of cluster headache. *Neurol Sci*. 2019;40(1):25-39. doi:10.1007/s10072-018-3598-5
11. Diener HC, May A. Drug Treatment of Cluster Headache. *Drugs*. 2022;82(1):33-42. doi:10.1007/s40265-021-01658-z
12. Ekbom K. Lithium for Cluster Headache: Review of the Literature and Preliminary Results of Long-term Treatment. *Headache J Head Face Pain*. 1981;21(4):132-139. doi:10.1111/j.1526-4610.1981.hed2104132.x
13. Guo XN, Lu JJ, Ni JQ, Lu HF, Zhao HR, Chen G. The role of oxygen in cluster headache. *Med Gas Res*. 2019;9(4):229-231. doi:10.4103/2045-9912.273961
14. Nesbitt AD, Marin JCA, Tompkins E, Ruttledge MH, Goadsby PJ. Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. *Neurology*. 2015;84(12):1249-1253. doi:10.1212/WNL.0000000000001394
15. Barloese M, Petersen A, Stude P, Jürgens T, Jensen RH, May A. Sphenopalatine ganglion stimulation for cluster headache, results from a large, open-label European registry. *J Headache Pain*. 2018;19(1):4-11. doi:10.1186/s10194-017-0828-9
16. Kudrow D, Andrews JS, Rettiganti M, et al. Treatment Outcomes in Patients Treated With Galcanezumab vs Placebo: Post Hoc Analyses From a Phase 3 Randomized Study in Patients With Episodic Cluster Headache. *Headache*. 2020;60(10):2254-2264. doi:10.1111/head.14011
17. Elbadawi ASA, Albalawi AFA, Alghannami AK, et al. Cluster Headache and Associated Risk Factors: A Systemic Review and Meta-Analysis. *Cureus*. 2021;13(11). doi:10.7759/cureus.19294
18. Waung MW, Taylor A, Qualmann KJ, Burish MJ. Family History of Cluster Headache: A Systematic Review. *JAMA Neurol*. 2020;77(7):887-896. doi:10.1001/jamaneurol.2020.0682
19. Manzoni GC, Micieli G, Granella F, Tassorelli C, Zanferrari C, Cavallini A. Cluster headache--course over ten years in 189 patients. *Cephalalgia*. 1991;11(4):169-174. doi:10.1046/j.1468-2982.1991.1104169.x
20. Diamond S, Urban G. Cluster Headache. *Pain Manag*. 2006;1:474-491. doi:10.1016/B978-0-7216-0334-6.50048-0
21. Brandt RB, Doesborg PGG, Meilof R, et al. Repeated greater occipital nerve injections with corticosteroids in medically intractable chronic cluster headache: a retrospective study. *Neurol Sci*. 2022;43(2):1267-1272. doi:10.1007/s10072-021-05399-5

Article topic: Huntington's Disease.

Author: Omar AL Khateeb.

Editor: Hatem Gharaibeh.

Reviewer: Ethar Hazaimeh.

Keywords: Chorea, tremor, dementia, congenital, depression, movement.

Overview

The name Huntington was coined for a great share of aspects; however, it also refers to a "crippling" disease, "no pun intended".
Huntington's disease (HD) is a rare, genetic condition that causes nerve cells in the brain to break down (degenerate) over time. This disease usually disrupts the patient's life with physical and mental disorders. Huntington's disease (HD) is named after George Huntington, who described it as hereditary chorea among residents of East Hampton, Long Island in 1872 [2]. It eventually causes jerky or uncontrollable movements, medically known as chorea. It progressively worsens over time and is fatal after up to 20 years. Usually, it appears at ages between 30 and 50. If appearing at lower ages, then we would refer to it as Juvenile Huntington's disease. Even though Huntington's is treatable, the treatments will not prevent the decline of mental, physical, and behavioral symptoms associated with this disease, Figure (1).

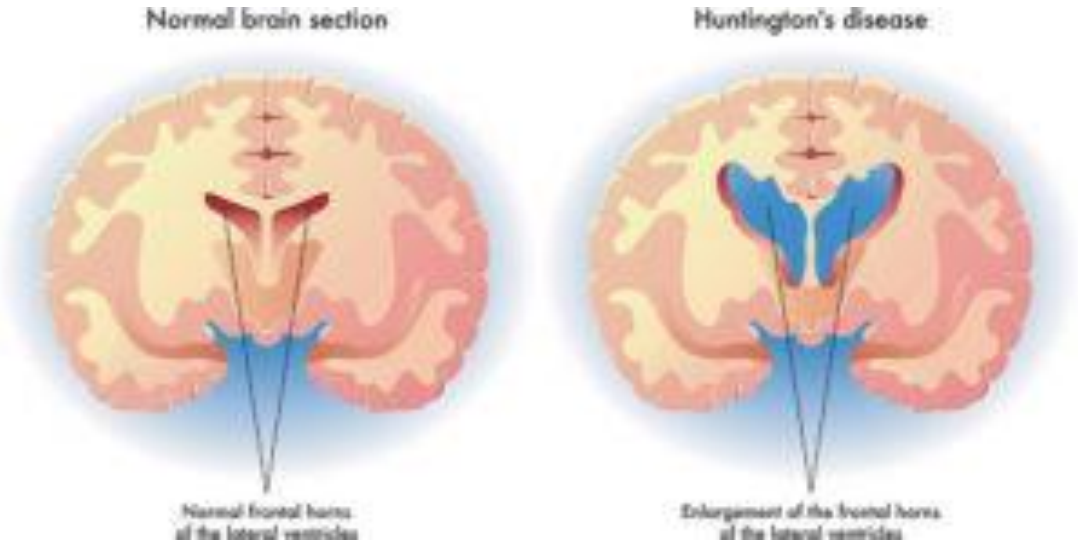


Figure (1): Medical illustration of the symptoms of Huntington's disease in the brain.

Etiology and epidemiology

A mutation in the gene for the protein huntingtin causes Huntington's disease. The deficiency causes the DNA building units cytosine, adenine, and guanine (CAG) to repeat several times more than they should [4]. Since it's an autosomal dominant disorder, a person would need only one copy of the defected gene to develop the disorder. "The defect causes the cytosine, adenine, and guanine (CAG) building blocks of DNA to repeat many more times than is normal" [4]. Moreover, the mutation is caused on a gene on the 4th chromosome. The more the CAG repeats, the sooner the onset and the greater is the phenotype. The clinical picture seen in cases with HD can be explained by selective neuronal malfunction and subsequent death of neurons in the striatum, cerebral cortex, and other areas of the brain [5].

The involvement of local cortical and striatal microcircuits still remains greatly unexplored. Moreover, when the father passes the mutation down through the generations, the number of CAG repeats might grow, leading to increasingly severe phenotypes within a family (called anticipation) [1]. Figure (2).

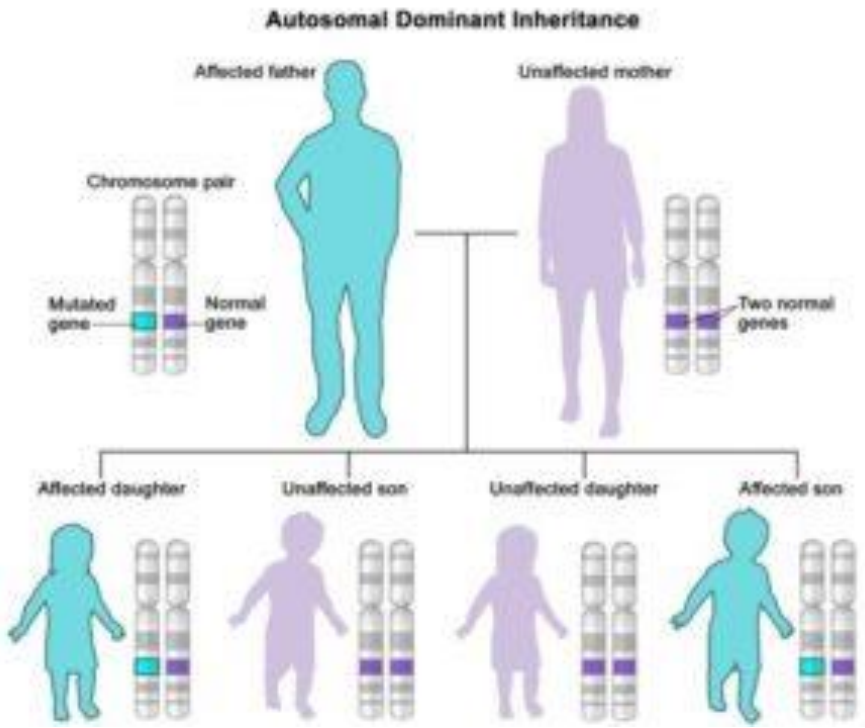


Figure (2): Autosomal dominant inheritance pattern in HD.

Unfortunately, precise estimates of HD are not available, yet it varies from one county to the other. A founder effect appears to have resulted in an extremely high frequency of HD in a few isolated groups of western European heritage [5]. "These include the Lake Maracaibo region in Venezuela (700 per 100,000 people) [12], the island of Mauritius off the South African coast (46 per 100,000 people), and Tasmania (17.4 per 100,000 people). The prevalence in most European countries ranges from 1.63-9.95 per 100,000 people. The prevalence of HD in Finland and Japan is less than 1 per 100,000 people

[5]. Most studies reveal that the average age of onset is between 35 and 44 years old. However, the age range is wide, ranging from 2 years to over 80 years. It is uncommon for symptoms to appear in people less than 10 years old or older than 70 years old. When compared to Americans (37.47 years) and Canadians (34.35 years), Venezuelan relatives have a younger mean age of onset (34.35 years) (40.36 years). In these distinct populations, changing genes and environmental factors are hypothesized to alter the age of onset [5].

Symptoms and signs

The onset of symptoms varies from person to person. Some people experience depression first and then changes in motor skills. Mood swings and abnormal behavior are common early signs [6]. As we said, symptoms can appear at any age.

Some of the key symptoms are:

- Mood and personality changes
- Depression
- Memory, thinking, and judgment problems
- Difficulty in swallowing and speaking
- Loss of coordination and control over movements [6].

Sadly, if none of the family members haven't been previously diagnosed, doctors may not be able to recognize the early symptoms of Huntington's disease.

Early signs and symptoms include:

- Slight uncontrollable movements and stumbling
- Small changes in coordination
- Slight emotional changes
- Difficulty focusing
- Lapses in short term memory
- Depression
- Irritability
- Losing motivation and focus
- Lethargic

One of the common signs is forgetting common information or people's names. Yes, this is a common appearance in many healthy people, but it appears more severe in patients with HD [6]. In later stages of the disease, we can notice more physical, emotional, and cognitive changes.

Physical changes:

- Slurring and problems with finding words
- Weakness and weight loss
- Difficulty with eating and swallowing and risk of choking (mouth and diaphragm muscles lose function).
- Uncontrollable movements such as jerking of the head and face
- Fidgety movements of arms, legs, and body
- Rigid muscles
- Stumbling [6].

Emotional changes:

- Aggression
- Antisocial
- Apathy
- Mania
- Frustration
- Lack of emotion
- Moodiness
- Low organizational skills and difficulty focusing
- Can’t multitask

According to the Huntington's Disease Society of America (HDSA), cognitive abnormalities such as disinhibition and impulsivity raise the likelihood of suicide in people with Huntington's by up to ten times the national average. It is suggested that loved ones and caregivers of people with the disease be aware of the warning signals of suicidal ideation [6]. As we can notice, the farther we progress, the more the patient loses his ability to move. Alas, in later stages, patients will lose the ability to move or talk and will probably need a full-time nurse. However, they will still be able to hear and understand their loved ones to some extent.

Investigations

A neurologist will have to rule out other illnesses that cause similar symptoms and confirm that the patient has Huntington's. The following tests are blood testing, genetic testing, neuroimaging like MRI [8].

Blood Testing

Thanks to the continuous and extensive medical research on Huntington's disease, a simple blood test developed by University College London (UCL) and University College London Hospitals (UCLH) researchers can detect early physiological abnormalities induced by Huntington's disease. The researchers developed a toolkit that can evaluate

two early biomarkers of Huntington's disease in blood and brain fluid during the most recent investigation, which involved 40 participants [13]. According to Ed Wild, a consultant neurologist at UCLH, the biomarkers are the neurofilament light (NFL) which is a protein associated with nerve damage, and the disease-causing mutant Huntington (mHTT). He added that the blood test can detect the prodromal stage of Huntington even before imaging does [13]. The prodromal stage refers to the earliest symptoms of Huntington, which are changes in mood and coordination. Though the blood test still needs more research, it would be a key to developing a drug that cures Huntington's.

Genetic Testing

There are a couple of genetic tests done to diagnose Huntington's disease. They include diagnostic, prenatal, and predictive or pre-symptomatic investigations. The latter is usually done if Huntington's disease runs through the family. All these tests are usually ordered by a genetic counselor.

The genetic test identifies the number of CAG repeats in the HTT gene. A normal HTT gene has 26 or less CAG repeats and is not linked to the development of Huntington's disease. The number of CAG repeats in a HTT gene is classified into 3 subtypes. “Full penetrance or HTT positive” means that the patient has 40 or more CAG repeats. Alas, Huntington's disease is quite likely to strike the individual at some point in their lives. The longer the CAG repeat region, the earlier the illness manifests itself. “Reduced penetrance” shows the patient having 36 to 39 CAG repeats. In this case, it is impossible to determine whether or not the individual would get Huntington's disease. Lastly, "Intermediate" describes an HTT gene with 27 to 35 CAG repeats. The person will not get Huntington's disease in this situation. An HTT gene with an intermediate number of CAG repeats, on the other hand, is unstable, and the number of repeats may rise as the gene is passed down through the generations. As a result, there's a chance that the condition will spread to future generations [14].

Prenatal testing may be recommended for a woman who has Huntington's disease or has a family history of the disease. It is also divided into 3 different tests: chronic villus sampling, amniocentesis, and pre-implantation genetic diagnosis. Chronic villus sampling is possible to be done between the 10th and 14th weeks of pregnancy. A little sample of the chorion, the uterine lining that subsequently develops into the placenta, is taken for this test. Amniocentesis is done during the 15th to 20th week of pregnancy. For the test, a little sample of amniotic fluid is obtained. Pre-implantation genetic diagnosis is a sort of prenatal testing that involves the genetic testing of embryos created through in vitro fertilization before they are put into the uterus [14].

Neuroimaging

The caudate, putamen, and globus pallidus show bilateral atrophy on MRI. This is especially noticeable in the caudate nucleus, which is the most commonly affected area of the brain. The combination results in enlargement of the frontal horns, often giving them a "box" like configuration.

This can be quantified by several measurements:

- Frontal horn width to intercaudate distance ratio (FH/CC)
- Intercaudate distance to inner table width ratio (CC/IT)

Both of these ratios are useful in younger patients with suspected Huntington's disease and become abnormal before the caudates appear abnormal to visual inspection alone (16).

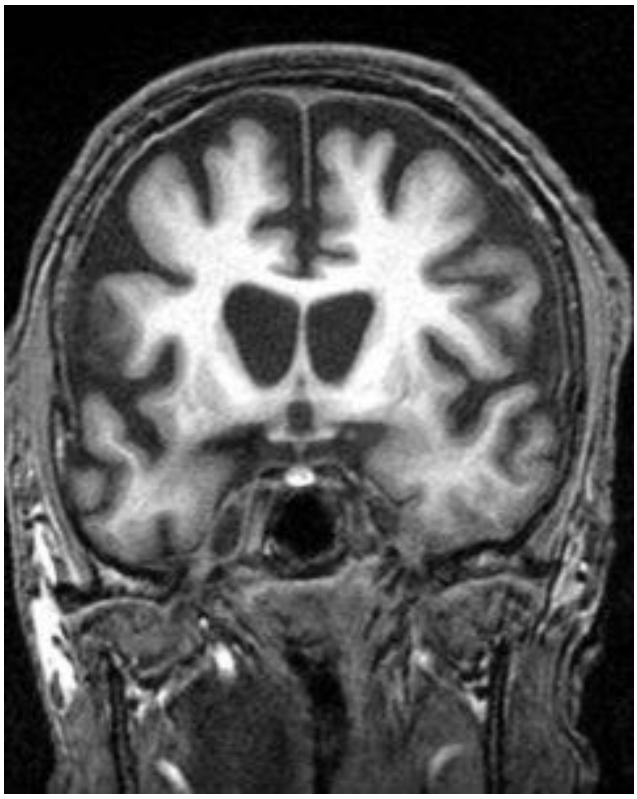


Figure (3): An image of a patient with known Huntington's disease demonstrates marked atrophy of the caudate head bilaterally (15).

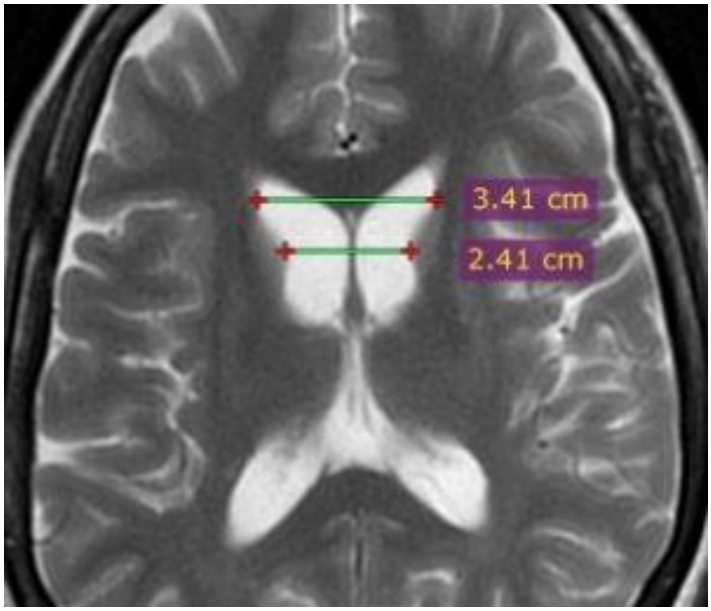


Figure (4): Frontal horn width to intercaudate distance ratio (FH/CC) = 1.4 (normal range 2.2 to 2.6). Case courtesy of Dr Ammar Haouimi (16).

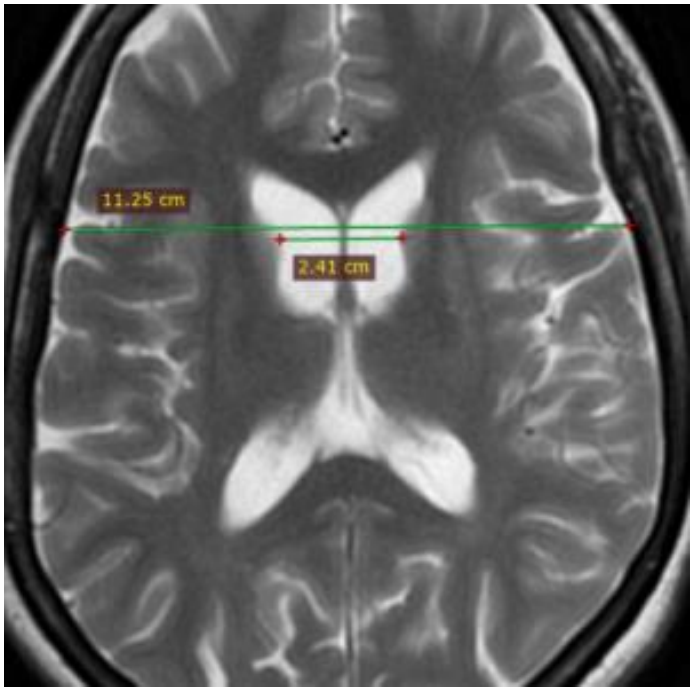


Figure (5): Intercaudate distance to inner table width ratio (CC/IT) = 0.21 (normal range 0.09 to 0.12) Case courtesy of Dr Ammar Haouimi (16).

Management

There is still no cure for Huntington's disease, nor is there any method to prevent it from progressing. However, treatment and support can help to alleviate some of the issues brought on by the illness. Medicines can help alleviate some of the symptoms of Huntington's disease, but they do not cure or delay the disease [10].

Firstly, Tetrabenazine (Xenazine) and deutetrabenazine (Austedo) are two drugs that have been licensed by the Food and Drug Administration to treat uncontrollable jerking and writhing motions (chorea) associated with Huntington's disease.

Secondly, Antipsychotic medications including haloperidol (Haldol) and fluphenazine inhibit mobility as a side effect. As a result, they may be useful in the treatment of chorea. Treatment for psychiatric disorders can vary depending on the symptoms. However, doctors usually prescribe antidepressants, antipsychotics, and mood-stabilizing drugs.

Also, a psychotherapist can help with behavioral issues, coping methods, managing expectations as the disease progresses, and facilitating effective communication among family members through talk therapy. Speech, physical p, and occupational therapies can be used to improve the life of a Huntington patient [1].

Complications

The complications are severely dangerous. HD has endless symptoms, but ultimately, they don't cause death. The complications do! Two of the leading causes of death are pneumonia and suicide, respectively. Twenty-five percent of patients make an attempt to take their own lives. Also, complications of immobility, such as pneumonia, heart problems, or infection, are frequently the cause of mortality. Larger amplitude chorea might result in damage and poor placement. Fractures and head injuries are other possible outcomes. Behavioral problems can be extremely debilitating, generating stress not just for the patient but also for their family and carers [12].

References

1) Haskins BA, Harrison MB. Huntington's disease. Curr Treat Options Neurol. 2000;2(3):243-262. doi:10.1007/s11940-000-0007-0

2) Mennitto D. About Huntington's disease and related disorders at the johns Hopkins hospital. Hopkinsmedicine.org. Published December 3, 2018. Accessed February 5, 2022. https://www.hopkinsmedicine.org/psychiatry/specialty_areas/huntingtons_disease/patient_family_resources/education_whatis.html

3) Haskins BA, Harrison MB. Huntington's disease. Curr Treat Options Neurol. 2000;2(3):243-262. doi:10.1007/s11940-000-0007-0

4) Huntington's disease information page. Nih.gov. Accessed February 14, 2022. https://www.ninds.nih.gov/Disorders/All-Disorders/Huntingtons-Disease-Information-Page

5) Huntington disease. Medscape.com. Published June 14, 2021. Accessed February 14, 2022. https://emedicine.medscape.com/article/1150165-overview

6) Brazier Y. Huntington's disease: Symptoms, causes, and treatment. Medicalnewstoday.com. Published November 30, 2020. Accessed February 14, 2022. https://www.medicalnewstoday.com/articles/159552

7) Blumenstock S, Dudanova I. Cortical and striatal circuits in Huntington's disease. Front Neurosci. 2020;14:82. doi:10.3389/fnins.2020.00082

8) Huntington's disease: Genetics, juvenile cases & chorea. Cleveland Clinic. Accessed February 15, 2022. https://my.clevelandclinic.org/health/diseases/14369-huntingtons-disease

9) Singh-bains DM. Managing and treating Huntington's disease. The Medical Republic. Published August 8, 2018. Accessed February 15, 2022. https://medicalrepublic.com.au/managing-treating-huntingtons-disease/16164

10) Huntington's disease - Treatment and support. nhs.uk. Accessed February 15, 2022.

https://www.nhs.uk/conditions/huntingtons-disease/treatment/
11) Researchgate.net. Accessed February 15, 2022. https://www.researchgate.net/figure/Therapeutics-for-the-treatment-and-management-of-Huntingtons-disease-FDA-Food-and_fig1_349439561
12) Ajitkumar A, De Jesus O. Huntington Disease. In: StatPearls [Internet]. StatPearls Publishing; 2021.
13) Tirumalaraju, D. (2018, September 16). Blood test to detect early changes in Huntington's disease. Medical Device Network. https://www.medicaldevice-network.com/news/blood-test-huntingtons-disease/
14) Neidler, S. (2018, September 12). Genetic testing and counseling. Huntington's Disease News. https://huntingtonsdiseasenews.com/genetic-testing-and-counseling/
15) Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org. From the case rID: 8052
16) Case courtesy of Dr Ammar Haouimi, Radiopaedia.org. From the case rID: 88279

Article topic: Physiotherapy Intervention for Spinal Cord Injury.

Author: Yara Abu Al Halaweh.

Editor: Ethar Hazaimeh.

Reviewer: Adam M Abdallah.

Keywords: Trauma, physiotherapy, spinal cord.

Introduction

Traumatic spinal cord injury (TSCI) is a devastating, life-altering condition usually correlated with morbidity, continued disability and dependency, psychological issues, and financial load [(1)]. Worldwide spinal cord injury prevalence has been increasing over 30 years and varies from 236 to 1298 patients per million in several countries [(2)].

Figure 1[21] cervical spinal cord injury.

Types of (TSCI)

Spinal cord injuries are either complete or incomplete cuts, depending on the International Standards for the Neurological SCI1 Classification and the American

Spinal Injuries Association Impairment Scale (AIS). Complete injuries are described as AIS A, and incomplete injuries are described as AIS B, AIS C, AIS D, or AIS E. Frankel system whereby a patient was categorized as having an incomplete injury if they had any motor or sensory preservation more than three levels below the level of injury. The International Standards for the Neurological Classification of SCI [3] differentiate between complete and incomplete injuries on the presence of sensory and motor preservation in the S4/5 segments. An injury is described as complete if a patient has no voluntary anal contraction (indicative of S4/5 motor preservation) and/or sensation in or all over the anus (indicative of S4/5 sensory preservation).

Spinal cord injuries syndromes

There are various spinal cord syndromes involving injuries to a single segment that has a much more diverse and delicate presentation. These syndromes can be missed or misdiagnosed if an overall neurologic examination and well-differential diagnosis are not done. [4] Table 1 is the cause, diagnosis, and management of the most common syndromes. The managing doctor must be aware of this Central cord syndrome is a flexion/extension injury in an elderly patient with existing spinal stenosis. Although spinal immobilization is preserved because of the presence of neurologic deficits, it is usually not an unstable spine injury, and there is no proven evidence of immobilization with a neck collar. Brown-Se´quard (or “cord hemisection”) is rare and seen after a direct penetrating injury to the spinal cord that affects different unilateral and contralateral manifestations. Anterior cord syndrome is usually a vascular cause leading to injury or hindering of flow through the anterior spinal artery. All the spinal cord syndromes presented with fixed and settled defects, management is mostly predictable and aimed at treating pain and symptoms. [5,6] Yet, for any patient with a gradual worsening neurologic deficit, urgent consultation with a neurosurgeon for decompression is necessary.

Table 1 syndromes, cause, findings, examination, and management

Syndrome	Cause	Findings & Examination	Management
Central cord	Extension or hyperflexion	sacral sensory sparing with Motor weakness of arms > legs	Physical therapy and rehabilitation Spinal decompression

Anterior cord	Direct injury or ischemia from anterior 2/3 spinal artery injury	Loss of pain temperature function and motor function with kept light touch sensation and proprioception	Bad prognosis with a low chance of muscle recovery Physical and occupational therapy
Brown-Se´quard (cord hemisection)	Spinal hemisection is usually gunshot or knife wound	Loss of motor on the same side and proprioception. opposite loss of pain and temperature sensation	Spinal stabilization if needed Physical therapy Course of steroids
Conus medullaris	Injury to sacral cord and lumbar nerve roots, upper lumbar (L1) fractures, tumors, disk herniation	normal leg motor function. Bowel, bladder, and sexual dysfunction with areflexia, bulbocavernosus present with high lesion	Urgent surgical decompression Course of steroids intravenous (IV) training for Bowel/bladder
Cauda equina	Injury to lumbar/sacral nerve roots, lumbar (L2 or lower), or sacral fractures, also pelvic tumors, herniated disk	Flaccid leg paralysis or weakness, high lesions spare bowel/bladder, bulbocavernosus absent	Surgical decompression Course of steroids Bowel/bladder training

Acute care management

Treatment begins on the spot and a streamlined program for management in the acute phase is necessary. Check figure (2)[7]

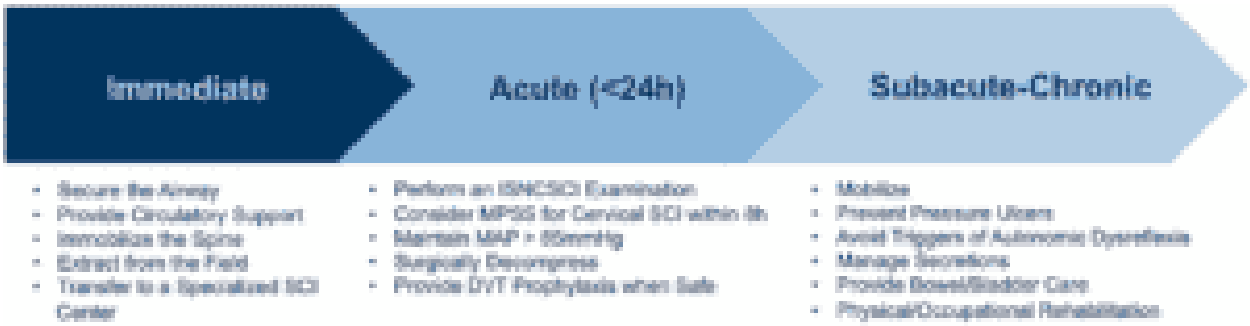


Figure 2 Describes each phase and its prober management following spinal cord injury.

Diagnostic Assessments tools

Once the patient is medically stable, clinical assessment using the ASIA International Standards for Neurological Classification of SCI (ISNCSCI) must be done to classify the level of injury and range of functional impairment[8]. This detailed baseline examination is essential for treatment options, observation of recovery, clinical trial worthiness, and prognosis. The ISNCSCI determines SCI as neurologically complete injury when there is no sacral sparing or sensory and/or motor function at the lowest sacral level (sensory function in dermatome S4-5, deep anal pressure [DAP], or voluntary anal contraction [VAC])[9].

Spinal shock

Immediately in the period following critical SCI, spinal shock has been defined as complete loss of sensory and motor function below the level of injury, loss of sphincter reflex, and loss of deep tendon reflexes. The absence of the sphincter reflex indicates spinal shock making attempts at prognostication inaccurate. Recurrence of the bulbocavernosus reflex usually indicates the end of spinal shock and persistent complete motor and sensory loss is an indication of complete spinal cord injury at that time[7]. In the beginning, the phase of missing or reduced reflexes occurs in the first 24 hours post-injury where the deep tendon and cutaneous reflexes below the level of injury are both missed. The second phase is seen between 1 to 3 days after the injury and is defined by an initial presence of cutaneous reflexes such as the bulbocavernosus reflex. After this and lasting up to one month, a phase of early hyperreflexia results in the return of deep tendon reflexes as an outcome of axon-mediated synapse growth. The terminal phase of spinal shock lasts between 1 to 12 months post-injury and is described by hyperreflexia and spasticity of cutaneous and deep tendon reflexes.

Respiratory interventions

The need for proper airway management is essential for patients with cervical level SCIs. Most patients with high cervical SCIs present with quadriplegia and respiratory discomfort or arrest and surely need intubation. Respiratory issues are considered a serious cause of morbidity and mortality in patients with acute spinal cord injury. High cervical level injuries can affect phrenic innervation of the diaphragm which leads to being ventilator dependent. Injuries below C5 can still contribute to the weakness of respiratory muscles. It's important to prevent mucous plugs, atelectasis, and pneumonia. Vibration, Percussion, or assisted suctioning may be helpful in secretions mobilization[10]. There is a high possibility of deep vein thrombosis (DVT) and pulmonary embolus in patients with SCI because of prolonged immobility period[11].

Cardiovascular issues

Autonomic dysreflexia (AD) is most common in patients with T6 level injury or above and is defined by unexpected, sudden hypertension that can be life-threatening. The sympathetic release triggered by a stimulus below the level of injury leads to peripheral vasoconstriction with a strong parasympathetic response above the level of injury resulting in headaches, sinus congestion, and sweating. Common stimulators such as bowel or bladder distension and proper voiding and bowel prober regimens are a critical role in preventing AD events. Treatment of AD includes conservative methods such as upright positioning and removing any stimulators or possible noxious stimuli. If SBP stays high although conservative methods, fast-acting antihypertensive agents such as instantly release nifedipine, captopril or nitroglycerine should be given[12].

Musculoskeletal Complications

Charcot Joints or neuropathic arthropathy is defined by progressive damage of a joint that has diminished sensation because of unchecked recurrent microtraumas and local hyperemia in response to changes in autonomic innervation. Charcot spinal arthropathy (CSA), despite its rare, can proceed fast and carry crucial morbidity.

With the presence of spinal deformity, sitting imbalance and backache are suspected by the present of disco-vertebral deterioration, vacuum discs, and osseous joint wrack[13]. Conservative management includes a multimodality program with physiotherapy, Bracing for stability, and pain management. Surgeries might be required in advanced cases to correct the deformity and improve stability[14].

Pressure Sores

Pressure sores are a usual complication post-SCI that morbidity/ can cause significant mortality, long period of hospitalization, and act as a stimulus for autonomic dysreflexia. The most common site is on the buttocks (31%), over the greater trochanter (26%), and on the sacrum (18%)[15]. Prevention techniques have to be started instantly

post injury and accurate adherence should be established for the long-term Daily skin check. It's highly recommended that individuals should change their position every 2 hours in the initial phases of injury.

Physiotherapy intervention

Classical rehabilitation techniques post SCI contain a range of motion and strengthening exercises, transfer and bed mobility exercises along with locomotor training. Passive and soon mobilization is a critical tenet of rehabilitation post-SCI. Body weight supported treadmill training (BWSTT) improves task-specific sensory input and is a proven strategy to promote locomotor function after SCI[16]. Weakness is the most apparent impairment that limits patients with SCI from practicing motor tasks. Thus, strengthening training is well administered by physiotherapists. Diminished strength in patients with SCI can be neurologically caused, as in patients with Grade 2 or 3 strength in the quadriceps muscle who are training to walk. Otherwise, affected strength might be due to diminished muscle mass[17]. The patient needs a progressive resistance training program, and the load is appropriately and progressively elevated. This training is usually best performed in the context of functional skills, giving the basics of progressive resistance training can be preserved. Functional Electrical Stimulation (FES) depends on the idea of providing electrical currents to the nerve and muscles that give movements in order to improve their activation for the short and long term. Used as a complement during the rehabilitation process to improve movements that way raising sensory feedback and muscle function and provide a degree of cardiorespiratory conditioning[18]. Stimulation for trunk muscles using FES has been shown to enrich trunk posture and stability[19].

Walking post spinal cord injury

The determination of return to walking after (SCI) depends on the initial level and seriousness of the injury, the extent of lower extremity motor function, and the age of the patient. Other common complications include balance, spasticity, truncal control, and proprioception, with cognition, which also affects walking. In 1973, Hussey and Stauffer[20] showed that a reciprocatory gait type may be used when there was pelvic muscle control with minimum of 3/5 strength in both hip flexors and 1quadriceps (knee extensor) with more than or equal to 3/5 in minimum of one leg.

Motor tasks

Physiotherapy intervention is focused on enhancing patients' wellness by doing different motor tasks such as transferring, walking, pushing a wheelchair, and using the upper limbs. Intervention is based on the basics of motor learning. Repeating practice is an essential element. For example, if a patient has overall paralysis and the goal was to walk with walking aids and orthosis, this means the patient has to practice walking with

orthoses and walking aids[17]. Robotic devices and treadmills could be used to make gait training easier and to provide a chance for intensive repetitive practice using a gait strategy that is similar to an able-bodied person.

References

1. MH Khorasanizadeh, M Yousefifard, M Eskian, Y Lu... - Journal of Neurosurgery ..., 2019
2. Furlan JC, Sakakibara BM, Miller WC, Krassioukov AV:Global incidence and prevalence of traumatic spinal cord injury. Can J Neurol Sci 40:456–464, 2013
3. Waring III WP, Biering-Sorensen F, Burns S, Donovan W, Graves D, Jha A, et al.Review and revisions of the International Standards for the Neurological Classification of Spinal Cord Injury. J Spinal Cord Med. 2010;33:346–352.
4. MJ Eckert, MJ Martin - Surgical Clinics, 2017
5. Brooks NP. Central cord syndrome. Neurosurg Clin N Am 2017;28(1):41–7.
6. Radcliff KE, Kepler CK, Delasota LA, et al. Current management review of thoracolumbar cord syndromes. Spine J 2011;11(9):884–92.
7. LD Hachem, CS Ahuja, MG Fehlings - The journal of spinal cord medicine, 2017... selection, monitoring of recovery, clinical trial eligibility, and prognostication. Early ... spinal column injury, assess for missed associated injuries, and ultimately guide further treatment. CT ...
8. Hadley MN, Walters BC, Aarabi B, Dhall SS, Gelb DE, Hurlbert RJ, et al. Clinical assessment following acute cervical spinal cord injury. Neurosurgery 2013;72 Suppl 2:40–53.
9. American Spinal Injury Association. International standards for neurological classification of spinal cord injury. Richmond (VA): ASIA; 2019.
10. Galeiras Vazquez R, Rascado Sedes P, Mourelo Farina M, Montoto Marques A, Ferreiro Velasco ME. Respiratory management in the patient with spinal cord injury. Biomed Res Int 2013;2013:168757.
11. Dhall SS, Hadley MN, Aarabi B, Gelb DE, Hurlbert RJ, Rozzelle CJ, et al. Deep venous thrombosis and thromboembolism in patients with cervical spinal cord injuries. Neurosurgery 2013;72 Suppl 2:244–54.
12. Krassioukov A, Eng JJ, Warburton DE, Teasell R, Spinal Cord Injury Rehabilitation Evidence Research T. A systematic review of the management of orthostatic hypotension after spinal cord injury. Arch Phys Med Rehabil 2009;90(5):876–85.
13. Aebli N, Potzel T, Krebs J. Characteristics and surgical management neuropathic (Charcot) spinal arthropathy after spinal cord injury. Spine J 2014;14(6):884–91.
14. Moreau S, Lonjon G, Jameson R, Judet T, Garreau de LoubresseC. Do all Charcot Spine require surgery? Orthop Traumatol SurgRes 2014;100(7):779–84.
15. Sezer N, Akkus S, Ugurlu FG. Chronic complications of spinal cord injury. World J Orthop 2015;6(1):24–33.
16. Lam T, Eng JJ, Wolfe DL, Hsieh JT, Whittaker M. A systematic review of the efficacy of gait rehabilitation strategies for spinal cord injury. Top Spinal Cord Inj Rehabil 2007;13(1):32–57.
17. LA Harvey - Journal of physiotherapy, 2016
18. Ho CH, Triolo RJ, Elias AL, Kilgore KL, DiMarco AF, Bogie K, et al. Functional electrical stimulation and spinal cord injury. Phys Med Rehabil Clin N Am 2014;25(3):631–54, ix
19. Triolo RJ, Bailey SN, Miller ME, Lombardo LM, Audu ML. Effects of stimulating hip and trunk muscles on seated stability,posture, and reach after spinal cord injury. Arch Phys MedRehabil 2013;94(9):1766–75
20. Hussey RW, Stauffer ES. Spinal cord injury: requirements for ambulation. Arch Phys Med Rehabil 1973;54:544–7.
21. https://en.wikipedia.org/wiki/Spinal_cord_injury#/media/File:Cervical_Spine_MRI_(T2W).jpg

Article Topic: Secondary Stroke Prevention.

Author: Manar Ezzat Mahmood.

Editor: Haneen A. Banihani, Haneen Al-Abdallat.

Reviewer: Neebal Algallab, Ethar Hazaimeh.

Keywords: Embolic, hemorrhage, infarction, hypertension.

Overview

Stroke is a neurological deficit attributed to focal injury of the central nervous system (CNS) due to a vascular cause and is considered a significant cause of disability and death worldwide.[1]

Stroke can affect the old and the young, though less commonly published, but young stroke patients are faced in clinical practice and have a disproportionately large economic impact.[2]

Stroke recurrence is defined as an event resulting in a neurological deficit different from the initial stroke, as it may involve a different anatomic site or vascular territory or a different stroke subtype from that of the initial stroke. [3,4] Risk of recurrence poststroke is higher in the first year [5,6] which explains the high average annual risk of recurrence recorded in studies with short follow-up compared to those of more extended follow-up periods. The risk of recurrence following primary intracerebral hemorrhage is similar to that following cerebral infarction.[7]

Strokes pose a significant conflict for survivors due to the risk of recurrence, which may be the final insult to regaining independence. [8,9] Recurrence in the immediate post-stroke period prolongs hospital stay and significantly increases neurological disability and the chance of death. [10]

Epidemiology

Stroke is the second leading cause of death globally[11]. It has a global burden that is increasing dramatically. Current data indicate that 16.9 million people suffer a stroke every year, representing a global incidence of 258/100,000/year, with men having an incidence that is 1.5 times higher than women.[12]

Cultural and environmental mechanisms play a role in racial-ethnic stroke disparities, including socioeconomic class, access to care, discrimination, and cultural variations in

risk factors. It is observed that blacks in the U.S. have higher stroke incidence and higher death rates for all stroke subtypes compared to other racial groups. [13]

Trends in stroke incidence and mortality rates have decreased in recent decades in high-income countries, and this reflects reasonable control of risk factors, as well as an improvement in life expectancy. The opposite has been reported in low-to-middle-income countries [14]

Etiology and Pathogenesis

Strokes can be subdivided into ischemic and hemorrhagic, with ischemic strokes being more prevalent than hemorrhagic, making up approximately 80% of all strokes. [15]

An ischemic stroke is when a vessel is occluded and can be broadly subdivided into thrombotic and embolic strokes. Damaged areas of an atherosclerotic plaque can cause a blood clot to form, blocking the blood vessel hence a thrombotic stroke. Embolic strokes are blood clots or debris from elsewhere in the body that blocks a cerebral artery, typically from the heart valves.

Further sub-classifications are

- Large artery disease; atherosclerosis of large vessels.
- Small vessel disease: these changes happen due to chronic diseases, such as diabetes, hypertension, hyperlipidemia, and smoking.
- Embolic stroke: which could be due to atrial fibrillation
- Strokes of determined and undetermined etiologies.

In ischemic strokes, a volume of functionally impaired but structurally intact tissue surrounds the ischemic region; this tissue is known as the ischemic penumbra. [16] Also, in the core, where blood flow is most severely restricted, excitotoxic and necrotic cell death occurs within minutes.

As for the periphery of the ischemic area (the penumbra), where collateral blood flow is present, buffering of the full effect of stroke can be seen; hence the degree of ischemia and outcome of individual cells is dependent on the timing of reperfusion.[17] The penumbra is the site for therapeutic interventions as it hosts a cascade of neurochemical events disrupting ion homeostasis.[16]

As for the second type of stroke, the hemorrhagic (intracerebral) stroke mostly happens due to pre-existing or newly diagnosed hypertension or could be due to intracranial vascular malformations like cavernous angiomas.

Pathogenesis of ischemic stroke

Variable pathological changes occur to the affected tissue to eventually reach apoptosis, Initially, excitotoxicity, excitotoxicity, and ionic imbalance:

The brain requires large amounts of oxygen to generate sufficient ATP by oxidative phosphorylation to maintain and restore ionic gradients, e.g., Na/K ATPase. This ion pump maintains the high intracellular K+ concentration and the low intracellular Na+ concentration, which are essential for the propagation of action potentials.

When ischemia happens, the mitochondria are incapable of generating ATP due to oxygen depletion; hence when neuronal depolarization happens, the neuron is incapable of restoring resting potential, usually done through the Na+/K+ ATPase. [18] Alongside the Na intracellular increase, Ca++ increases as well since plasma membrane Ca++ ATPase does not maintain a normal low Ca++ concentration intracellularly.[17]

Membrane depolarization also releases neurotransmitters like glutamate, which plays a crucial role in ischemic pathology. The sodium-dependent glutamate transmembrane porters of presynaptic and postsynaptic membranes maintain a large concentration gradient. Membrane depolarization and sodium accumulation inside the cells during ischemia causes the reversal of glutamate transporters allowing glutamate to exit the cell along its concentration gradient. [17]

This increased synaptic glutamate concentration leads to the activation of N-Methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. NMDA receptors are calcium-permeable, further exacerbating intracellular calcium overload (excitotoxicity). [19]

Another factor that further exacerbates calcium overload is acidosis, one of the consequences of anaerobic metabolism of ischemia; hyperglycemia increases lactate in the ischemic environment, further depressing PH. [17]

Peri-infarct depolarization

In the affected brain tissue's core region, cells undergo anoxic depolarization and never repolarize. Cells in the penumbral region can repolarize, but at the expense of further energy consumption, they depolarize once again in response to the increase of glutamate or K+ levels, or both, which accumulate in the extracellular space. This cycle leads to repetitive depolarizations, also called 'peri-infarct depolarizations.' [20]

Oxidative and nitrative stress

Elevated levels of intracellular Ca++, Na+, and ADP cause the mitochondria to produce high levels of reactive oxygen species, which the brain is especially vulnerable to due to the low endogenous antioxidant levels in neurons. [21]

The abundant oxygen radicals destroy cellular macromolecules signaling cells to undergo apoptotic cell death. [22]

Workup and diagnosis

When comparing ischemic stroke to intracerebral hemorrhage, it is found that the most common feature is its acute onset compared to intracerebral hemorrhage, which gradually worsens. [25]

All patients with stroke symptoms should undergo urgent neuroimaging with non-contrast computed tomography (CT) or MRI.[26] To distinguish between intracerebral hemorrhage and ischemic stroke, patients should undergo neuroimaging since both entities are characterized by “acute onset of focal symptoms.” [25]

MRI scans have a better resolution than CT scans; however, they are less available, more expensive, and cannot be used in patients with implanted devices, e.g., pacemakers and metallic stents. [25]

MRIs are recommended if the patient is within the time window of acute stroke intervention and if they can be obtained as fast as a CT scan. If not, then CT scans are the recommended modality because acute stroke treatments should not be delayed for detailed imaging when both the history and physical presentation are consistent with acute stroke. [27]

It is worth mentioning that strokes can sometimes be confused with stroke mimics and are considered a differential diagnosis. The duration of the symptoms distinguishes strokes from Transient ischemic attacks (TIA), a focal ischemic neurologic event resolving within 24 hours. [29]

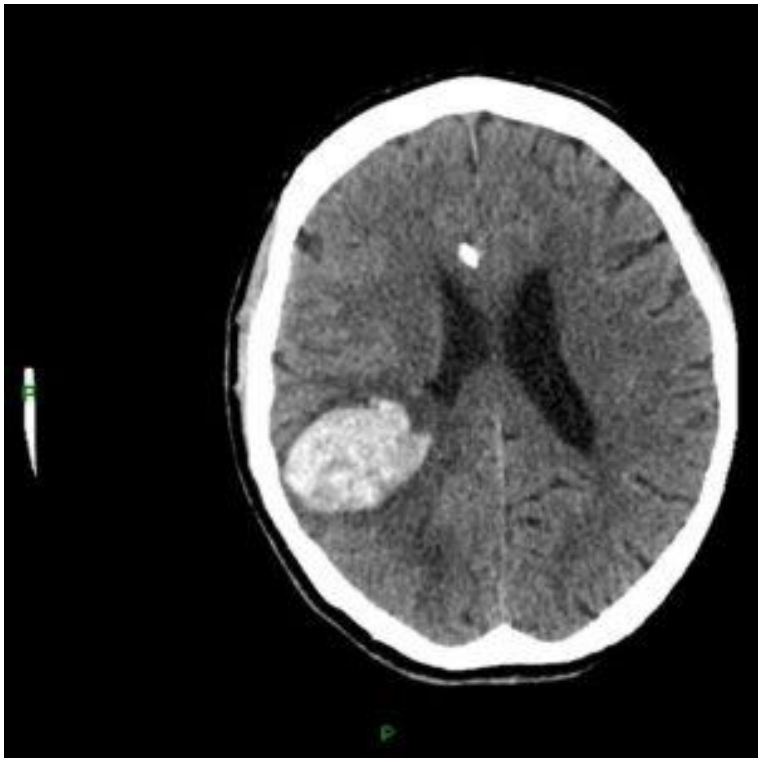


FIGURE (1): AXIAL NON-CONTRAST CT SCAN OF RIGHT FRONTOPARIETAL HEMORRHAGE WITH SURROUNDING EDEMA Case courtesy of Dr. Derek Smith rID: 34366.

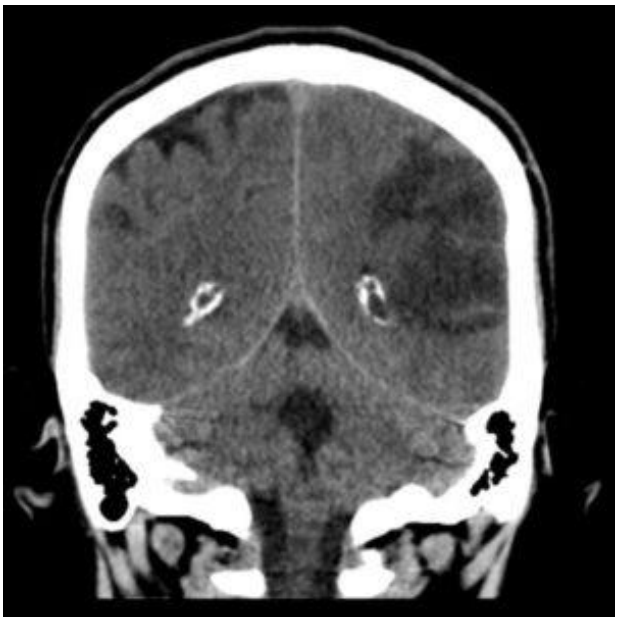


FIGURE (2): CT SCAN SHOWING TWO REGIONS OF ISCHEMIC STROKE IN THE TERRITORY OF THE LEFT MIDDLE CEREBRAL ARTERY. Case courtesy of Dr. David Cuete rID: 26882

Prevention of stroke

One of the best ways to primarily prevent Strokes is by making healthy lifestyle choices:

- Choosing a healthy diet.
- Bearing a healthy weight.
- Maintaining physical activity.
- Avoiding smoking.
- Limiting alcohol.

Secondary prevention of stroke

- **Antithrombotic therapy:**

Aspirin: 50-325 mg daily is the recommended initial therapy to prevent the recurrence of an ischemic stroke. The major adverse effect of using aspirin is gastrointestinal bleeding, its prevalence increases when the dose increases [39]. If the patient has recurrent strokes during aspirin therapy, increasing the aspirin dose won't cause a difference as there is no evidence that this increase will decrease the risk of another event [40]. Note that Aspirin is the most cost-effective therapy option.

Clopidogrel: monotherapy of 75 mg daily is recommended and can also be used in patients allergic to aspirin [40]. Clopidogrel is as safe as Aspirin, with fewer bleeding episodes[41]. Effectiveness may be decreased with the use of proton pump inhibitors because of the possible cytochrome p450 2C19 interactions. Hence, patients are recommended to use histamine H2 blocker or pantoprazole because of its decreased effects on CYP2C19. [42]

Dipyridamole: Dipyridamole is a 'mild' antiplatelet agent compared with the more 'aggressive' antiplatelet agent clopidogrel. The more modest platelet inhibition provided by Dipyridamole is better suited for secondary prevention in stroke/TIA patient populations and is less likely to cause adverse bleeding complications. [43]. Dipyridamole exerts antithrombotic effects, at least partially, through vessel wall [36]. It also has antioxidant [44], anti-inflammatory [45,] and anti-proliferative properties[46]. However, Dipyridamole is associated with a headache that may cause the patient to discontinue the medication [47]. Dose titration by initiating therapy with once-daily dosing may help to overcome that headache[48].

Aspirin Plus Clopidogrel:

The CHANCE trial (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) was a clinical trial that aimed to evaluate the effectiveness of clopidogrel alone in preventing recurrent stroke in high-risk Chinese patients who have had a minor ischemic stroke or high-risk TIA [49]. The trial was conducted in China and enrolled over 5,000 patients. The results of the trial showed that the use of clopidogrel for 21 days reduced the risk of recurrent stroke by 25% compared to placebo. The trial

supports the use of clopidogrel for 21 days in this population to reduce the risk of recurrent stroke, without increasing the risk of major bleeding.

The POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) was a clinical trial that aimed to evaluate the effectiveness of combining two antiplatelet drugs, clopidogrel and aspirin, in preventing recurrent stroke in patients who have had a minor ischemic stroke or high-risk TIA. The trial was conducted internationally and enrolled over 20,000 patients. The results of the trial showed that the combination of clopidogrel and aspirin reduced the risk of recurrent stroke by 21% compared to aspirin alone. Additionally, the combination therapy was found to be safe, with no increase in major bleeding events. The POINT trial provided convincing evidence for the use of combination antiplatelet therapy in patients with minor ischemic stroke or high-risk TIA, to reduce the risk of recurrent stroke.

However, due to the increased risk of bleeding, this combination is not recommended for long-term use (more than 2 or 3 years) [40] Use of each drug alone did not improve recurrent stroke or TIA rates, and the combination increased bleeding. [50]

Aspirin/Dipyridamole: 25 mg/200 mg twice daily is indicated as initial therapy for prevention of ischemic stroke recurrence and after TIA[40]. This combination, although not as well tolerated as aspirin monotherapy, was as effective as Aspirin alone for secondary stroke prevention[40].

The selection of appropriate therapy depends not only on efficacy but also on the side-effect profile of antiplatelet agents, affordability, and the patient's preference[51].

Secondary stroke prevention mechanisms in specific underlying pathologies:

In cardio-embolism, where embolism from the heart accounts for around 25% of ischemic stroke cases, these occur in atrial fibrillation, cardiomyopathy, myocardial infarction, left ventricular thrombus, valve prostheses, and patent foramen ovale.

Atrial fibrillation: it accounts for 10% to 12% of all ischemic strokes. [52] Occult atrial fibrillations may be the underlying mechanism for up to one-third of cryptogenic strokes [53]. For patients with non-valvular atrial fibrillation and adequate renal function, DOACs are indicated. [54] As for patients with valvular atrial fibrillation or impaired renal function, warfarin is to be used.[55]

MI and left ventricular thrombus: VKA anticoagulation for three months is indicated for secondary prevention after stroke due to LV thrombus.

Cardiomyopathy: Patients with dilated cardiomyopathy are at increased stroke risk due to turbulent blood flow, stagnation, and occult thrombus formation. Anticoagulation with warfarin is a secondary prevention. Atrial cardiopathy is an emerging mechanism for cardioembolic stroke and is under investigation.[52]

Prosthetic heart valve: Vitamin K antagonists are recommended for secondary prevention. The ideal International Normalized Ratio (INR) range depends on valve position and history of prior embolism.[52]

Patent Foramen Ovale (PFO): PFO alone is associated with cryptogenic stroke, especially in younger patients (<55) with a substantial right to left-sided shunting and atrial septal aneurysm. PFO closure may be considered for long-term secondary stroke prevention.[52]

Hypercholesterolemia: Low-density lipoprotein cholesterol (LDL-C) is a risk marker for ischemic stroke.[56] It has been shown that statin therapy reduces the risk of stroke recurrence.[57] First-line statins like atorvastatin or rosuvastatin, are indicated for patients following ischemic strokes regardless of their cholesterol level [58], as it has been reported that statins improve all-cause mortality, functional outcome, and the risk of stroke regardless of type. [59]

Carotid artery stenosis and reperfusion interventions: Two therapeutic procedures are available: carotid endarterectomy (CEA) and carotid artery angioplasty and stenting (CAS). CEA is a surgical intervention in which atherosclerotic plaque is removed from the internal carotid artery. CAS is a percutaneous, minimally invasive approach in treating carotid artery stenosis.[57] In older patients, CAS is associated with a higher risk of death and stroke. [60]

Stroke due to coagulation disorders: If a patient is found to have abnormal findings on coagulation testing after primary ischemic stroke or TIA if anticoagulation therapy is not administered, Antiplatelet therapy is recommended.[40]

Blood Pressure Management: The targeted blood pressure should be less than 140 mmHg systolic.[58] After a stroke, ACE inhibitors, calcium channel blockers, and thiazide diuretics are first-line options for blood pressure control,[61] with beta blockers inferior to other anti-hypertensive drugs. [62]

Risk factors of stroke recurrence

Unmodifiable risk factors:

- Age

- Previous history of cerebrovascular events, especially among older stroke patients compared to younger ones. [63]
- Stroke subtype; ischemic stroke subtypes are significant independent predictors of stroke recurrence.[64]

Modifiable risk factors:

- Hypertension[65]
- Atherogenic dyslipidemia (AD) and hyperlipidemia[65]
- Diabetes mellitus[65]
- Atrial Fibrillation.[66]

Prognosis

Stroke severity is one of the most critical determinants of the prognosis of the outcome. Stroke severity is correlated with diastolic blood pressure and serum cholesterol level in a way in a direct way. Hence, measurement and control of these prognostic factors help assess stroke outcomes and improve stroke rehabilitation.[67]

Prognosis is worse for those with intracerebral and subarachnoid hemorrhage because the 1-month mortality is especially high, approaching around 50%. The primary cause of early mortality is neurological deterioration, but later deaths are more commonly associated with cardiac disease or stroke complications.[68]

Recent Findings

A global study into the causes of stroke found that one in 11 survivors experienced a period of extreme emotions in the hour leading up to the stroke. In a research analysis of behavioral patterns in patients who suffered an ischemic stroke, the most common behavioral patterns were anger and emotional upset and were linked to an approximately 30% increase in the risk of stroke one hour after an episode. [69]

Neurons do not regenerate, though the brain can sometimes remap its neural pathways to restore some visual function after a stroke, the process is slow and inefficient and never happens for some patients. Stem cell therapy can help by reprogramming the local glial cells into neurons without the need to implant new cells, which means there is no immunogenic rejection.[70]

References

1. Sacco RL, Kasner SE, Broderick JP, et al. An Updated Definition of Stroke for the 21st Century. Stroke. 2013;44(7):2064-2089. doi:10.1161/STR.0b013e318296aeca
2. Smajlović D. Strokes in young adults: epidemiology and prevention. Vasc Health Risk Manag. 2015;11:157-164. doi:10.2147/VHRM.S53203
3. Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR. Determinants of early recurrence of cerebral infarction. The Stroke Data Bank. Stroke. 1989;20(8):983-989. doi:10.1161/01.str.20.8.983
4. Hier DB, Foulkes MA, Swiontoniowski M, et al. Stroke recurrence within 2 years after ischemic infarction. Stroke. 1991;22(2):155-161. doi:10.1161/01.str.22.2.155
5. Matsumoto N, Whisnant JP, Kurland LT, Okazaki H. Natural history of stroke in Rochester, Minnesota, 1955 through 1969: an extension of a previous study, 1945 through 1954. Stroke. 1973;4(1):20-29. doi:10.1161/01.str.4.1.20
6. Viitanen M, Eriksson S, Asplund K. Risk of Recurrent Stroke, Myocardial Infarction and Epilepsy during Long-Term Follow-Up after Stroke. Eur Neurol. 1988;28(4):227-231. doi:10.1159/000116272
7. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. Stroke. 1994;25(2):333-337. doi:10.1161/01.str.25.2.333
8. Leppävuori A, Pohjasvaara T, Vataja R, Kaste M, Erkinjuntti T. Generalized Anxiety Disorders Three to Four Months after Ischemic Stroke. Cerebrovasc Dis. 2003;16(3):257-264. doi:10.1159/000071125
9. Goldberg G, Berger GG. Secondary prevention in stroke: a primary rehabilitation concern. Arch Phys Med Rehabil. 1988;69(1):32-40.
10. Moroney JT, Bagiella E, Paik MC, Sacco RL, Desmond DW. Risk factors for early recurrence after ischemic stroke: the role of stroke syndrome and subtype. Stroke. 1998;29(10):2118-2124. doi:10.1161/01.str.29.10.2118
11. Kuriakose D, Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. Int J Mol Sci. 2020;21(20):7609. doi:10.3390/ijms21207609
12. Béjot Y, Daubail B, Giroud M. Epidemiology of stroke and transient ischemic attacks: Current knowledge and perspectives. Rev Neurol (Paris). 2016;172(1):59-68. doi:10.1016/j.neurol.2015.07.013
13. WRITING GROUP MEMBERS, Lloyd-Jones D, Adams RJ, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation. 2010;121(7):e46-e215. doi:10.1161/CIRCULATIONAHA.109.192667
14. Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355-369. doi:10.1016/S1474-4422(09)70025-0
15. Thrift AG, Dewey HM, Macdonell RA, McNeil JJ, Donnan GA. Incidence of the major stroke subtypes: initial findings from the North East Melbourne stroke incidence study (NEMESIS). Stroke. 2001;32(8):1732-1738. doi:10.1161/01.str.32.8.1732
16. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. The Lancet. 2008;371(9624):1612-1623. doi:10.1016/S0140-6736(08)60694-7
17. Doyle KP, Simon RP, Stenzel-Poore MP. Mechanisms of ischemic brain damage. Neuropharmacology. 2008;55(3):310-318. doi:10.1016/j.neuropharm.2008.01.005
18. Caplan, L., 2000. Caplan's Stroke. A Clinical Approach. Butterworth Heinemann.
19. Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. Science. 1969;164(3880):719-721. doi:10.1126/science.164.3880.719
20. Hossmann KA. Periinfarct depolarizations. Cerebrovasc Brain Metab Rev. 1996;8(3):195-208.
21. Coyle JT, Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. Science. 1993;262(5134):689-695. doi:10.1126/science.7901908
22. Halliwell B. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet Lond Engl. 1994;344(8924):721-724. doi:10.1016/s0140-6736(94)92211-x
23. Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. N Engl J Med. 2006;354(4):387-396. doi:10.1056/NEJMra052732
24. Chohan SA, Venkatesh PK, How CH. Long-term complications of stroke and secondary prevention: an overview for primary care physicians. Singapore Med J. 2019;60(12):616-620. doi:10.11622/smedj.2019158
25. Yew KS, Cheng E. Acute Stroke Diagnosis. Am Fam Physician. 2009;80(1):33-40.
26. Wintermark M, Sanelli PC, Albers GW, et al. Imaging recommendations for acute stroke and transient ischemic attack patients: A joint statement by the American Society of Neuroradiology, the American College of Radiology, and the Society of NeuroInterventional Surgery. AJNR Am J Neuroradiol. 2013;34(11):E117-127. doi:10.3174/ajnr.A3690
27. Adams HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Circulation. 2007;115(20):e478-534. doi:10.1161/CIRCULATIONAHA.107.181486
28. Masdeu JC, Irimia P, Asenbaum S, et al. EFNS guideline on neuroimaging in acute stroke. Report of an EFNS task force. Eur J Neurol. 2006;13(12):1271-1283. doi:10.1111/j.1468-1331.2006.01507.x

29. Albers GW, Caplan LR, Easton JD, et al. Transient Ischemic Attack — Proposal for a New Definition. http://dx.doi.org/10.1056/NEJMsb020987. doi:10.1056/NEJMsb020987
30. Angeli F, Verdecchia P, Reboldi GP, et al. Calcium channel blockade to prevent stroke in hypertension: a meta-analysis of 13 studies with 103,793 subjects. Am J Hypertens. 2004;17(9):817-822. doi:10.1016/j.amjhyper.2004.06.002
31. Bowler RP, Sheng H, Enghild JJ, Pearlstein RD, Warner DS, Crapo JD. A catalytic antioxidant (AEOL 10150) attenuates expression of inflammatory genes in stroke. Free Radic Biol Med. 2002;33(8):1141-1152. doi:10.1016/s0891-5849(02)01008-0
32. Barreto AD. Intravenous thrombolytics for ischemic stroke. Neurother J Am Soc Exp Neurother. 2011;8(3):388-399. doi:10.1007/s13311-011-0049-x
33. Segura T, Calleja S, Jordan J. Recommendations and treatment strategies for the management of acute ischemic stroke. Expert Opin Pharmacother. 2008;9(7):1071-1085. doi:10.1517/14656566.9.7.1071
34. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood Pressure Management in Acute Intracerebral Hemorrhage. Stroke. 2004;35(6):1364-1367. doi:10.1161/01.STR.0000128795.38283.4b
35. Owens WB. Blood Pressure Control in Acute Cerebrovascular Disease. J Clin Hypertens. 2011;13(3):205-211. doi:10.1111/j.1751-7176.2010.00394.x
36. Lindsberg PJ, Roine RO. Hyperglycemia in Acute Stroke. Stroke. 2004;35(2):363-364. doi:10.1161/01.STR.0000115297.92132.84
37. Hackam DG, Spence JD. Antiplatelet Therapy in Ischemic Stroke and Transient Ischemic Attack. Stroke. 2019;50(3):773-778. doi:10.1161/STROKEAHA.118.023954
38. Patel AT, Duncan PW, Lai SM, Studenski S. The relation between impairments and functional outcomes poststroke. Arch Phys Med Rehabil. 2000;81(10):1357-1363. doi:10.1053/apmr.2000.9397
39. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry. 1991;54(12):1044-1054. doi:10.1136/jnnp.54.12.1044
40. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(7):2160-2236. doi:10.1161/STR.0000000000000024
41. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360(4):354-362. doi:10.1056/NEJMoa0809171
42. Drepper MD, Spahr L, Frossard JL. Clopidogrel and proton pump inhibitors - where do we stand in 2012? World J Gastroenterol WJG. 2012;18(18):2161-2171. doi:10.3748/wjg.v18.i18.2161
43. Booze CD, Serebruany VL. The action of Dipyridamole to prevent thrombosis: practical implications for the treatment and prevention of stroke. Curr Treat Options Cardiovasc Med. 2006;8(3):221-227. doi:10.1007/s11936-006-0015-9
44. Iuliano L, Pedersen JZ, Rotilio G, Ferro D, Violi F. A potent chain-breaking antioxidant activity of the cardiovascular drug dipyridamole. Free Radic Biol Med. 1995;18(2):239-247. doi:10.1016/0891-5849(94)e0123-z
45. Weyrich AS, Denis MM, Kuhlmann-Eyre JR, et al. Dipyridamole selectively inhibits inflammatory gene expression in platelet-monocyte aggregates. Circulation. 2005;111(5):633-642. doi:10.1161/01.CIR.0000154607.90506.45
46. Ingerman-Wojenski CM, Silver MJ. Model system to study interaction of platelets with damaged arterial wall: II. Inhibition of Smooth Muscle Cell Proliferation by Dipyridamole and AH-P719. Exp Mol Pathol. 1988;48(1):116-134. doi:10.1016/0014-4800(88)90050-0
47. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci. 1996;143(1-2):1-13. doi:10.1016/s0022-510x(96)00308-5
48. Lindgren A, Husted S, Staaf G, Ziegler B. Dipyridamole and headache--a pilot study of initial dose titration. J Neurol Sci. 2004;223(2):179-184. doi:10.1016/j.jns.2004.05.011
49. Wang Y, Pan Y, Zhao X, et al. Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) Trial: One-Year Outcomes. Circulation. 2015;132(1):40-46. doi:10.1161/CIRCULATIONAHA.114.014791
50. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet Lond Engl. 2004;364(9431):331-337. doi:10.1016/S0140-6736(04)16721-4
51. Hankey GJ. Antiplatelet therapy for the prevention of recurrent stroke and other serious vascular events: a review of the clinical trial data and guidelines. Curr Med Res Opin. 2007;23(6):1453-1462. doi:10.1185/030079907X199727
52. Caprio FZ, Sorond FA. Cerebrovascular Disease: Primary and Secondary Stroke Prevention. Med Clin North Am. 2019;103(2):295-308. doi:10.1016/j.mcna.2018.10.001
53. Sanna T, Diener HC, Passman RS, et al. Cryptogenic Stroke and Underlying Atrial Fibrillation. http://dx.doi.org/10.1056/NEJMoa1313600. doi:10.1056/NEJMoa1313600
54. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet Lond Engl. 2014;383(9921):955-962. doi:10.1016/S0140-6736(13)62343-0
55. Tawfik A, Bielecki JM, Krahn M, et al. Systematic review and network meta-analysis of stroke prevention treatments in patients with atrial fibrillation. Clin Pharmacol Adv Appl. 2016;8:93-107. doi:10.2147/CPAA.S105165
56. Prospective Studies Collaboration, Lewington S, Whitlock G, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet Lond Engl. 2007;370(9602):1829-1839. doi:10.1016/S0140-6736(07)61778-4
57. Jensen M, Thomalla G. Causes and Secondary Prevention of Acute Ischemic Stroke in Adults. Hamostaseologie. 2020;40(1):22-30. doi:10.1055/s-0039-1700502

58. (Australian) Clinical Guidelines for Stroke Management - Chapter 4 of 8: Secondary prevention. Accessed February 10, 2022. https://app.magicapp.org/#/guideline/5017
59. Ziff OJ, Banerjee G, Ambler G, Werring DJ. Statins and the risk of intracerebral haemorrhage in patients with stroke: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2019;90(1):75-83. doi:10.1136/jnnp-2018-318483
60. Voeks JH, Howard G, Roubin GS, et al. Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. Stroke. 2011;42(12):3484-3490. doi:10.1161/STROKEAHA.111.624155
61. Pk W, Rm C, Ws A, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertens Dallas Tex 1979. 2018;71(6). doi:10.1161/HYP.0000000000000066
62. Mukete BN, Cassidy M, Ferdinand KC, Le Jemtel TH. Long-Term Anti-Hypertensive Therapy and Stroke Prevention: A Meta-Analysis. Am J Cardiovasc Drugs Drugs Devices Interv. 2015;15(4):243-257. doi:10.1007/s40256-015-0129-0
63. Fu GR, Yuan WQ, Du WL, et al. Risk Factors Associated with Recurrent Strokes in Young and Elderly Patients: A Hospital-based Study. Int J Gerontol. 2015;9(2):63-66. doi:10.1016/j.ijge.2015.02.004
64. Kang K, Park TH, Kim N, et al. Recurrent Stroke, Myocardial Infarction, and Major Vascular Events during the First Year after Acute Ischemic Stroke: The Multicenter Prospective Observational Study about Recurrence and Its Determinants after Acute Ischemic Stroke I. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2016;25(3):656-664. doi:10.1016/j.jstrokecerebrovasdis.2015.11.036
65. Suanprasert N, Tantirithisak T. Impact of risk factors for recurrent ischemic stroke in Prasat Neurological Institute. J Med Assoc Thail Chotmaihet Thangphaet. 2011;94(9):1035-1043.
66. Xu G, Liu X, Wu W, Zhang R, Yin Q. Recurrence after ischemic stroke in chinese patients: impact of uncontrolled modifiable risk factors. Cerebrovasc Dis Basel Switz. 2007;23(2-3):117-120. doi:10.1159/000097047
67. Faraji F, Ghasami K, Talaie-Zanjani A, Mohammadbeigi A. Prognostic factors in acute stroke, regarding to stroke severity by Canadian Neurological Stroke Scale: A hospital-based study. Asian J Neurosurg. 2013;8(2):78-82. doi:10.4103/1793-5482.116378
68. Hankey GJ, Jamrozik K, Broadhurst RJ, et al. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. Stroke. 2000;31(9):2080-2086. doi:10.1161/01.str.31.9.2080
69. Smyth A, O'Donnell M, Hankey GJ, et al. Anger or emotional upset and heavy physical exertion as triggers of stroke: the INTERSTROKE study. Eur Heart J. 2022;43(3):202-209. doi:10.1093/eurheartj/ehab738
70. Tang Y, Wu Q, Gao M, et al. Restoration of Visual Function and Cortical Connectivity After Ischemic Injury Through NeuroD1-Mediated Gene Therapy. Front Cell Dev Biol. 2021;9:720078. doi:10.3389/fcell.2021.720078

Article topic: Occipital Neuralgia

Author: Rana Jaffal.

Editors: Rawan Hamamreh, Mohammad Assaf.

Reviewer: Ethar Hazaimeh.

Keywords: Headache, Neuralgia, Neck Pain, Neuropathic pain, Occipital.

Overview

Neuralgia is defined by The International Classification of Headache Disorders ICHD-3 as "pain in the distribution(s) of a nerve or nerves, presumed to be due to dysfunction or injury to those neural structures. Common usage implies a paroxysmal pain quality as neuralgia, but the term neuralgia should not be reserved for paroxysmal pains". The most common neuralgias are trigeminal neuralgia, occipital neuralgia, glossopharyngeal neuralgia, and nervus intermedius neuralgia.[1,2]

Occipital neuralgia (ON), as defined by the International Headache Society, “is a headache characterized by piercing, electric-shock-like, or throbbing chronic pain in the upper neck, back of the head, and behind the ears. Usually, it is unilateral. In most cases, the pain of occipital neuralgia begins in the neck and then goes upwards, the pain could be in the scalp, forehead, and behind the eyes. The location of the pain is related to the parts supplied by the lesser and greater occipital nerves, which are run from the area where the spinal column meets the neck, up to the scalp at the back of the head.” [3]

Epidemiology

ON is a well-known disorder, but its incidence remains not accurately determined. As mentioned in a study that investigated the incidence of facial pain in a Dutch population, ON comprised 8.3% of facial pain cases. The total incidence of ON was 3.2 per 100,000 people, with a mean age of diagnosis of 54.1 years (standard deviation of 16.2 years), female dominance was present but not significant, and no time and seasonal variations were found.[4]

Pathogenesis and etiology

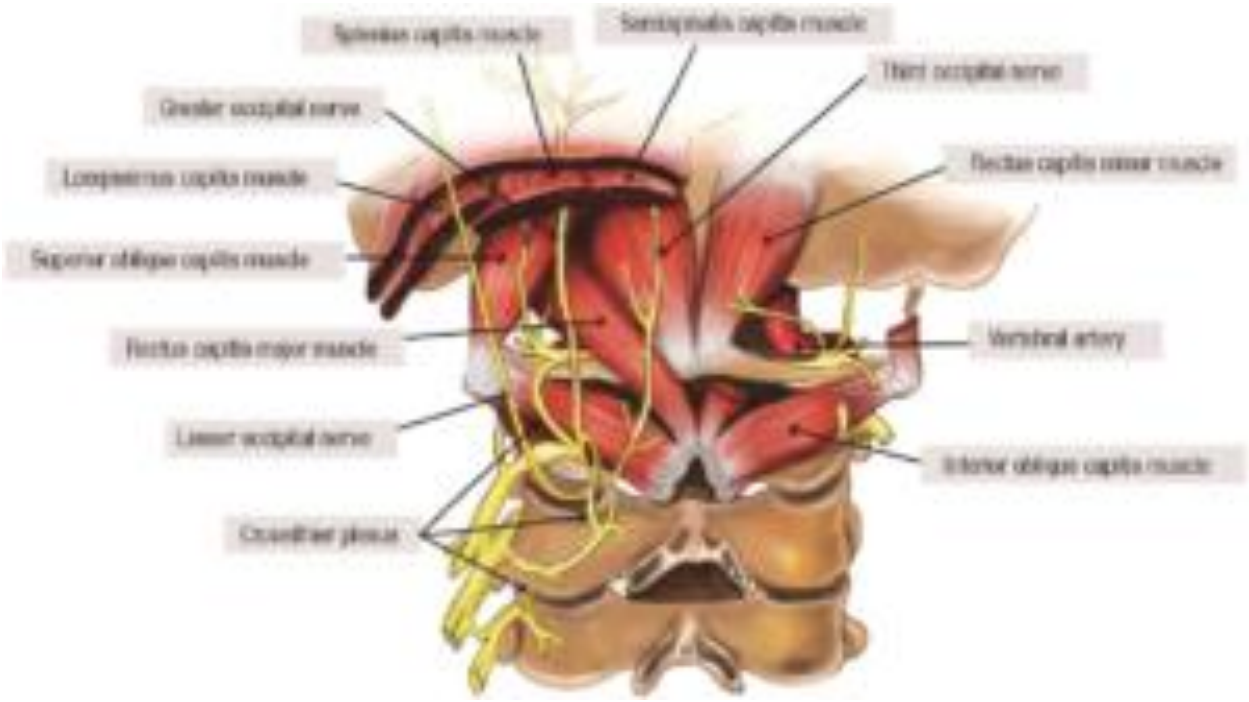


Figure (1): Anatomy of occipital nerve[/caption]

To understand ON we need to revise some basic knowledge of the anatomy of the occipital nerves, Figure (1):

Greater Occipital Nerve (GON)

Arises from the C2 dorsal ramus and then passes medially to the lower border of the obliquus capitis inferior muscle then crosses the suboccipital triangle. It then runs along the rectus capitis posterior major muscle, innervates, and pierces the semispinalis capitis muscle, pierces the tendon of the trapezius muscle passes the superior nuchal line of the occipital bone, and courses toward the apex of the scalp in the near of the occipital artery.

Lesser Occipital Nerve (LON)

Arises from the C2 ventral ramus then loops inferior to the spinal accessory nerve then ascends along the posterior border of the sternocleidomastoid muscle penetrating the deep cervical fascia and runs across the posterior edge of the sternocleidomastoid muscle then splits into three branches: the auricular, mastoid, and occipital which called cutaneous branches of LON.

Third Occipital Nerve (TON)

Arises from the dorsal ramus of C3 which divides into lateral and medial branches then, the medial branch gives rise to superficial and deep branches and the superficial branch is the third occipital nerve then curves around the dorsolateral surfaces of C2-C3 and travels along the semispinalis capitis muscle. It turns dorsally at the C2 spinous process and penetrates the semispinalis capitis, splenius capitis, and trapezius muscles and exits the muscles, and innervates a small cutaneous area right below the nuchal line. TON sends many branches to the greater occipital nerve and lesser occipital nerve which makes it difficult to distinguish the symptoms of isolated third occipital neuralgia.[5]

For GON, many areas may be compressed and result in neuralgia which include:
• C2 nerve root.
• Obliquus capitis inferior muscle.
• Semispinalis capitis muscle.
• Instances where the nerve penetrates the trapezius muscle.
• Instances where the occipital artery and greater occipital nerve intersect.

The occipital nerve is large, measuring 2.5 to 3.5 mm in diameter, which makes it more likely to be compressed.
Muscle hypertrophy, tensing, or spasm of muscles in the area contribute to compression. The condition is associated with stress and anxiety in many patients, and surgical sectioning of muscles in close approximation with the greater occipital nerve shows a relief of the pain of occipital neuralgia. In some instances, trauma and the formation of fibrocartilage calluses or other structural changes to the bony anatomy of the skull or spine can lead to this condition. Additionally, arteriovenous malformations may contribute to nerve compression.[5]

The pain is caused by irritation or injury to the occipital nerves which can be a result of 6:
• Trauma to the back of the head.
• Pinching of the nerves by overly tight neck muscles.
• Compression of the occipital nerves as they leave the spine due to osteoarthritis, tumors such as schwannomas, or other types of lesions in the neck.
• Localized inflammation or infection, gout, diabetes, blood vessel inflammation (vasculitis).
• Frequent lengthy periods of keeping the head in a downward and forward position.

However, in many cases, no cause can be found, and we confirm the diagnosis with a positive response (relief of the pain) after administration of an anesthetic drug causing nerve block.[5] Causes of ON can be classified into vascular, neurogenic, muscular, and osteogenic causes as summarized in the table:

Category	**Causes of irritation**
Vascular	•Irritation of the C1/C2 nerve roots by an aberrant branch of the posterior inferior cerebellar artery. • Dural arteriovenous fistula at the cervical level. • Bleeding from bulbocervical cavernomas. • Cervical intramedullary cavernous hemangioma. • Giant cell arteritis. • Fenestrated vertebra artery pressing on C1/C2 nerve roots. • Aberrant course of the vertebra artery.
Neurogenic	• Schwannoma in the area of the craniocervical junction: schwannoma of the occipital nerve. • C2 myelitis. • Multiple sclerosis.
Osteogenic	• C1/C2 arthrosis, atlantodental sclerosis. • Hypermobile C1 posterior arch. • Cervical osteochondroma. • Osteolytic lesion of the cranium. • Exuberant callus formation after C1/C2 fracture.

Diagnosis:

Diagnostic Criteria of The International Classification of Headache Disorders 3 (ICHD3) [6]:

A. Unilateral or bilateral pain in the distribution(s) of the greater, lesser, and/or third occipital nerves and fulfilling criteria B-D
B. Pain has at least two of the following three characteristics:
    1. recurring in paroxysmal attacks lasting from a few seconds to minutes
    2. severe in intensity
    3. shooting, stabbing, or sharp in quality
C. Pain is associated with both of the following:
    1. dysesthesia and/or allodynia apparent during innocuous stimulation of the scalp and/or hair
    2. either or both of the following:
        a. tenderness over the affected nerve branches
        b. trigger points at the emergence of the greater occipital nerve or in the distribution of C2
D. Pain is eased temporarily by a local anesthetic block of the affected nerve(s)
E. Not better accounted for by another ICHD-3 diagnosis.

Clinical Presentation

Patients with ON present with a shooting or stabbing pain in the neck that radiates over the cranium. The pain is characterized as persistent, paroxysmal aggravating, and lasts for seconds to minutes also vision impairment, ocular pain, tinnitus, dizziness, nausea, and nasal congestion can be present.[5]

Sensitivity to all forms of stimulation is common including sensitivity to light and touch, and dental pain may be present as the occipital nerve innervates the area around the ear, so patients with occipital neuralgia may feel pain in their back teeth. Developing one of these symptoms can indicate other conditions, but when they are developed together, they provide indicators for an occipital neuralgia diagnosis.[6]

Also, we can diagnose it in addition to patients' history by physical examination shows:
○ The tenderness that is detected by palpation along the course of the GON (over the occipital protuberance) and/or the LON (about 3 cm superomedially to the tip of the mastoid process).
○ Tingling may be evoked by light pressure or percussion on the nerve (Tinel's sign).
○ When patients lie on a pillow and hyperextend or rotate their neck, pain can occur ("pillow sign").

On physical examination, tenderness along the course of the GON and LON can be observed and positive Tinel's sign may be present over the nerve's distribution, especially where the GON emerges at the base of the skull, hypoesthesia or dysesthesia can also occur. The pain is located in the occipital area and may spread toward the vertex. The pain may be unilateral or bilateral but almost always begins unilaterally and may extend into a bilateral distribution over time. Bilateral symptoms are present in one-third of cases.[7]

work up:

Imaging studies.[6]

MRI is the most useful tool in the diagnosis of ON because it enables visualization of the surrounding cervical and occipital soft tissues to exclude their related diseases.

A simple X-ray is useful to exclude underlying pathologies, such as arthritis and craniocervical instability.

CT scan of the craniocervical junction can show neoplastic or degenerative bony diseases.

Diagnostic block

This is done by anesthetic drugs with or without steroid injections that reduce inflammation and block the transmission of pain signals to the brain, thus inhibiting the sensation of headache pain, but it isn't used only as a treatment tool but also used as a diagnostic tool. If a block in the occipital nerve relieves the pain, it can help confirm the diagnosis of ON, we need to know that occipital nerve block relief is not specific for ON and that false-positive results occur with migraine and cluster headaches.[6]

Risk Factors [7.8]

People with these conditions have a higher risk for ON:

• Current or previous neck injuries either whiplash which is commonly caused by rear-end car accidents or other types of injury which can be caused due to falling or an injury while playing sports.
• Previous surgery to the head or neck.
• Congenital or acquired structural defects in the head or neck/ spine such as fractures, scoliosis, kyphosis, etc.
• Repetitive stress/strain on the neck as in looking downwards on a regular basis may lead to stiff neck muscles that begin to compress one or more occipital nerves.
• Tumors and infections: tumors along the neck and spine or infections may result in nerve compression or inflammation along the muscles of the neck and shoulders. These two causes of occipital neuralgia are rare.
• Inflamed blood vessels
• Diabetes: diabetic patients are at a higher risk of headaches and head pain related to damage to their vascular system because poorly controlled diabetes can result in highly variable blood sugar that damages veins. Although diabetic pain is usually confined to the lower extremities, it can occur in the form of occipital neuralgia as well.
• Arthritis.
• Gout: is not a common cause of occipital neuralgia, but it still can occur. It is a type of arthritis that occurs when uric acid collects in the joints which causes inflammation and pain.

Differential diagnoses:

Several disorders have some similar features to ON, such as pain in the back of the neck and head, so sometimes difficult to distinguish these disorders unless other features are present.

First, we should exclude tumors, infections, and congenital anomalies such as Arnold-Chiari malformation. It is important to exclude these conditions because if they are missed by clinicians, catastrophic results may occur.[6]

Second, ON may be mistaken for migraine, cluster headache, tension headache, or hemicrania continua. ON must be distinguished from the cervicogenic headache which is a referred pain from the cervical structures as bones or soft tissues in the neck such as atlantoaxial or upper zygapophyseal joints or from trigger points in neck muscle or their insertions, ON can be distinguished from it by knowing that ON is a neuralgia from the occipital nerve, whereas cervicogenic headache is nociceptive referred pain from cervical structures.[6]

Treatment

There are many options for ON treatment, but the most conservative treatments, such as immobilization of the neck by the cervical collar, physiotherapy, and cryotherapy don't show better performance than a placebo.
Drugs such as non-steroidal anti-inflammatory drugs, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and anticonvulsants may help to relieve symptoms, and also doing therapeutic blocks after the diagnostic nerve blocks may be done.[4]

Botulinum Toxin injection has appeared as a treatment with lower side effects than many other techniques, with most recent trials showing 50% or more improvement.
It is still a common practice to use a landmark-only approach when performing greater and lesser occipital nerve blocks. For the blockade of both nerves, medication is infiltrated along the nuchal ridge although it's easy to perform and safe if done correctly, this technique may not be remarkably accurate and, as a result, could theoretically increase the risk of a false-positive result. To improve accuracy, ultrasound-guided techniques were developed. The original ultrasound-guided technique for injection of the GON targets the nerve as it courses superficially to the obliquus capitis inferior muscle at the C1-C2 level.

There are several advanced interventional procedures in clinical use including:

• Pulsed or thermal radiofrequency ablation (RFA) is used for longer-lasting relief after a diagnostic local anesthetic blockade is done. Thermal RFA aimed at destroying the nerve architecture can render long-term analgesia but also causes the potential risks of hypesthesia, dysesthesia, anesthesia Dolorosa, and painful neuroma formation. Chemical neurolysis with alcohol or phenol carries equal risks as thermal RFA, there is no such risk with pulsed RF; however, some questions compare its efficacy with other procedures.

• Neuromodulation of the occipital nerve(s) involves the placement of nerve stimulator leads in a horizontal or oblique orientation at the base of the skull where the greater occipital nerve emerges. Patients first should trial with temporary leads, and if it shows more than 50% pain relief for several days, so

is considered a successful trial, after which permanent implantation can be done. Neuromodulation also carries potential risks such as surgical site infection and lead or generator displacement or fracture after the operation.

• Ultrasound-guided percutaneous cryoablation of the GON is a commonly performed procedure. At the correct temperature, there should be stunning but not permanent damage to the nerve, but at temperatures below negative 70
degrees Celsius, nerve injury is possible.

• Surgical decompression is often considered to be the last option. A study of 11 patients shows that only two patients don't experience significant pain relief postoperatively. By surgical decompression, the mean pain episodes per month decreased from 17.1 to 4.1, also mean pain intensity scores decreased from 7.18 to 1.73. Resection of part of the obliquus capitis inferior muscle shows success in patients who experience exacerbating pain with flexion of the
cervical spine.[4]

Another popular surgical procedure is C2 gangliotomy, even though patients get several days of intermittent nausea and dizziness. As with any large nerve resection, there is a risk of developing a deafferentation syndrome, but the risk
is lower if the resection is pre-ganglionic.[4]

References

1. Tepper SJ. Cranial Neuralgias. Continuum (Minneap Minn). 2018;24(4,Headache):1157-1178. doi:10.1212/CON.0000000000000637
2. Nova CV, Zakrzewska JM, Baker SR, Riordain RN. Treatment Outcomes in
Trigeminal Neuralgia-A Systematic Review of Domains, Dimensions and Measures. World Neurosurg X. 2020;6:100070. doi:10.1016/j.wnsx.2020.100070
3. Sweet, J. A. et al. Occipital nerve stimulation for the treatment of patients with medically refractory occipital neuralgia: Congress of neurological surgeons systematic review and evidence-based guideline. Neurosurgery 77, 332–341 (2015).
4. Eapen, B. C. & Subbarao, B. S. Occipital Neuralgia. Essentials Phys. Med. Rehabil. Musculoskelet. Disord. Pain, Rehabil. 581–586 (2022) doi:10.1016/B978-0-323-54947-9.00106-1.
5. Lake S, Iwanaga J, Oskouian RJ, Loukas M, Tubbs RS. A Case Report of an Enlarged Suboccipital Nerve with Cutaneous Branch. Cureus. 2018 Jul 06;10(7):e2933.
6. Finiels PJ, Batifol D. The treatment of occipital neuralgia: Review of 111 cases. Neurochirurgie. 2016 Oct;62(5):233-240.
7. Choi I, Jeon SR. Neuralgias of the Head: Occipital Neuralgia. J Korean Med Sci. 2016 Apr;31(4):479-88.
8. Cesmebasi A, Muhleman MA, Hulsberg P, Gielecki J, Matusz P, Tubbs RS, Loukas M. Occipital neuralgia: anatomic considerations. Clin Anat. 2015 Jan;28(1):101-8.

Title of article: Foot Drop.

Author: Yahya Firas Mohammad Al-shgerat.

Editors: Almutazballlah Qablan, Sadeen Eid.

Reviewer: Adam M. Abdallah.

Keywords: Peroneal neuropathy, foot drop, drop foot, sciatic nerve, Leg crossing, Radiculopathy, common peroneal nerve palsy, common fibular nerve palsy

Overview

One of the common problems that lead to falls and injuries is foot drops. Foot drop, or common fibular nerve (CFN) palsy, describes a significant weakness of ankle and toe dorsiflexors including tibialis anterior, extensor hallucis longus (EHL), and extensor digitorum longus (EDL) which are innervated by the peroneal nerve. These muscles control the swinging of the foot during walking and control plantarflexion on heel strikes. Foot drop can occur due to conditions including muscular, neurologic, spinal, autoimmune, and musculoskeletal disorders. Depending on the etiology, treatment options differ.[1]

Anatomy

Lumbar Nerve Roots

There are 5 lumbar vertebrae. The lumbar nerve roots arise from the lateral spinal recess. The L5 nerve root emerges between the L5 and S1 vertebrae.

Lumbar Plexus

The spinal nerves L1–L4's anterior rami combine to create the lumbar plexus. Multiple nerves exit this plexus. The iliohypogastric and ilioinguinal nerves innervate the transversus abdominis and internal oblique muscles. The obturator nerve provides neural supply to the adductor muscles of the thigh. The femoral nerve is a major nerve that supplies the quadriceps femoris group and continues as the saphenous nerve, which is the sensory nerve to the medial leg.

Sciatic Nerve

The sciatic nerve is the largest branch of the lumbosacral plexus and includes nerve roots L4-S4. It courses in the posterior thigh to the popliteal fossa. Here it splits into 2 branches: the tibial and the common fibular (historically peroneal) nerves. The tibial nerve supplies the hamstrings, plantar flexors, and investors of the foot.

Common Fibular Nerve

The deep fibular nerve innervates the anterior compartment of the leg. It is an offshoot of the common fibular nerve, of the sciatic nerve. The sciatic nerve splits at the apex of the popliteal fossa into the tibial and common fibular nerves. The tibial nerve further courses down the leg, posterior to the tibia, supplying the deep muscles of the posterior leg. It terminates by separating into the medial and lateral plantar nerves of the foot. The common fibular nerve twists around the neck of the fibula and then divides and terminates into the superficial and deep fibular nerves. The superficial peroneal innervates the lateral compartment of the leg and the sensation to the dorsum of the foot. The deep fibular will supply the motor innervation to the anterior compartment of the leg and sensation to the first dorsal toe webspace.[2]

Etiology

Compressive Disorders

Entrapment syndromes of the fibular nerve at any spot along its anatomical pathway can lead to compressive neuropathy. Common fibular neuropathy at the fibular head is the most common mononeuropathy that alters the leg.[3] The fibular nerve is quite superficial near the head of the fibula, making it prone to pressure palsies. Anatomic variations of the biceps femoris muscle, between the gastrocnemius and distal biceps, can contribute to forming a tunnel that can increase the chances of nerve compression. Other contributing factors include weight loss, prolonged bedridden position, tight casts, space-occupying lesions, and bone metastasis involving the fibular head. According to reports, the piriformis muscle's two heads can compress the sciatic nerve, causing foot drop.

Compression palsies in the ICUs due to prolonged bed rest can occur. 10% of patients who stay in the ICU for longer than four weeks may develop paresis of the fibular nerve. Critical illness polyneuropathy in motor and sensory nerves can present with foot drop.[4] Weakness can be bilateral. Diabetic patients are more vulnerable to such compression neuropathies.

Lumbar radiculopathy is a common cause of foot drop; L5 radiculopathy is the most common lumbar radiculopathy and often results from lumbar disc herniation or spondylitis in the spine.[5]

There were cases of disc herniations, bony (osteophytes or sacral ala) or ligamentous (lumbosacral band and sacroiliac ligament) compression of the L5 nerve which occurs extraforaminately.[6]Bone metastasis at the fibular head, can rarely cause foot drop.

Traumatic Injuries

Traumatic injuries occur associated with orthopedic injuries such as knee dislocations, fractures, blunt trauma, and musculoskeletal injuries. Sciatic neuropathy results from a traumatic injury of the hip or secondary to surgery. Sciatic neuropathy is the second most common mononeuropathy of the lower extremity and presents with foot drop.[7]

A less common cause is lumbosacral plexopathies, resulting from traumatic injury, a complication of abdominal or pelvic surgery, or a complication of neoplasm or radiation therapy.

Neurologic Disorders

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND) or Lou Gehrig disease, is a neurodegenerative condition that causes muscular weakness, difficulties speaking and swallowing, and motor neuron loss in the anterior horn cells. The first presentation can be a painless foot drop.

Cerebrovascular disease (CVA) can manifest as hemiplegia. Foot drop is a domain of this presentation. Additional signs of upper motor neuron involvement include heightened muscular tone, hyperreflexia, and circumduction of the lower extremities when walking. Depending on the site of ischemia, aphasia can be present.

Mononeuritis multiplex involves one or more sensory and peripheral motor nerves. It is painful and asymmetrical. It can be along with AIDS, leprosy, hepatitis, granulomatosis with polyangiitis (Wegener granulomatosis), and rheumatoid arthritis. Specific nerve dysfunction can cause loss of sensation and movement. A common issue is a sciatic nerve. Vasculitis of small epineuria arteries leads to damage to the axons disrupting nerve conduction and causing muscle weakness.

Acute inflammatory demyelinating polyneuropathy (AIDP), also called Guillain-Barré syndrome, is an autoimmune process that presents progressive motor weakness, sensory loss, and areflexia. Sensory symptoms oftentimes precede motor weakness. Autonomic dysfunction usually comes with this condition. Disruption in the myelin

sheath leads to segmental demyelination. Slowing of nerve conduction velocities and conduction block is a hallmark of AIDP. Foot drops can be in the clinical presentation.

One of the most common hereditary neuropathies, Charcot-Marie Tooth (CMT) is a primary congenital demyelinating peripheral neuropathy. It affects motor and sensory nerves. The reported incidence is 1 in 25000. One of the major symptoms is foot drop and atrophy of the lower leg muscles, presenting a typical “stork leg” appearance.[8]

Somatization disorder and conversion reaction can cause foot drop. Consider a psychiatric evaluation if the workup is unremarkable. Needle electromyography (EMG) and nerve conduction studies (NCS) will appear normal in cases of poor or no effort for ankle dorsiflexion or other motor groups**.**

Epidemiology

The incidence of fibular neuropathy is variable. According to research, the prevalence was 19 per 100000 persons, with more men than women affected. After total knee replacement, the incidence is reported as 0.79 with a slight male overbalance of 2.8: 1, respectively.[9] 90% are unilateral. The effect was equal on both sides.

ALS -The worldwide incidence of ALS yearly is assessed to be 1.54 per 100000.[10] ALS can affect people at any age, but the highest incidence is at 50 to 75 years. The actual incidence of mono neuritis multiplex in the United States and the rest of the world is unknown. The reported incidence of AIDP was 1.0 to 1.2 per 100000 every year and increased linearly with age, men are more affected than women by 1.5 times.[11]

Pathophysiology

To understand pathophysiology and predict the future prognosis of peripheral nerve injury, it is necessary to understand the nerve injury classification. In 1943 Seddon and 1953, Sunderland proposed the classification: (1) neurapraxia, (2) axonotmesis, and (3) neurotmesis.

In neuropraxia, myelin is damaged, but the axons are intact. The endoneurium, perineurium, and epineurium remain uninjured. The conduction of nerve impulses is changed at the site of injury. This is clinically interpreted as sensory loss and weakness. In EMG, this reflects latency and slow nerve conduction velocity across the compressed segment. This type of injury heals the best.

In axonotmesis, the axon is damaged, but the epineurium and perineurium remain undamaged. These nerves show sensory and motor deficits below the location of nerve injury when stimulated. Recovery is possible in the long term but unguaranteed.

Neurotmesis is the worst type of nerve injury. Myelin, axons, and supportive connective tissue are altered. Wallerian degeneration happens distal to the site of injury. This is clinically manifested as sensory and motor deficits. Unplanned recovery is not possible. Surgical intervention, including nerve grafting or tendon transfer, is sometimes necessary.[12,13]

Histopathology

Depending on the level of compression, inflammation, or trauma, neurapraxia, axonotmesis, or complete neurotmesis can happen.

Neurapraxia results in transient damage to the myelin sheath but spares the nerve. Recovery is often complete. Axonotmesis includes the interruption of the axon and myelin. While the connective tissue is preserved. Wallerian degeneration occurs. EMG performed 2 to 4 weeks later shows denervation potentials called fibrillations and positive sharp waves in the included muscles distal to the injury.

Axonotmesis is usually the result of a more severe crush or contusion but can occur when the nerve is extended (without damage to the epineurium). Through regeneration, the nerves regrow distally as fast as 2 to 3 mm per day or as slowly as 1.5 mm per day. Regeneration happens over weeks to years.

Neurotmesis is an injury in which the nerve is completely cut, such as in penetrating trauma. There is no intact myelin, and the axons are completely damaged. Endoneurium tubes and connective tissue components are damaged, disrupted, and/or transected, and the perineurium may be protected. Recovery has no chance to occur without surgical re-anastomosis.

Toxicokinetic

A wide variety of chemicals and other toxins can affect skeletal muscles, central, and peripheral nervous systems directly. The properties of these agents and their effects are not always symmetric and are beyond the intended scope of this article, however, toxic effects and a thorough history of chemical exposure should be thought of in the workup of any patient with weakness.

History and Physical

A careful history and physical exam can help recognize the cause of foot drops.

You should watch the patient do the toe stand, heel stand, and deep knee bend exercises prescribed by standard musculoskeletal testing. Medical research council (MRC) scale

rating 0-5 for the major muscle groups to the lower extremities, including ankle plantarflexion, ankle dorsiflexion, ankle inversion, ankle eversion, knee extension, knee flexion, and hip flexion, should be attained. Finding peripheral nerves and lumbar dermatomes should be the aim of a neurosensory pinprick examination in the distribution. Manual motor testing may effectively measure muscle mass using a side-by-side comparison, identifying the primary muscle group bulk locations. Side-to-side circumference measurements can be obtained and documented to note the progression or recovery of mass further down the road. The ASIA (American Spinal Cord Injury Association) point and motor groups are a standardization convenient for communication between healthcare professionals, but it does not include evaluation of specific peripheral sensory nerves.

A formal electrodiagnostic medicine consult, including EMG and NCS, is an extension of the physical examination and may need to be obtained from the subspecialist who is not commonly the first clinician to be involved in the care of the patient.

Any damage affecting the neuraxis from the roots to the peripheral nerve can incapacitate the muscles supplied by that nerve.

A lesion of the L5 root, lumbar plexus, sciatic nerve, common peroneal, or deep peroneal nerve can lead to foot drop due to the weakness of the anterior compartment musculature. The presenting symptom is the inability to walk as before. Weakness of the muscles in the foot that aids in dorsiflexion. Pain may or may not be present. The person will not be able to dorsiflex during the heel strike. The foot will remain flat on the ground. Sometimes it can also cause toe drag and incapability to clear the foot. This can lead to falls.

Radiculopathy affecting the fifth lumbar nerve root results in neuropathic pain starting in the lumbar region and radiating down the posterior thigh, anterolateral leg to the foot down to the big toe. Sensory symptoms include the medial aspect of the foot and the first webspace. Motor symptoms involve weakness of dorsiflexion and eversion of the foot.

Lumbosacral plexopathies can present with similar sensory and motor problems that are similar to sciatic neuropathy. Weaknesses may also involve hip girdle muscles, including hip abduction (gluteus Medius) and hip extension (gluteus maximus).

Sciatic neuropathy presents with sensory loss of the whole foot and weakness of ankle plantar flexors (gastrocnemius, soleus) and ankle inversion. A "flail foot" may result from it. Knee flexion may alter because of the involvement of the hamstring muscles as well. Incomplete sciatic neuropathy can present as a common peroneal neuropathy. Often, the peroneal fascicles in the sciatic nerve are more prone to injury than the tibial fascicles.

In common fibular neuropathy, the patient complains of sensory and motor deficits. History may include leg crossing, continuous kneeling, immobility, or trauma. Sensory loss or paresthesia impacts the lateral leg below the knee and the anterolateral foot. Muscle weakness affects ankle dorsiflexion (tibialis anterior), toe extension (e.g., extensor hallucis longus), and ankle evertor muscles (peroneus longus and brevis).

If only the deep fibular portion is affected, minimal sensory deficits (limited to the web space between the first two digits) and isolated weakness of toe and ankle extensors are seen. Ankle eversion and inversion will be normal.

Isolated superficial fibular neuropathy is infrequent and presents as the sensory deficit of the foot except for the first webspace. Ankle eversion/inversion may be affected merely.

60% of the normal gait cycle forms the stance phase and 40% of the swing phase. When one foot is in the swing phase, the other foot is in the stance phase. The cycle starts with a heel strike and ends with a heel strike on the same side. Throughout the stance phase, the foot remains flat. The foot is in dorsiflexion in the heel strike, preparing for gradual lowering prior to the stance phase. In the malfunction of dorsiflexion, the foot remains in plantar flexion during the stance phase. This arrests the ability to clear the ground and prepare for the next phase of the gait cycle. The patients either pull their toes or lift their foot high to clear the ground.

Evaluation

After a thorough physical exam, diagnostic testing should include plain radiographs of the pelvis and tibia, and fibula to rule out fracture or dislocation. MRI can be indicated in suspected plexopathies due to space-occupying masses. MRI of the lumbar spine, knee, and or ankle may be indicated for possible soft tissue masses in cases of compressive neuropathies. MSK ultrasound is also obtained for evidence of swelling at or proximal to the site of compression.

In the case of collagen vascular diseases, rheumatoid factors, ANA, and relevant labs should be checked. You might consider performing a CBC differential and a chemistry panel to exclude other etiologies.

In many cases, an electrodiagnostic study is an important test to confirm the clinical diagnosis or provide an alternative localization and diagnosis. This study can also assess the injury severity and provide information regarding prognosis. This study contains two domains: NCS (nerve conduction studies) and needle electromyography (EMG).

Nerve conduction studies provide information about the viability of myelin. Nerve compression is interpreted as a delay in conduction latency. The presence of delayed

latency, and slow velocity, along with the conduction block at the involved segment, indicates nerve compression.

Needle electromyography: Muscles supplied by the nerve under study get injections from monopolar needles. Motor unit potential thus obtained is noticed for amplitude, firing rates, and recruitment patterns. Positive sharp waves and fibrillation potentials, which indicate axonal involvement, are potentials that indicate the presence of muscle innervation. Nerve conduction studies and EMG together help the observer to identify the site, and severity of the lesion and estimate the prognosis for recovery. The absence of denervation potentials along with the presence of sufficient, viable motor units on needle EMG points to a good prognosis.[14]

Evidence of denervation potential coupled with an absence of viable motor units denotes a poor prognosis for recovery.

Autoimmune and critical illness neuropathy and myopathy usually exist across the spectrum, and often a thorough, extensive workup simply results in a "clinical syndrome" rather than a perfect crystal-clear diagnosis.

Management

Approach to the Patient

The approach to a patient counts on the etiology of foot drop and the nature of the compressive lesion. Based on the evaluation and diagnostic findings, multiple options exist.

Surgical Options

In trauma cases, for nerve transection, nerve reconstruction must take place within 72 hours of injury. Primary nerve repair techniques and autologous nerve grafts are usually performed.

For complete nerve compression, necrolysis and nerve decompression surgery should be performed. Return to function has accounted for about 97%.[15] A surgical release may be necessary for patients with equinus deformity.

When there is severe nerve dysfunction, tendon or nerve transfers may be necessary.[5] A detailed discussion of surgical modalities is beyond the scope of this article.

For the other etiologies, treatment is conservative as a first step because there may be a chance of partial or complete resolution of symptoms spontaneously over time.

Conservative Management

This includes physical therapy and or splinting and pharmacological therapy to control pain. The goals of conservative management are to stabilize the gait and prevent falls and contractures. Muscle strengthening and stretching are the main focuses of physical therapy. Electrical stimulation techniques for weakened dorsiflexion have shown some hope. A home exercise program should be an integral part of therapy- specifically to maintain muscle groups' strength and range of motion that prevent flexion contracture.

Using splinting reduces contractures. For complete nerve palsies with insufficient recovery, an ankle-foot orthosis (AFO) is indicated to prevent further plantarflexion. Sufficient education and training should be included to aid in the proper usage and maintenance of the brace. For patients with numbness, instructions for skincare to prevent abrasions and ulcerations are an important part of management and are often coordinated with the orthotist fabricating the AFO.

The management of pain may involve the use of opioids, membrane stabilizers, serotonin reuptake inhibitors, and topical analgesics. But are not likely to result in clinical recovery.

Follow-up electrodiagnostic studies to reappraise the situation and look for reinnervation should also be part of the treatment planning.

Differential Diagnosis

Upper motor neuron involvement

Stroke can induce weakness of the whole extremity. Due to spasticity, the limb appears artificially long. To ambulate, the person rotates the leg in a semicircular fashion, also known as circumduction. Dysphagia, aphasia, or upper limb weakness are also apparent.

Cerebellar gait, the cerebellum is responsible for the delicate and balanced gait. Cerebellar gait deficits exhibit ataxia and failure to walk in tandem.

Ataxic gait, Presents bilaterally. Due to the involvement of long tracks of the spinal cord, position, and vibration impulses are lost. This leads to excessive steppage and swaying from side to side, a symptom of alcohol use disorder.

Extreme L5 lumbar radiculopathy.
Parkinsonian gait

Involvement of substantia nigra causes failure of the smooth transition of the gait cycle leading to initiation problems along with short and fast steps called festinate gait.

Lumbar plexus pathologies

The potential exists for the space-occupying lesion to affect the lumbosacral plexus and end in leg weakness. In situations with otherwise inexplicable weakness, it is important to investigate underlying cancer as well as any other constitutional complaints. However, a propensity for genital femoral neuropathy and weakness of knee extension is more common in these cases.

A history of radiation treatment can cause radiation-induced plexopathy. Typically, the electrodiagnostic study manifests specific "myokymic discharges." Patients who need radiation therapy to the region should take the possibility of recurrence into consideration. It is essential to plan the patient's early range of motion and potential strengthening. If the patient requires long-term bracing, the electrodiagnostic examination may be useful in determining whether this is the best course of action. It may also aid in determining whether the weakness is likely to worsen or spread to other motor groups. Early placement into the ankle dorsiflexor brace improves gait mechanics, decreases falls, and aids in minimizing other secondary musculoskeletal complaints from the altered gait cycle.

Diabetic amyotrophy

Medical Oncology

Medical oncologic issues may emerge in cases of underlying malignancy, or space-occupying lesions. Previous chemotherapeutic agents can also result in peripheral neuropathy, which is often symmetric and distal. However, this or any etiology for underlying peripheral neuropathy may cause peripheral nerves to be more prone to compression.

Conversion reaction, somatization disorder, and malingering should be investigated if the workup is unremarkable, and there is potential for substantial secondary gain, depression, anxiety, or other suspected psychological issues.

Staging

It is essential to consider bracing, adapted equipment, and long-term management preparation. In addition to treating the foot drop itself, rehabilitation medicine treatments and other forms of therapy should target the underlying etiology. Staging will depend upon the underlying pathology such as multiple sclerosis or Lou Gehrig's disease being treated differently in terms of staging compared to lumbar spinal pathology.

Prognosis

The prognosis depends both upon the degree of insult and the underlying diagnosis.

Neurapraxia has the best prognosis, and patients often recover in about three months. In the case of axonal loss, recovery shows over 6 to 12 months. Neurotmesis has a guarded prognosis and may require surgery with either a nerve transfer or tendon transfer. The best time to refer to a peripheral nerve surgeon is approximately 6 to 9 months after injury. Denervated muscle does not recover significantly after 18 months.[15]

In cases of other etiologies such as Lou Gehrig's disease or space-occupying lesions, the prognosis will be different and depend upon the diagnosis itself rather than the peripheral nerve involvement.

Complications

Complications can be a result of nerve damage itself or a result of gait aids and braces. Nerve damage leading to foot drops impairs the ability to clear the foot resulting in a fall. Gait aids such as walkers and canes can also be helpful, especially on uneven surfaces. Anesthetic skin can be a source of ulceration and infection. Abrasions can be a consequence of poorly fitting braces. Bracing may need to be variable depending upon muscle bulk change. In cases such as renal failure and congestive heart failure, different brace sizes for different phases of edema and swelling may need to be provided.

Postoperative and Rehabilitation Care

As outlined above, physical therapy and occupational therapy can play an important role in whether the patient had conservative or surgical management.

The involvement of the patient in every step of the decision-making process is essential for a successful outcome. It is important to educate the patient and their family on the pathology, etiology, diagnosis, and severity of the disease process. Handouts and specific instructions should involve home exercise programs, skincare, and brace maintenance.

Conclusion

Foot drop is an inability to lift the forefoot because of weakness in the dorsiflexors. This can be a result of muscular-skeletal or nervous system pathology. A full evaluation should include medical history, physical examination and necessary imaging, and or electrodiagnostic studies. There are surgical and non-surgical procedures available, depending on the etiology. The prognosis depends upon the range of nerve damage and the viability of the remaining muscles. A comprehensive approach, including referrals to appropriate services, will give a better outcome. Careful analysis of the presenting history and physical examination is vital to arrive at the proper diagnosis. Management is subjunctive upon diagnosis and severity.

References

1. Stewart, J. D. Foot drop: where, why and what to do? *Pract Neurol* **8**, 158–169 (2008).
2. Lezak, B. & Summers, S. Anatomy, Bony Pelvis and Lower Limb, Leg Anterior Compartment. *StatPearls* (2021).
3. van Zantvoort, A., Setz, M., Hoogeveen, A., van Eerten, P. & Scheltinga, M. Chronic lower leg pain: entrapment of common peroneal nerve or tibial nerve. *Der Unfallchirurg 2019 123:1* **123**, 20–24 (2019).
4. García-Martínez, M. Á., Montejo González, J. C., García-de-Lorenzo y Mateos, A. & Teijeira, S. Muscle weakness: Understanding the principles of myopathy and neuropathy in the critically ill patient and the management options. *Clinical Nutrition* **39**, 1331–1344 (2020).
5. Carolus, A. E. *et al.* The Interdisciplinary Management of Foot Drop. *Dtsch Arztebl Int* **116**, 347 (2019).
6. Takaishi, Y. *et al.* [Surgical Results of Lumbar Degenerative Disease with Foot Drop]. *No Shinkei Geka* **47**, 851–857 (2019).
7. Distad, B. J. & Weiss, M. D. Clinical and Electrodiagnostic Features of Sciatic Neuropathies. *Phys Med Rehabil Clin N Am* **24**, 107–120 (2013).
8. Pisciotta, C. & Shy, M. E. Neuropathy. *Handb Clin Neurol* **148**, 653–665 (2018).
9. Speelziek, S. J. A., Staff, N. P., Johnson, R. L., Sierra, R. J. & Laughlin, R. S. Clinical spectrum of neuropathy after primary total knee arthroplasty: A series of 54 cases. *Muscle Nerve* **59**, 679–682 (2019).
10. Punjani, R., Wagner, L., Horton, K. & Kaye, W. Atlanta metropolitan area amyotrophic lateral sclerosis (ALS) surveillance: incidence and prevalence 2009–2011 and survival characteristics through 2015. *https://doi.org/10.1080/21678421.2019.1682614* **21**, 123–130 (2019).
11. Leung, J., Sejvar, J. J., Soares, J. & Lanzieri, T. M. Guillain-Barré syndrome and antecedent cytomegalovirus infection, USA 2009–2015. *Neurological Sciences* **41**, 885–891 (2020).
12. Bowley, M. P. & Doughty, C. T. Entrapment Neuropathies of the Lower Extremity. *Med Clin North Am* **103**, 371–382 (2019).
13. Lezak, B. & Summers, S. Anatomy, Bony Pelvis and Lower Limb, Posterior Tibial Artery. *StatPearls* (2019).
14. Cherian, R. P. & Li, Y. Clinical and Electrodiagnostic Features Of Nontraumatic Sciatic Neuropathy. *Muscle Nerve* **59**, 309–314 (2019).
15. Matejcik, V. & Penzesova, G. Surgery of the peripheral nerves. *Bratisl Lek Listy* **107**, 89–92 (2006).

Article Topic: Central Pontine Myelinolysis.

Author: Hosam Aldeen Katba Badar.

Editors: Almutazballlah Qablan, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: pons, demyelination, hyponatremia, osmolyte, electrolyte.

Introduction

Central pontine myelinolysis (CPM) is a neurological disorder defined as well-formed symmetric damage to the myelin and to the oligodendrocytes in the pons with the preservation of neurons and axons. Extrapontine myelinolysis (EPM) on the other hand, is characterized by lesions in the thalamus, cerebral cortex, striatum, and other areas [1]. Typical clinical manifestations of myelinolysis include paralysis, dysarthria, and altered mental status [2]. Typically, CPM is secondary to the rapid correction of hyponatremia [1].

The condition was first reported by Adams and Victor in 1959, who reported "pontine myelinolysis" in alcoholic patients on pathophysiological and forensic findings [3]. As an increasing number of manifestation sites in addition to the pons were detected, CPM and EPM were combined and are commonly referred to as osmotic demyelination syndrome (ODS)[1].

Although early authors including Adams and Victors who first documented the condition focused on alcoholism as an etiology for CPM, it was not until the late 1970s that the association with electrolyte abnormalities [4] and the connection to rapid correction of hyponatremia was entrenched [5-7].

CPM is one manifestation of ODS. However, brain demyelination that is associated with the rapid correction of hyponatremia may be more diffuse and it is not always limited to the pons [8-12].

Etiology

There are many underlying causes and important comorbidities. All share the development of CPM because of a severe prior disease or its treatment. While most of the early publications described chronic alcohol use and alcohol withdrawal as being the critical comorbidity in more than 40% of cases, more recent work as well as some of the older literature places prior hyponatremia and the rapid correction of it as the most common cause, occurring in 30% to 78% of cases [13-16]. Severe hyponatremia (serum

sodium levels <120 mmol/L) is often present in around 47% of reported cases [17]; however, the bulk of cases have additional concomitant cofactors, each of which alone can trigger CPM [14].

Hyponatremia is the leading pathology in the majority of cases, in addition to hyponatremia, other electrolyte imbalances can be the cause of CPM. General electrolyte disequilibria and osmotic imbalances have been reported, especially hypernatremia, hypophosphatemia, and hypokalemia [17].

Almost any electrolyte imbalance can be the causative agent. Severe hypokalemia is especially important as a sole determining factor as well as a cofactor, particularly for patients in intensive care units [17,18].

The brain's adaptation to hyponatremia

The brain can adapt to hypotonicity and hyponatremia that develops over more than two to three days and is not associated with severe brain swelling; it is therefore much less likely to be complicated by seizures and comas, or brain herniations [8]. However, once the brain has already adapted to hypotonicity, the rate of correction of hyponatremia becomes extremely significant. Rapid correction of hyponatremia and especially severe hyponatremia can lead to CPM.[10] By contrast, rapid correction is not likely to induce CPM in patients with severe hyponatremia that has only been present for several hours or for a short amount of time since cerebral adaptation is at an early stage. An example includes acute water intoxication in marathon runners or psychotic patients, the rapid correction, in this case, does not usually lead to CPM in these patients. [8-12]

The significance of the Duration of hyponatremia

Studies conducted on experimental animals showed that brain damage does not occur when hyponatremia of less than one day's duration is swiftly corrected [19,20] nevertheless if hyponatremia persists for more than 2 days, the same exact treatment results in usually fatal demyelinating brain lesions. [19-29]

Similar findings have been found in humans. Neurologic deterioration after a rapid correction of hyponatremia is improbable in patients with severe hyponatremia that develops over a few hours, especially in those whose normal water excretory capacity rapidly returns the serum sodium to a normal level. Examples include the ingestion of massive amounts of water over the span of several hours by marathon runners, psychotic patients, and users of ecstasy. [9,10,30,31]

In these patients, hyponatremia develops swiftly, and the brain does not have time to fully adapt to the change in osmolarity. On the other hand, patients who develop

hyponatremia over the span of several days have time for brain adaptation to occur and may develop CPM after rates of correction that are typically tolerated in patients with self-induced acute water intoxication. [8-12,30]

Clinical presentation

Clinical manifestations of CPM are highly variable. However, its time course is distinctive and central to diagnosis. Rapid elevation of the serum sodium concentration stereotypically precedes the process of demyelination and its symptoms by 1 to 14 days. The relatively stable clinical interval is then followed by CPM-induced secondary deterioration [14,32].

If the pons and the corticospinal and bulbar tracts are affected, patients present with recurrent encephalopathies and signs of insult to the brainstem[14]. With the involvement of the corticobulbar pathway, patients are affected by dysarthria and dysphagia (3.2% to 11.5% of cases), and brisk jaw jerks are commonly present. [14,11]

If the corticospinal tracts are affected, initially flaccid and later spastic quadriparesis of varying severity materialize (in 9.8% to 28.8% of cases) this is usually seen in the first 5 days of the onset of symptoms, hyperreflexia, and bilateral Babinski signs are a common finding during this stage. [14,11]

If tegmental lesions are present, ocular, and pupillary motility may also be affected (about 8% of all CPM). [14] In severe cases, the symptoms may lead to locked-in syndrome, a rare neurological disorder in which there is complete paralysis of all voluntary muscles except for the ones that control the movements of the eyes. [32] Severe disorders of consciousness occur in 6.1% to 14% of cases. [14]

Other common physical findings include increased muscle tone, facial weakness, and snout, grasp, or rooting reflexes. [11]

Workup and diagnosis

No correlation can be shaped between the diagnostic findings and the clinical outcome, due to insufficient research evidence. [33,34]

Laboratory workup

Knowing that the primary predisposing factors are electrolyte disturbances (especially the rapid correction of chronic hyponatremia). A suspected diagnosis of CPM should be supplemented by laboratory diagnostics and a good medical history. The laboratory parameters to be examined are serum sodium, serum potassium, and liver values

(especially in the cases of previous liver transplants), as well as parameters for evaluation of the nutritional status (e.g., vitamin B12, methylmalonic acid, folic acid, and phosphate in serum). [35]

Imaging

Magnetic resonance imaging

MRI is more sensitive than computed tomography for detecting the typical demyelination lesions in CPM. [36,37] Nonetheless, even an MRI may not become positive for as long as four weeks after the beginning of the disease. Therefore, an initially negative radiologic study in a patient who developed neurologic symptoms after overly rapid correction of hyponatremia does not exclude CPM, a repeat MRI should be obtained after several weeks. [37,38]

There is no clear best timing of MRI imaging. A positive MRI finding can sometimes be present as recently as the first day after the onset of symptoms. [38,39] However, cases have also been reported where the MRI findings were initially unobtrusive and first pointed to the diagnosis at a follow-up examination several weeks later. [37,38]

MRI is likewise beneficial in providing evidence for milder courses of the disease[37,38]. This has considerably improved the assessment and prognosis of CPM. [37]

MRI course and sequences: Demyelination sites display hyperintensity in T2-weighted and T2-FLAIR sequences and show hypointensity in T1-weighted sequences, occasionally gadolinium enhancement is also demonstrated (Figure 1) [36,40,41].

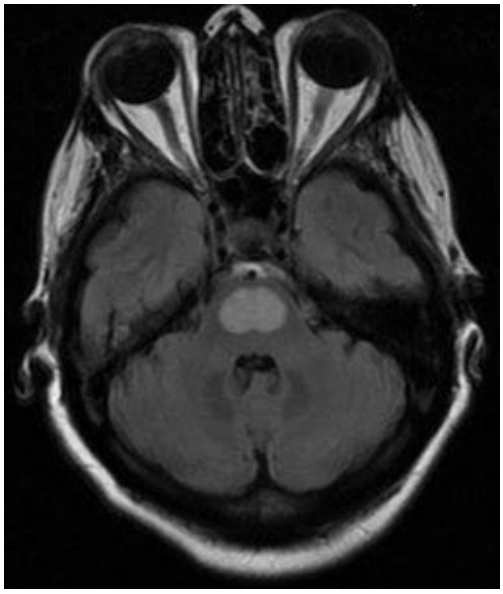


Figure (1A): Axial FLAIR, Oval lesion on pons that hyperintense on T2 and FLAIR, in CPM case. (62)

Figure (1B): Axial T2, Oval lesion on pons that has hyperintense on T2 and FLAIR. Symmetrical. (62)

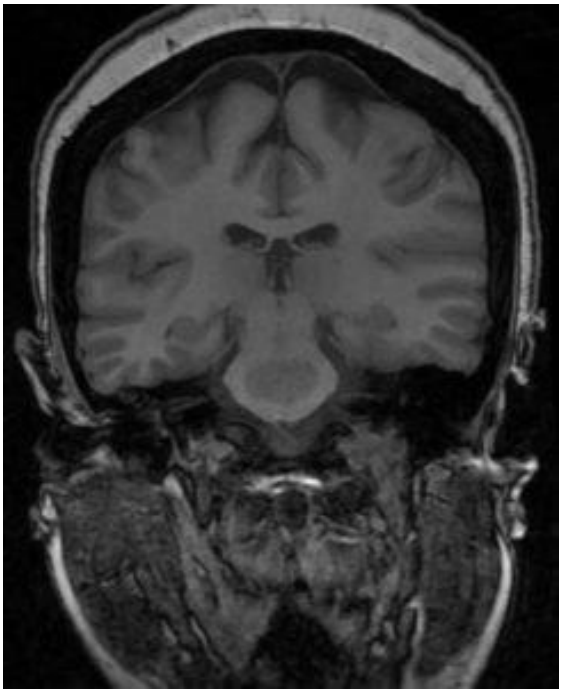


Figure (1C): Coronal T1, Oval lesion on pons that has a hypo-intense signal on T1 (62).

Cranial computed tomography

Cranial computed tomography (CCT) can also be used to confirm clinical CPM but has significantly lower sensitivity than MRI imaging. (initial detection rate of CCT: 25% to 28.5%). [36,39]

Management

Patients who have developed CPM as a result of hyponatremia correction typically require intensive supportive therapy and should have their serum sodium re-lowered .[51]

Serum sodium re-lowering

The optimal target serum sodium and rate of relowering in patients with CPM have not been defined[51]. Data in humans are currently limited to case reports that suggest benefit from the early relowering of the serum sodium in patients who have developed symptoms of CPM. [42-45] As an example, a case report published in the journal of clinical nephrology described the case of a 71-year-old woman who developed symptomatic hyponatremia with serum sodium of 106 mEq/L in association with a thiazide diuretic. [43] The administration of isotonic saline solution was associated with an increase in serum sodium of 21 mEq/L in the first 24 hours. After initial neurologic improvement, the patient's condition deteriorated after 72 hours. The administration of hypotonic fluid and desmopressin relowered serum sodium so that the final elevation was only 9 mEq/L. The patient then recovered without any neurologic sequelae .[43]

A similar result was documented in another case report in which serum sodium was raised by 23 mEq/L in the first 48 hours (figure 2). [44] After the onset of the neurological symptoms, the patient's serum sodium was lowered from 132 to 120 mEq/L. The patient then had a full neurologic recovery over the ensuing 36 hours. [44]

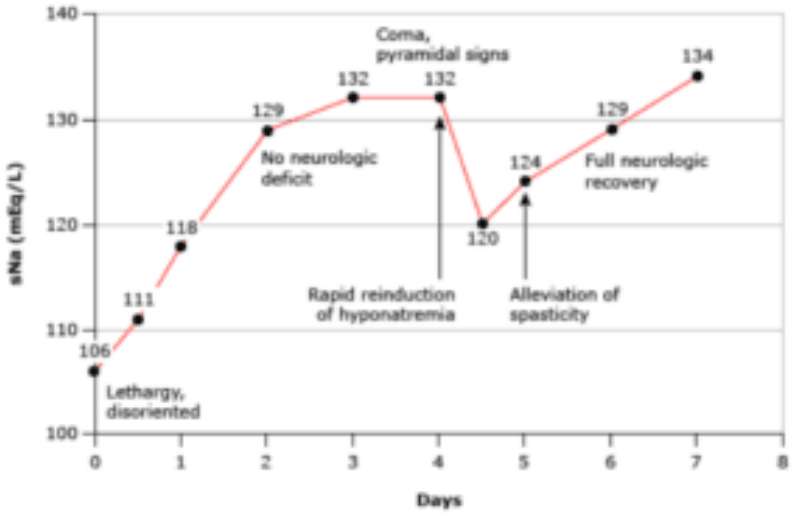


Figure 2: Reinduction of hyponatremia to treat central pontine myelinolysis 60.

Supportive therapy

Some patients with CPM recover functionally after extended periods of severe neurologic impairment .[47] Therefore, aggressive supportive therapy should be provided to all patients who were functioning well prior to the onset of CPM[47]. Since patients with severe CPM commonly develop aspiration pneumonia and respiratory failure, endotracheal intubation and ventilator support are usually required. Recovery from hopeless neurologic deficits does occur, thus, supportive therapy should be continued for a minimum of six to eight weeks before concluding that the newly acquired neurological deficits are irreversible [12,46,47].

Prevention

The severity of the initial electrolyte disturbance and the rate of its correction plays a critical role in developing CPM. In severe hyponatremia (<120 mmol/L), the incidence of CPM is substantially reduced by very slow correction of sodium, no more than <0.5 mmol/L per hour and <12 mmol/L per day.[48] For hyponatremia (>120 mmol/L), the rate of sodium correction does not seem to play an important role in developing CPM. [32]

The goal of treatment for hyponatremia is to initially achieve euvolemia, then to attain balanced osmolality. If hypokalemia is also present with hyponatremia, it must be treated first. [49]

Depending on the cause of the hyponatremia, another potential approach is the use of vasopressin antagonists to enhance the elimination of water without concomitant loss of electrolytes. The selective V2 receptor antagonist 'tolvaptan' has been approved for this indication. [50] Due to the associated risks and a lack of outcome data [51], however, the use of this antagonist is reserved for severe refractory cases after careful consideration. [51] The risks include the danger of overcorrection, onset of hyperkalemia, and dangers associated with an initially critical, highly frequent monitoring of electrolyte and volume status. [51]

Risk factors for developing CPM

Several risk factors appear to increase susceptibility to osmotic demyelination and CPM. When these factors are present, CPM can develop even at less severe degrees of hyponatremia and at slower rates of correction. [9,10,19,52-56] These include alcoholism, malnutrition, liver diseases, liver transplantation, and hypokalemia. [52,57] In a large study that included 83 patients with MRI-documented CPM, for example, 70% of the patients had an alcohol use disorder and 68% had hypokalemia. [52] Women of childbearing age are thought to be more vulnerable to fatal cerebral edema associated with acute

hyponatremia. [58] Nevertheless, there is no evidence that gender increases the risk of CPM. [57]

Prognosis

Up to the mid-1980s, CPM was thought to have a consistently poor outcome because the diagnosis was only confirmed by autopsy[5]. However, recent work has shown that good recovery from CPM is not rare, and that total or near-total remission of the severe symptoms is possible. [47]

Recent work describes a much brighter prognosis, with a good outcome in about 33% to 50% of cases. [34,36] About 24% to 39% of CPM patients reach normal neurological function; while another 16% to 34% are minorly affected and are self-sufficient in all activities of daily life. [59,34,37] In contrast, approximately 33% to 55% of patients will require some care, be fully dependent on care, or will die. [59,34,36]

Predictors of a poor outcome were severe hyponatremia of <114 mmol/L and hyponatremia with hypokalemia[14]. Liver transplant patients who have clinically noticeable symptoms have the worst outcome. [14,61]

References

1. Singh TD, Fugate JE, Rabinstein AA (2014) Central pontine and extrapontine myelinolysis: a systematic review. Eur J Neurol 21(12):1443–1450. https://doi.org/10.1111/ene.12571
2. Sterns RH, Riggs JE, Schochet SS Jr (1986) Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med 314(24):1535–1542. https://doi.org/10.1056/nejm198606123142402
3. ADAMS RD, VICTOR M, MANCALL EL. Central pontine myelinolysis: a hitherto undescribed disease occurring in alcoholic and malnourished patients. AMA Arch Neurol Psychiatry. 1959 Feb;81(2):154-72. PMID: 13616772.
4. Tomlinson BE, Pierides AM, Bradley WG: Central pontine myelinolysis: two cases with associated electrolyte disturbance, Q J Med 45:373-86, 1976
5. Kleinschmidt –DeMasters BK, Rojiani AM, Filley, CM: Central and extrapontine myelinolysis: then and now, J Neuropathol Exp Neurol 65: 1-11, 2006
6. Kleinschmidt-Demasters BK, Norenberg MD: Rapid correction of hyponatremia causes demyelination: relation to central pontine myelinolysis, Science 211:1068-70, 1981
7. Brown WD: Osmotic demyelination disorders: central pontine and extrapontine myelinolysis, Curr Opin Neurol 13: 691-97, 2000
8. Berl, T. “Treating hyponatremia: damned if we do and damned if we don't.” Kidney international vol. 37,3 (1990): 1006-18. doi:10.1038/ki.1990.78
9. Sterns, R H. “Severe symptomatic hyponatremia: treatment and outcome. A study of 64 cases.” Annals of internal medicine vol. 107,5 (1987): 656-64. doi:10.7326/0003-4819-107-5-656
10. a Sterns, R H et al. “Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective.” Journal of the American Society of Nephrology : JASN vol. 4,8 (1994): 1522-30. doi:10.1681/ASN.V481522
11. a Karp, B I, and R Laureno. “Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia.” Medicine vol. 72,6 (1993): 359-73.
12. a Sterns, R H et al. “Osmotic demyelination syndrome following correction of hyponatremia.” The New England journal of medicine vol. 314,24 (1986): 1535-42. doi:10.1056/NEJM198606123142402
13. Berlit, P. “Die zentrale pontine Myelinolyse” [Central pontine myelinolysis]. Der Nervenarzt vol. 57,11 (1986): 624-33.
14. Singh, T D et al. “Central pontine and extrapontine myelinolysis: a systematic review.” European journal of neurology vol. 21,12 (2014): 1443-50. doi:10.1111/ene.12571
15. Lampl, Christian, and Kambiz Yazdi. “Central pontine myelinolysis.” European neurology vol. 47,1 (2002): 3-10. doi:10.1159/000047939

16. Burcar, P J et al. “Hyponatremia and central pontine myelinolysis.” Neurology vol. 27,3 (1977): 223-6. doi:10.1212/wnl.27.3.223
17. Rao, Parnandi Bhaskar et al. “Osmotic demyelination syndrome in Intensive Care Unit.” Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine vol. 19,3 (2015): 166-9. doi:10.4103/0972-5229.152760
18. Sugimoto, T et al. “Central pontine myelinolysis associated with hypokalaemia in anorexia nervosa.” Journal of neurology, neurosurgery, and psychiatry vol. 74,3 (2003): 353-5. doi:10.1136/jnnp.74.3.353
19. a Kleinschmidt-Demasters, B K et al. “Central and extrapontine myelinolysis: then...and now.” Journal of neuropathology and experimental neurology vol. 65,1 (2006): 1-11. doi:10.1097/01.jnen.0000196131.72302.68
20. a Sterns, R H et al. “Brain dehydration and neurologic deterioration after rapid correction of hyponatremia.” Kidney international vol. 35,1 (1989): 69-75. doi:10.1038/ki.1989.9
21. a Mount, David B. “The brain in hyponatremia: both culprit and victim.” Seminars in nephrology vol. 29,3 (2009): 196-215. doi:10.1016/j.semnephrol.2009.03.021
22. a Soupart, A et al. “Treatment of chronic hyponatremia in rats by intravenous saline: comparison of rate versus magnitude of correction.” Kidney international vol. 41,6 (1992): 1662-7. doi:10.1038/ki.1992.239
23. a Soupart, A et al. “Prevention of brain demyelination in rats after excessive correction of chronic hyponatremia by serum sodium lowering.” Kidney international vol. 45,1 (1994): 193-200. doi:10.1038/ki.1994.23
24. a Soupart, A et al. “Azotemia (48 h) decreases the risk of brain damage in rats after correction of chronic hyponatremia.” Brain research vol. 852,1 (2000): 167-72. doi:10.1016/s0006-8993(99)02259-3
25. a Soupart, Alain et al. “Rapid (24-hour) reaccumulation of brain organic osmolytes (particularly myo-inositol) in azotemic rats after correction of chronic hyponatremia.” Journal of the American Society of Nephrology : JASN vol. 13,6 (2002): 1433-41. doi:10.1097/01.asn.0000017903.77985.cd
26. a Suzuki, Haruyuki et al. “Minocycline prevents osmotic demyelination syndrome by inhibiting the activation of microglia.” Journal of the American Society of Nephrology : JASN vol. 21,12 (2010): 2090-8. doi:10.1681/ASN.2010040438
27. a Gankam-Kengne, Fabrice et al. “Minocycline protects against neurologic complications of rapid correction of hyponatremia.” Journal of the American Society of Nephrology : JASN vol. 21,12 (2010): 2099-108. doi:10.1681/ASN.2010050467
28. a Gankam Kengne, Fabrice et al. “Re-induction of hyponatremia after rapid overcorrection of hyponatremia reduces mortality in rats.” Kidney international vol. 76,6 (2009): 614-21. doi:10.1038/ki.2009.254
29. a Soupart, A et al. “Reinduction of hyponatremia improves survival in rats with myelinolysis-related neurologic symptoms.” Journal of neuropathology and experimental neurology vol. 55,5 (1996): 594-601. doi:10.1097/00005072-199605000-00011
30. a Verbalis, Joseph G et al. “Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations.” The American journal of medicine vol. 126,10 Suppl 1 (2013): S1-42. doi:10.1016/j.amjmed.2013.07.006
31. a Cheng, J C et al. “Long-term neurologic outcome in psychogenic water drinkers with severe symptomatic hyponatremia: the effect of rapid correction.” The American journal of medicine vol. 88,6 (1990): 561-6. doi:10.1016/0002-9343(90)90518-i
32. Martin, R J. “Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes.” Journal of neurology, neurosurgery, and psychiatry vol. 75 Suppl 3,Suppl 3 (2004): iii22-8. doi:10.1136/jnnp.2004.045906
33. Odier, Céline et al. “Central pontine and extrapontine myelinolysis: from epileptic and other manifestations to cognitive prognosis.” Journal of neurology vol. 257,7 (2010): 1176-80. doi:10.1007/s00415-010-5486-7
34. Menger, H, and J Jörg. “Outcome of central pontine and extrapontine myelinolysis (n = 44).” Journal of neurology vol. 246,8 (1999): 700-5. doi:10.1007/s004150050435
35. Lambeck J, Hieber M, Dreßing A, Niesen WD. Central Pontine Myelinosis and Osmotic Demyelination Syndrome. Dtsch Arztebl Int. 2019 Sep 2;116(35-36):600-606. doi: 10.3238/arztebl.2019.0600. PMID: 31587708; PMCID: PMC6804268.
36. Kallakatta, Ramesha Nekkare et al. “Clinical and functional outcome and factors predicting prognosis in osmotic demyelination syndrome (central pontine and/or extrapontine myelinolysis) in 25 patients.” Journal of neurology, neurosurgery, and psychiatry vol. 82,3 (2011): 326-31. doi:10.1136/jnnp.2009.201764
37. Graff-Radford, Jonathan et al. “Clinical and radiologic correlations of central pontine myelinolysis syndrome.” Mayo Clinic proceedings vol. 86,11 (2011): 1063-7. doi:10.4065/mcp.2011.0239
38. Förster, A et al. “Value of diffusion-weighted imaging in central pontine and extrapontine myelinolysis.” Neuroradiology vol. 55,1 (2013): 49-56. doi:10.1007/s00234-012-1083-z
39. Chua, G C et al. “MRI findings in osmotic myelinolysis.” Clinical radiology vol. 57,9 (2002): 800-6.
40. Miller, G M et al. “Central pontine myelinolysis and its imitators: MR findings.” Radiology vol. 168,3 (1988): 795-802. doi:10.1148/radiology.168.3.3406409
41. Case courtesy of Dr Augusto César Vieira Teixeira, Radiopaedia.org, rID: 23095
42. a Sterns, Richard H et al. “Treatment of hyponatremia.” Current opinion in nephrology and hypertension vol. 19,5 (2010): 493-8. doi:10.1097/MNH.0b013e32833bfa64
43. a Soupart, A et al. “Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia.” Clinical nephrology vol. 51,6 (1999): 383-6
44. a Oya, S et al. “Reinduction of hyponatremia to treat central pontine myelinolysis.” Neurology vol. 57,10 (2001): 1931-2. doi:10.1212/wnl.57.10.1931
45. a Croxson, Michael et al. “Diluting delirium.” The New Zealand medical journal vol. 118,1222 U1661. 16 Sep. 2005

46. a Menger, H, and J Jörg. “Outcome of central pontine and extrapontine myelinolysis (n = 44).” Journal of neurology vol. 246,8 (1999): 700-5. doi:10.1007/s004150050435
47. a Louis, Guillaume et al. “Long-term outcome of patients hospitalized in intensive care units with central or extrapontine myelinolysis*.” Critical care medicine vol. 40,3 (2012): 970-2. doi:10.1097/CCM.0b013e318236f152
48. Sterns, R H et al. “Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective.” Journal of the American Society of Nephrology : JASN vol. 4,8 (1994): 1522-30. doi:10.1681/ASN.V481522
49. Lohr, J W. “Osmotic demyelination syndrome following correction of hyponatremia: association with hypokalemia.” The American journal of medicine vol. 96,5 (1994): 408-13. doi:10.1016/0002-9343(94)90166-x
50. Berl, Tomas et al. “Oral tolvaptan is safe and effective in chronic hyponatremia.” Journal of the American Society of Nephrology : JASN vol. 21,4 (2010): 705-12. doi:10.1681/ASN.2009080857
51. Spasovski, Goce et al. “Clinical practice guideline on diagnosis and treatment of hyponatraemia.” Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association vol. 29 Suppl 2 (2014): i1-i39. doi:10.1093/ndt/gfu040
52. a Aegisdottir, Hildur et al. “Incidence of osmotic demyelination syndrome in Sweden: A nationwide study.” Acta neurologica Scandinavica vol. 140,5 (2019): 342-349. doi:10.1111/ane.13150
53. a Tanneau, R S et al. “High incidence of neurologic complications following rapid correction of severe hyponatremia in polydipsic patients.” The Journal of clinical psychiatry vol. 55,8 (1994): 349-54.
54. a Sterns, Richard H et al. “The treatment of hyponatremia.” Seminars in nephrology vol. 29,3 (2009): 282-99. doi:10.1016/j.semnephrol.2009.03.002
55. a Martin, R J. “Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes.” Journal of neurology, neurosurgery, and psychiatry vol. 75 Suppl 3,Suppl 3 (2004): iii22-8. doi:10.1136/jnnp.2004.045906
56. a Lohr, J W. “Osmotic demyelination syndrome following correction of hyponatremia: association with hypokalemia.” The American journal of medicine vol. 96,5 (1994): 408-13. doi:10.1016/0002-9343(94)90166-x
57. a George, Jason C et al. “Risk Factors and Outcomes of Rapid Correction of Severe Hyponatremia.” Clinical journal of the American Society of Nephrology : CJASN vol. 13,7 (2018): 984-992. doi:10.2215/CJN.13061117
58. a Ayus, J C et al. “Postoperative hyponatremic encephalopathy in menstruant women.” Annals of internal medicine vol. 117,11 (1992): 891-7. doi:10.7326/0003-4819-117-11-891
59. de Souza, Aaron. “Movement disorders and the osmotic demyelination syndrome.” Parkinsonism & related disorders vol. 19,8 (2013): 709-16. doi:10.1016/j.parkreldis.2013.04.005
60. Courtesy of Dr. Oya, S et al. “Reinduction of hyponatremia to treat central pontine myelinolysis.” Neurology 2001; 57:1931
61. Morard, Isabelle et al. “Identifying risk factors for central pontine and extrapontine myelinolysis after liver transplantation: a case-control study.” Neurocritical care vol. 20,2 (2014): 287-95. doi:10.1007/s12028-013-9928-9
62. Case courtesy of The Radswiki, Radiopaedia.org. From the case rID: 11286

Article Topic: Vagus nerve stimulation (VNS).

Author: Malek AlHourani.

Editor: Almutazballlah Qablan, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: vagus nerve stimulation, vagus nerve, refractory epilepsy, electrical stimulation

Overview of the vagus nerve

The Latin word vagus means 'wandering' and it explains the unique course of the 10th cranial nerve, the vagus nerve. The vagus nerve travels from the medulla to the colon innervating the thoracic and abdominal organs. During this course, branches innervate various structures such as the larynx, pharynx, heart, lungs, and gastrointestinal tract. [1] The vagus nerve is a mixed nerve, composed of 80% afferent nerve fibers and the remaining 20 % efferent fibers. The afferent nerves transmit sensory information throughout the body to the brain, on the other hand, the efferent cholinergic fibers are the main parasympathetic component of the autonomic nervous system. [2]

The afferent fibers terminate in the nucleus tractus solitarius, which is located in the brainstem. Then sends fibers that connect to different brain regions, such as but not limited to, the dorsal raphe nuclei, locus ceruleus, amygdala, hypothalamus, thalamus, and orbitofrontal cortex. [3]

Vagus nerve stimulation brief history

Vagus nerve stimulation (VNS) can be used to describe any technique that will stimulate the vagus nerve.[4]

James L. Corning was an American neurologist who pioneered the first device for stimulating the vagus nerve to treat epilepsy towards the end of the 19th century. Despite Corning's claims of dramatic benefit, his treatments were inconsistent and were not adopted by colleagues and were abandoned. VNS was not revived as a treatment for seizures until a century later. After safety and efficacy studies conducted in animals yielded positive results, evaluations of implanted devices for intermittent VNS in humans began in 1988. [5]

In 1997, The US Food and Drug Administration (FDA) later approved an implanted left cervical VNS device for managing medically refractory partial-onset seizures in adults

and adolescents. For some patients with partial-onset seizures, the side effects of antiepileptic drugs (AEDs) are intolerable; for other patients, no single AED or combination of anticonvulsant agents is effective. Although cerebral respective surgery is an alternative to pharmacotherapy in some cases, many patients with partial-onset seizures are not best candidates for intracranial surgery. So, VNS presented itself as a promising new treatment for previously unmanageable cases. [6]

Although VNS was not originally developed to treat depression, patients using VNS for epilepsy reported mood improvement; consequently, VNS was expanded to include the treatment of depression. Later in 2005, the same device was given an FDA-approved indication for the treatment of chronic treatment-resistant depression (chronic TRD). [7]

Mechanism of action

It is difficult to comprehend why a peripheral nerve stimulator like the VNS would be therapeutic for a central process like epilepsy or depression. Nonetheless, there is substantial evidence that the VNS is a device with significant benefits in these conditions.[8] As of 2015, more than 100,000 VNS devices have been implanted. Despite the success of VNS to treat drug-resistant epilepsy, the mechanism underlying its effect is not completely understood. [8]

The basic hypothesis on the mechanism of action was based on the knowledge that the vagus nerve afferent fibers have many projections within the central nervous system and that in this way generating action potentials in the afferent fibers will affect the entire human being. [1]

The ascending fibers will induce central effects on the brainstem structures (NTS, locus coeruleus, and raphe nuclei), and many of these potential mechanisms have been researched. [1]

The locus coeruleus regulates central norepinephrine levels and VNS has been shown to increase the discharge rate of the locus coeruleus; subsequently increasing the central concentration of norepinephrine and increased levels of norepinephrine were associated with therapeutic efficacy. [9]

A study has also shown that VNS increases the firing rate at the raphe nuclei, which are serotonin-secreting cells. [10] Increased serotonin levels have been correlated to decreased seizure activity. [11]

Additionally, PET studies have shown increased blood perfusion to the thalamus and the primary somatosensory cortex and decreased blood perfusion to the limbic system in response to VNS therapy. [12] Furthermore, VNS raises the electrical current threshold needed to induce seizures. [12]

VNS activation halts seizure activity in less than 5 seconds, [13] moreover, the anticonvulsant efficacy improves with long-term use when comparing results at 3 months to 1 year. [14] The combined acute and chronic effects of VNS involve the recruitment of several different neuronal pathways and networks, both of which decrease seizure activity. [13,14]

As for how VNS treats depression, it is mentioned previously that VNS alters levels of hormones famous for playing a role in regulating mood. Thus, it is easy to envision the VNS as a device to treat depression. [9]

Current indications as per the FDA

Regarding epilepsy: The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications. [15]

Regarding depression: The VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. [16]

Potential Uses

VNS therapy has wide-ranging effects. Due to the extensive effects on the nervous system, VNS therapy is being investigated as a possible treatment for a number of other disorders that impact the CNS, including migraine headaches, Alzheimer's disease, and multiple sclerosis. [7]

Several studies have shown that vagal nerve stimulation attenuates inflammation. [17,18] Inflammation is implicated in numerous conditions including cardiovascular disease, Rheumatoid arthritis, and Alzheimer's disease. [19,20] Preliminary preclinical evidence suggests that VNS may reduce the inflammatory response by activating the cholinergic anti-inflammatory pathway (CAP). [7]

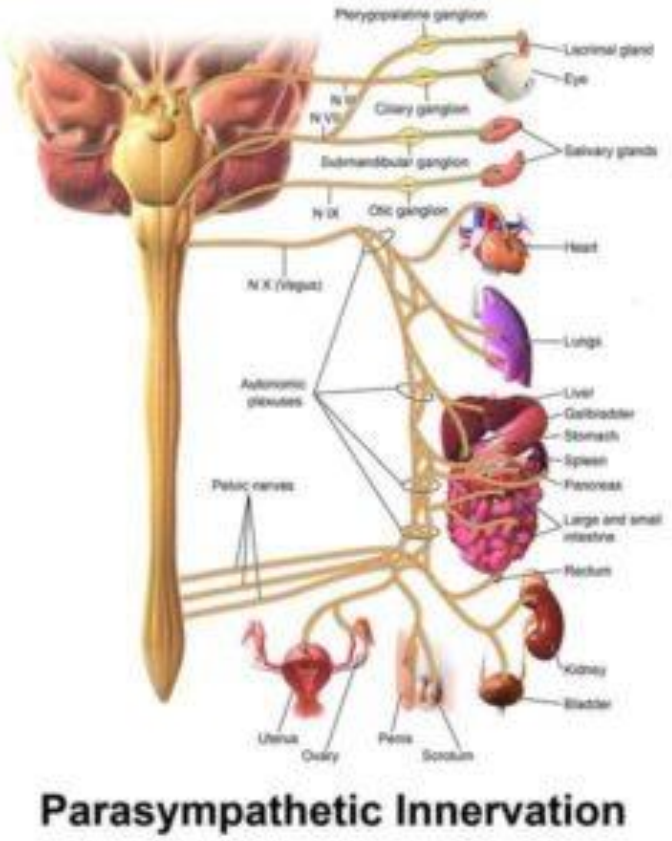


Fig 1 – Craniosacral distribution of the PNS, including the vagus nerve (33)

Right-sided VNS for the treatment of Heart failure showed therapeutic benefits in animal models. However, the two large, controlled trials-NECTAR-HF and INOVATE-HF-failed to demonstrate the expected benefit.[21] The lack of successful translation of preclinical results to clinical application is most likely a result of inadequate activation of the nerve fibers that produce therapeutic effects. [21]

The variety of changes brought about by VNS makes the potential applications of this device limitless, and it undoubtedly will be fascinating to watch what new findings come from future research.

VNS device implantation and complications

The most common use of VNS involves surgically implanting a commercially available programmable pulse generator device (NCP System; Cyberonics, Inc., Houston, TX, USA). The implant surgery is performed under general anesthesia in an outpatient setting. The electrodes which are made out of three spiral coils (anode, cathode, and anchor tether) are attached to the left vagus nerve where the superior and inferior

cervical cardiac branches come off .[22] Stimulation of these 2 cardiac branches may rarely cause bradycardia or asystole. [23]

A systematic review analyzed the data from two large VNS studies from the late 1990s — namely the E03 trial and the E05 trial provide information regarding the complications experienced by patients receiving VNS therapy. The commonest side effect of high-stimulation VNS from the E03 trial was hoarseness of voice (reported by 37%), followed by throat pain (11%), coughing (7%), shortness of breath (6%), tingling (6%), and muscle pain (6%). From the E05 trial, shortness of breath, voice alteration, and pharyngitis were common side effects. Implantation site infection occurred in 2% to 7% of cases, where systemic antibiotics, device removal, or open wound debridement is required. Infection risk at the VNS implantation site in children is increased compared to adults. [24]

Contraindications

The primary contraindication of VNS is baselining cardiac conduction disorders. Cardiac conduction abnormalities can worsen, especially on the right because there is the potential for efferent conduction through the vagus nerve. [25]

Since the right vagus nerve supplies the sinoatrial node, the device is usually implanted in the left vagus nerve to prevent any cardiac dysrhythmias, therefore, VNS therapy is a contraindication in patients who underwent bilateral or left cervical vagotomy procedures. [26]

Diathermy treatment specifically shortwave, microwave, and therapeutic ultrasound, could cause heating of the VNS system well above temperatures required for tissue destruction. As a result, it is contraindicated in people who have VNS implants. [4]

VNS can reportedly induce or worsen sleep apnea syndrome so it can technically be considered a relative contraindication. [27]

Non-invasive VNS

To avoid surgical implant-related complications, 2 types of non-invasive VNS were developed: transauricular and transcervical. The transauricular VNS (taVNS) stimulates the auricular branch of the vagus nerve that primarily supplies the concha and antihelix of the auricle. [28] The transcervical VNS (tcVNS) most likely stimulates both efferent and afferent VN fibers in the carotid sheath, moreover, tcVNS is approved by the FDA for the treatment of cluster headaches and migraines.[29]

Brain activity patterns after taVNS were somewhat like patterns observed in invasive VNS (e.g., diminished activity in the thalamus, amygdala, and cingulate hippocampus). [30] NEMOS® is a new taVNS device that received the European clearance (CE mark) for epilepsy and is available in Germany, Austria, Switzerland, and Italy in 2010. [31]

The gammaCore® device is a handheld tcVNS device used for headaches, epilepsy, and gastrointestinal disorders. [31]

Fig.2 – noninvasive VNS therapy 34

Transcutaneous VNS therapy warrants further study, not just as a treatment for depression or epilepsy, but also for its potentially favorable effects on the cardiovascular and nervous systems. [28]

Conclusion

The safety and tolerability of implanted VNS therapy to treat epilepsy and depression patients have been well-established based on the research conducted by George L. Morris, III, and colleagues

VNS corresponds with a >50% seizure reduction in 55% of 470 children with generalized or partial epilepsy. VNS is associated with a >50% seizure reduction in 55% of 113 patients with Lennox-Gastaut syndrome. VNS is associated with an increase in ≥50% seizure frequency reduction rates of ~7% from 1 to 5 years post-implantation. VNS is associated with a noteworthy improvement in mood scales in 31 adults with epilepsy. VNS is probably effective for both generalized or partial seizures and mood disorders in adults with epilepsy. VNS may have improved efficacy over time. [32]

The extensive interface of the tenth cranial nerve, between the brain, body, gut, and heart, opens a plethora of therapeutic possibilities that will inevitably unlock many diseases in the following years.

References

1. Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. Auton Neurosci. 2000 Dec 20;85(1-3):1-17. DOI: 10.1016/S1566-0702(00)00215-0. PMID: 11189015.
2. Ruffoli R, Giorgi FS, Pizzanelli C, et al. The chemical neuroanatomy of vagus nerve stimulation. J Chem Neuroanat. 2011; 42:288– 96.
3. Krahl SE. Vagus nerve stimulation for epilepsy: a review of the peripheral mechanisms. Surg Neurol Int. 2012;3
4. Howland RH. Vagus Nerve Stimulation. Curr Behav Neurosci Rep. 2014 Jun;1(2):64-73. doi: 10.1007/s40473-014-0010-5. PMID: 24834378; PMCID: PMC4017164.
5. Lanska, D. J. (2002). J.L. Corning and vagal nerve stimulation for seizures in the 1880s. Neurology, 58(3), 452–459. doi:10.1212/WNL.58.3.452
6. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology. 1998 Jul;51(1):48-55. DOI: 10.1212/wnl.51.1.48. PMID: 9674777.
7. Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. *J Inflamm Res*. 2018;11:203-213 https://doi.org/10.2147/JIR.S163248
8. Kohlberg GD, Samy RN. Central Effects of Cranial Nerve Stimulation. Otolaryngol Clin North Am. 2020 Feb;53(1):45-55. DOI: 10.1016/j.otc.2019.09.003. Epub 2019 Oct 21. PMID: 31648824.
9. Raedt R, Clinckers R, Mollet L, et al. Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model. J Neurochem 2011; 117:461–9.
10. Bagdy, G., Kecskemeti, V., Riba, P. and Jakus, R. (2007), Serotonin and epilepsy. Journal of Neurochemistry, 100: 857-873. https://doi.org/10.1111/j.1471-4159.2006.04277.x
11. Stella Manta; Mostafa El Mansari; Pierre Blier (2012). Novel attempts to optimize vagus nerve stimulation parameters on serotonin neuronal firing activity in the rat brain., 5(3), –. DOI: 10.1016/j.brs.2011.04.005
12. Henry, T.R., Bakay, R.A.E., Pennell, P.B., Epstein, C.M. and Votaw, J.R. (2004), Brain Blood-flow Alterations Induced by Therapeutic Vagus Nerve Stimulation in Partial Epilepsy: II. Prolonged Effects at High and Low Levels of Stimulation. Epilepsia, 45: 1064-1070. https://doi.org/10.1111/j.0013-9580.2004.03104.x
13. Zabara, J. (1992), Inhibition of Experimental Seizures in Canines by Repetitive Vagal Stimulation. Epilepsia, 33: 1005-1012. https://doi.org/10.1111/j.1528-1157.1992.tb01751.x
14. DeGiorgio CM, Schachter SC, Handforth A, et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia 2000; 41:1195–200.
15. Center for Devices and Radiological Health (CDRH). Summary of Safety and Effectiveness Data - VNS TherapyTM System (Epilepsy) [PDF file]. Food and Drug Administration (FDA) Website. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf/p970003s207b.pdf.
16. Center for Devices and Radiological Health (CDRH). Summary of Safety and Effectiveness Data - VNS TherapyTM System (Depression) [PDF file]. Food and Drug Administration (FDA) Website.Available at: www.accessdata.fda.gov/cdrh_docs/pdf/P970003S050b.pdf.
17. Falvey A. Vagus nerve stimulation and inflammation: expanding the scope beyond cytokines. Bioelectron Med. 2022 Dec 1;8(1):19. doi: 10.1186/s42234-022-00100-3. PMID: 36457107; PMCID: PMC9714105.
18. Caravaca AS, Gallina AL, Tarnawski L, Shavva VS, Colas RA, Dalli J, Malin SG, Hult H, Arnardottir H, Olofsson PS. Vagus nerve stimulation promotes resolution of inflammation by a mechanism that involves Alox15 and requires the α7nAChR subunit. Proc Natl Acad Sci U S A. 2022 May 31;119(22):e2023285119. doi: 10.1073/pnas.2023285119. Epub 2022 May 27. PMID: 35622894; PMCID: PMC9295760.
19. Ottaviani MM, Vallone F, Micera S, Recchia FA. Closed-Loop Vagus Nerve Stimulation for the Treatment of Cardiovascular Diseases: State of the Art and Future Directions. Front Cardiovasc Med. 2022 Apr 7;9:866957. doi: 10.3389/fcvm.2022.866957. PMID: 35463766; PMCID: PMC9021417.
20. Koopman FA, Schuurman PR, Vervoordeldonk MJ, Tak PP. Vagus nerve stimulation: a new bioelectronics approach to treat rheumatoid arthritis? Best Pract Res Clin Rheumatol. 2014 Aug;28(4):625-35. doi: 10.1016/j.berh.2014.10.015. Epub 2014 Nov 20. PMID: 25481554.
21. Dusi V, De Ferrari GM. Vagal stimulation in heart failure. Herz. 2021 Dec;46(6):541-549. doi: 10.1007/s00059-021-05076-5. Epub 2021 Oct 30. PMID: 34716778; PMCID: PMC8642334.
22. Terry RS, Tarver WB, Zabara J. The implantable neurocybernetic prosthesis system. Pacing Clin Electrophysiol. 1991 Jan;14(1):86-93. doi: 10.1111/j.1540-8159.1991.tb04052.x. PMID: 1705341.
23. Asconapé JJ, Moore DD, Zipes DP, Hartman LM, Duffell WH Jr. Bradycardia and asystole with the use of vagus nerve stimulation for the treatment of epilepsy: a rare complication of intraoperative device testing. Epilepsia. 1999 Oct;40(10):1452-4. doi: 10.1111/j.1528-1157.1999.tb02019.x. PMID: 10528943.
24. Ohemeng KK, Parham K. Vagal Nerve Stimulation: Indications, Implantation, and Outcomes. Otolaryngol Clin North Am. 2020 Feb;53(1):127-143. doi: 10.1016/j.otc.2019.09.008. Epub 2019 Nov 1. PMID: 31685239.
25. Schachter SC. Vagus nerve stimulation therapy for the treatment of epilepsy. UpToDate; 2018. Available at: https://www.uptodate.com/contents/vagus-nervestimulation-therapy-for-the-treatment-of-epilepsy.

26. Saper CB, Kibbe MR, Hurley KM, Spencer S, Holmes HR, Leahy KM, Needleman P. Brain natriuretic peptide-like immunoreactive innervation of the cardiovascular and cerebrovascular systems in the rat. Circ Res. 1990 Dec;67(6):1345-54. doi: 10.1161/01.res.67.6.1345. PMID: 1978807.
27. Marzec M, Edwards J, Sagher O, Fromes G, Malow BA. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. Epilepsia. 2003 Jul;44(7):930-5. doi: 10.1046/j.1528-1157.2003.56202.x. PMID: 12823576.
28. Wang Y, Li SY, Wang D, Wu MZ, He JK, Zhang JL, Zhao B, Hou LW, Wang JY, Wang L, Wang YF, Zhang Y, Zhang ZX, Rong PJ. Transcutaneous Auricular Vagus Nerve Stimulation: From Concept to Application. Neurosci Bull. 2021 Jun;37(6):853-862. doi: 10.1007/s12264-020-00619-y. Epub 2020 Dec 23. PMID: 33355897; PMCID: PMC8192665.
29. Ramkissoon CM, Güemes A, Vehi J. Overview of therapeutic applications of non-invasive vagus nerve stimulation: a motivation for novel treatments for systemic lupus erythematosus. Bioelectron Med. 2021 May 25;7(1):8. doi: 10.1186/s42234-021-00069-5. PMID: 34030736; PMCID: PMC8145832.
30. Bari AA, Pouratian N. Brain imaging correlates of peripheral nerve stimulation. Surg Neurol Int. 2012;3(Suppl 4):S260-8. doi: 10.4103/2152-7806.103016. Epub 2012 Oct 31. PMID: 23230531; PMCID: PMC3514912.
31. Ben-Menachem E, Revesz D, Simon BJ, Silberstein S. Surgically implanted and non-invasive vagus nerve stimulation: a review of efficacy, safety and tolerability. Eur J Neurol. 2015 Sep;22(9):1260-8. doi: 10.1111/ene.12629. Epub 2015 Jan 23. PMID: 25614179; PMCID: PMC5024045.
32. Morris GL 3rd, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013 Oct 15;81(16):1453-9. DOI: 10.1212/WNL.0b013e3182a393d1. Epub 2013 Aug 28. PMID: 23986299; PMCID: PMC3806910.
33. Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". *WikiJournal of Medicine* **1** (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436 Blausen 0703 Parasympathetic Innervation.png
34. Overview of therapeutic applications of non-invasive vagus nerve stimulation: a motivation for novel treatments for systemic lupus erythematosus - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Two-non-invasive-VNS-devices-NEMOS-is-a-transauricular-VNS-device-that-stimulates-the_fig3_351842748 [accessed 24 Oct, 2022]

Article topic: **Chorea and its Most Common Associated Pathologies.**

Author: Rama Amourah.

Editor: Haneen Al-Abdallat, Haneen A. Banihani.

Reviewer: Ethar Hazaimeh.

Keywords: Huntington's disease, Neuroacanthocytosis, Acquired chorea, Sydenham's chorea, Movement disorders.

Overview

Chorea is a distinct and debilitating hyperkinetic movement disorder that can result from various diseases. As a result, the underlying pathophysiology, prognosis, and treatment options of people who present with chorea are highly variable and can only be determined by further investigation. This article will focus on the most common causes of chorea, which can be split into two categories: primary; in which chorea is a classic symptom of a hereditary disorder; and secondary, in which the chorea is due to an exogenous insult or a hereditary disease that does not typically present with chorea. Understanding the most common causes of chorea and how they differ from each other in history, presentation, and further testing allows for more efficient and effective diagnosis and treatment of patients who suffer from this symptom.

Pathophysiology

The pathophysiology of chorea can be understood to be caused by *overexcitation or insufficient inhibition of the excitatory pathways in the basal ganglia.* It is commonly caused by damage to the basal ganglia leading to decreased function of the indirect inhibitory pathway, resulting in overexcitation of the direct pathway and hyperkinesia [1]. Dysregulation of basal ganglia pathways can be mediated by various endogenous and exogenous factors, including drugs, antibodies, ischemia (such as in stroke), dysfunctional metabolism, and aggregation of proteins [2] [3] [4].

Causes of chorea

Causes of chorea can be divided into primary and secondary.

Primary Chorea

Huntington's disease is an autosomal dominant hereditary neurodegenerative disorder caused by trinucleotide repeat expansions in the huntingtin gene on chromosome 4 (> 36 repeats). The resultant mutated huntingtin protein accumulates in the basal ganglia, leading to neurodegeneration which affects the putamen and head of the caudate nucleus (Figure 1) [3] [5]. A systematic review of 2,174 papers concerning neuroimaging of Huntington's disease showed that the disease was associated with findings of decreased glucose metabolism, perfusion, and D1 and D2 receptor binding in the basal ganglia [2]. It is the most common primary chorea, with the incidence being at least 4 cases per 100,000 people in the United States, Australia, and most European countries, sometimes reaching as high as 7 to 10 per 100,000 people [6]. Huntington's disease is diagnosed through genetic testing, and clinical treatment is guided by the Total Functional Capacity (TFC) scale, which assesses a person's ability to independently perform occupational, financial, domestic, and daily life tasks [7].

Neuroacanthocytosis is an umbrella term for multisystemic hereditary disorders characterized by acanthocytosis (thorny appearance of red blood cells due to membrane protein defects) and degeneration of the basal ganglia, leading to various movement disorders, including chorea [8]. Two well-studied diseases in this group which are most strongly associated with acanthocytosis, and neurological manifestations are McLeod syndrome and chorea-acanthocytosis, which are commonly referred to as "core diseases" [9]. McLeod syndrome is an X-linked recessive hereditary disorder caused by a mutation in the XK gene, which codes for a protein that may function in membrane transport associated with a lack of Kell antigens on the surface of red blood cells [10] [11]. Chorea-acanthocytosis (Figure 2) results from a hereditary autosomal-recessive mutation of the vacuolar protein sorting gene 13A gene (VPS13A) on chromosome 9q21, which leads to an absence of the ubiquitous VPS13A protein (also known as chorein). Chorein is still being studied, and little is understood about it apart from its role as a membrane transport protein [12] [13].

Secondary Chorea

Sydenham's chorea of rheumatic fever affects 20% of children and adolescents with rheumatic fever, and disproportionately children in socioeconomic circumstances where treatment and prophylaxis are difficult to access [14]. Rheumatic fever is caused by antibodies produced by the host immune system against group A beta-hemolytic streptococcus species (GAS). These antibodies persist even after the initial infection is cleared due to antigen cross-reactivity between the various M protein subtypes of GAS and different human tissues, resulting in the classical symptoms described by the Jones criteria, including Sydenham's chorea [15] [16]. It is most commonly seen in children aged 5 through 9 of both sexes and affects more post-pubertal females than males [17]. *Sydenham's chorea is most likely caused by cross-reactivity between GAS M-protein*

antigens and antigens of the basal ganglia and its dopamine receptors, resulting in infiltration and neuronal loss [18]. While Sydenham's chorea is classically expected to self-resolve within 1 - 6 months, evidence shows that treating it results in higher rates of remission and reduced socioeconomic burden due to reduced ability to participate in school, work, and society [19] [20].

Chorea as a complication of autoimmune diseases; Systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and celiac disease are three autoimmune diseases noted to have chorea as a complication. Up to 50% of SLE patients have neurological manifestations, but only 2% of those 50% develop chorea. Up to 25% of people with SLE have antiphospholipid antibodies, and that subset of SLE patients are more likely to develop antibody-induced chorea. The presence of antiphospholipid antibodies means that APS and SLE-associated chorea have similar pathophysiologies and complications. SLE and APS patients with chorea are at risk of arterial thrombosis secondary to a compromised blood-brain barrier, which can lead to cerebrovascular ischemia. There are a variety of proposed mechanisms, such as antibody-mediated platelet damage increasing platelet adhesion or antibodies preventing protein C from inhibiting thrombus formation. They are also both liable to worsen with oral contraceptives and pregnancy. People with celiac disease rarely experience chorea due to anti-gliadin antibodies crossing the blood-brain barrier and damaging the basal ganglia. In this case, the most effective treatment is ensuring the patient stops eating gluten [21] [22] [23].

*Chorea as a complication of metabolic abnormalities***;** hereditary metabolic disorders may present with chorea, but it is rare. The hereditary metabolic disorder most notable for presenting with chorea is Wilson's disease, an autosomal recessive defect on chromosome 13q14.3, which leads to defective ceruloplasmin and impaired ability to excrete copper. Chorea in Wilson's disease and other hereditary metabolic disorders usually presents with other neurological symptoms and movement disorders. Many other metabolic abnormalities may present with chorea, a few of which are vitamin B12 deficiency, hyperthyroidism, hypoparathyroidism, hyper- or hypoglycemia, and hyper- or hyponatremia [4] [24].

Drug-induced chorea; Alcohol, central nervous system stimulants, dopamine antagonists, benzodiazepines, antiepileptics, oral contraceptives, and many other drugs may induce chorea, possibly by overstimulating direct pathway neurons and postsynaptic dopamine receptors or by causing hypersensitization of postsynaptic dopamine receptors [25] [26]. Levodopa, the first-line treatment for Parkinson's disease, is associated with various movement disorders such as tardive dyskinesia and has been found to induce chorea in 40% or more of patients taking it. Levodopa does not cause chorea in people who do not already have basal ganglia damage [27]. Chorea induced by oral contraceptives only appears where there is prior antibody-mediated basal ganglia

damage and, as such, is associated with a history of Sydenham's chorea, chorea of SLE, and chorea gravidarum [25 28].

Presentation

Chorea typically presents as involuntary, flowing, "dance-like" movements. (Figure 4). In comparison to some other hyperkinetic like *Ballism* (hemiballism if unilateral) *is characterized by more proximal and extreme movements, often described in the literature as "flinging" in nature.* Hemiballism and ballism are associated with decreased subthalamic function or hyperactivity of the globus pallidus internus [26, 29]. *Athetosis*, which may also be referred to as dystonia with some choreic quality, *is often characterized in the literature as a more slow and writhing motion than chorea*. Cerebral palsy, kernicterus (bilirubin encephalopathy), stroke, neonatal asphyxia, and trauma are commonly associated with athetosis [26,30].

Figure (4): chorea movement

Differential diagnoses

Huntington's disease is most likely to appear in patients between 35 and 40 years old and is characterized by a suggestive family history, cognitive decline, personality changes, dementia, and many other psychiatric disturbances such as depression and suicidality [31]. Cognitive decline and psychiatric symptoms are the first signs to appear. Hyperreflexia, orofacial dystonia (such as involuntary tongue movements), and irregular eye movement precede chorea, with rigidity and parkinsonism typically presenting late in the course of the disease. Orofacial dystonia and abnormal, poorly controlled eye movement are also common findings. Patients who present at twenty years old or younger (juvenile Huntington's) are more likely to present with bradykinesia and parkinsonism than chorea, and they usually have an affected father [4 5 32 33].

Core neuroacanthocytosis (McLeod syndrome and chorea-acanthocytosis) present similarly to Huntington's disease as cognitive and psychiatric symptoms precede chorea, hyperkinesia, and parkinsonism happens late in the course of the disease. However, they are both characterized by dystonia, peripheral neuropathy, hypo- or areflexia, seizures, and acanthocytes on a peripheral blood smear (Table 2) [34]. Cognitive decline is markedly reduced compared to that seen in Huntington's disease [4]. McLeod syndrome, in particular, is characterized by elevated creatinine kinase due to myopathy and elevated lactate dehydrogenase and may have cardiac manifestations such as dilated cardiomyopathy [35]. Patients with McLeod syndrome may experience a hemolytic transfusion reaction if the blood donor expresses Kell antigens normally [36]. Choreic neck and truncal flexion, which presents as "head drop," as well as orofacial involvement characterized by tongue biting, dysphagia, and dysarthria, are characteristic of chorea-acanthocytosis [9,37].

	McLeod syndrome	**Chorea-acanthocytosis**
Gene	XK	VPS13A
Protein	XK	Chorein
Inheritance	X-linked recessive	Autosomal recessive
Onset	Usually ages 20 - 30	Usually ages 25 - 60
Acanthocytes	Strong association	Strong association
Serum creatinine kinase (IU/L)	300 - 3,000	300 - 3,000
Chorea	Strong association	Strong association
Other motor signs	Involuntary vocalizations	Orofacial dystonia, bradykinesia, and rigidity, gait dystonia
Seizures	Generalized	Partial-complex, generalized
Cardiac symptoms	Dilated cardiomyopathy, arrhythmias	None
Neuromuscular signs	Areflexia, weakness, atrophy	Areflexia, weakness, atrophy
Unique transfusion reactions	Kell positive donors	None

Table (1) [8] [9]. Characteristics of McLeod syndrome and chorea-acanthocytosis, two core neuroacanthocytosis syndromes.

Sydenham's chorea should be considered when a child with chorea between five and fifteen years of age presents with a history of recent infection, symptoms, and signs within the Jones criteria for rheumatic fever (Table 2), or a high Anti streptolysin O titer indicating recent group A beta-hemolytic streptococcal infection [38].

Drug-induced chorea should be considered based on drug history, alcohol consumption, and a previous history of chorea or basal ganglia damage [26].

Major (diagnostic: 2, 1 and 2 minor)	Minor
Carditis	Arthralgia
Arthritis	Hyperpyrexia
Sydenham's chorea	Elevated CRP and ESR
Subcutaneous nodules	Prolonged P-R interval
Erythema marginatum	

Table 2 [39]. Modified 1992 Jones criteria for diagnosing rheumatic fever.

Chorea due to autoimmune diseases such as antiphospholipid syndrome (APS), celiac disease, and systemic lupus erythematosus (SLE) may present with a medical history or other symptoms which are characteristic of autoimmune diseases such as rashes, arthralgia, thrombosis in cases of SLE and APS, and digestive symptoms in celiac disease. Testing for antibodies and other laboratory findings of autoimmune disease is also helpful [21].

Wilson's disease is a differential diagnosis in patients under 40 who present with chorea. A significant finding of Wilson's disease is Kayser-Fleischer rings, which are brown rings surrounding the cornea due to copper deposits (Figure 5). Low serum ceruloplasmin, high copper excretion, and hepatic injury due to copper deposits are also suggestive. Blood and genetic testing can confirm a diagnosis of Wilson's disease [4]. Other metabolic abnormalities should also be considered in children with chorea who do not have a history or findings suggestive of Sydenham's chorea. They may be confirmed by laboratory investigation, past medical and family history, characteristic associated symptoms, and genetic testing in cases of hereditary metabolic disorders.

Figure (5): Kayser-Fleischer ring.

Social history should be considered in case of drug-induced chorea without other risk factors.

Management

It is essential to address the underlying cause of secondary chorea, while primary chorea can only be treated symptomatically.

Primary

The underlying genetic diseases associated with primary chorea are best addressed in a multidisciplinary manner, in addition to the symptomatic treatment of chorea mentioned above. Huntington's disease, for example, may be addressed through patient education, assistive devices and clothing, and various therapies, including occupational therapy, physiotherapy, psychological therapy, and speech therapy [31]. This also applies to neuroacanthocytosis diseases such as McLeod syndrome and chorea-acanthocytosis, such as speech therapy and specialized feeding for people with orofacial dystonia associated with chorea-acanthocytosis. In McLeod syndrome, special care must be taken to prevent transfusion reactions and cardiologic complications. Dopamine depleters and antagonists such as tetrabenazine are effective in managing chorea associated with both Huntington's disease and neuro-acanthocytosis; however, care must be taken in patients with Huntington's disease for increased suicidality. Antiepileptics and neuroleptics are used to ameliorate chorea, treat neuro-acanthocytosis seizures, and ameliorate Huntington's disease's psychiatric complications [1 9 35 25 40].

Secondary

As diverse as the causes of secondary chorea are, they all have in common that addressing the underlying insult is key to management, and most secondary chorea stop once the first cause is treated.

The first and most crucial step in managing Sydenham's chorea is to address the underlying streptococcal infection. Intramuscular penicillin G is the first line of treatment, and macrolides such as erythromycin are used for patients allergic to penicillin [41] [20]. Several drugs have been used to treat Sydenham's chorea, including dopamine antagonists such as haloperidol, antiepileptics such as valproic acid, and steroids [42] [43]. While several institutions classically recommend dopamine antagonists, antiepileptics are favored by more recent sources for having fewer associated adverse effects and a similar response rate [14] [41] [1].

Chorea secondary to systemic lupus erythematosus and the primary antiphospholipid syndrome is best treated with valproic acid, tetrabenazine, haloperidol, and corticosteroids. Aspirin is also helpful in preventing thrombosis and its complications. Chorea due to celiac disease usually stops when the patient stops eating gluten and receives treatment [21] [23].

Wilson's disease is treatable with copper-chelating agents such as penicillamine. Metabolic chorea usually stops once the underlying disorder or deficiency is treated [4]. Most drug-induced chorea stops with the withdrawal of the drug; however, movement disorders may persist after drug withdrawal.

Prevention

Primary

Given that the primary chorea mentioned are hereditary, patient education and genetic counseling are essential to give patients the ability to make informed reproductive choices. In addition, prenatal testing is also a choice for patients to anticipate their children's future medical needs [31] [9].

Secondary

Prevention of secondary chorea varies based on the nature of the primary insult. Sydenham's chorea can be prevented by antibiotic prophylaxis of penicillin G, which protects against GAS infections and rheumatic fever [20]. Diagnosing and treating metabolic and autoimmune disorders minimizes, if not resolves, most of their associated symptoms, including more severe sequelae such as chorea.

Risk Factors

Primary

Metabolic chorea usually stops once the underlying disorder or deficiency is treated 4.

Secondary

Autoimmune diseases such as rheumatic fever secondary to GAS infection, SLE, and celiac disease are all risk factors for autoimmune-mediated chorea. Basal ganglia pathologies, including previous cases of chorea, will increase the risk of chorea in patients taking levodopa and oral contraceptives. Hereditary metabolic disorders and acquired deficiencies and abnormalities pose a small but significant risk of patients developing chorea. People taking central nervous stimulants, dopamine antagonists, antiepileptics, benzodiazepines, and other drugs are at risk of developing chorea even without a history of chorea or basal ganglia pathology. [4,25,24]

Prognosis

Primary chorea persists for life and cannot be cured. For example, in Huntington's disease, neurodegeneration progresses until it stabilizes after 15 - 30 years or the patient dies. Patients with Huntington's disease usually survive 10 to 30 years after diagnosis, and their most common cause of death is aspiration pneumonia [31].

Neuroacanthocytosis syndromes vary widely in prognosis. McLeod syndrome has a mean onset of around 30 years old, and patient life expectancy depends on the presence, severity, and management of neurological and cardiac sequelae [44]. Chorea-acanthocytosis has an average onset of 35 years old, although there is more variation in onset age and severity than there is for McLeod syndrome [8 9].

Most secondary chorea resolves with no further problems once the underlying insult or disease is addressed. The patient's prognosis depends not on the chorea but on the pathology that caused it.

Recent Developments

Deep brain stimulation (DBS) of various basal nuclei, particularly the globus pallidus internus, has been demonstrated to improve chorea in most Huntington's and non-Huntington's disease neurodegenerative disorders patients, such as chorea-acanthocytosis [45 46 37]. However, the evidence of the long-term efficacy of DBS is scarce, and there are concerns of high publication bias in favor of that evidence [32].

Chorein (VPS13A protein) and XK protein were recently found to form a complex and be involved in the same molecular pathways. The function of this lipid transport complex is

unclear, but it is essential to the structure and function of both neurons and red blood cells. These findings indicate that McLeod syndrome and chorea-acanthocytosis are more intricately linked than previously thought and may shape future understanding of neuroacanthocytosis syndromes and their pathophysiologies [13].

References

1. Feinstein, E., & Walker, R. (2018). *An Update on the Treatment of Chorea. Current Treatment Options in Neurology, 20(10).* doi:10.1007/s11940-018-0529-y
2. Ehrlich, D. J., & Walker, R. H. (2017). *Functional neuroimaging and chorea: a systematic review. Journal of Clinical Movement Disorders, 4(1).* doi:10.1186/s40734-017-0056-0
3. DiFiglia, M., Sapp, E., Chase, K. O., Davies, S. W., Bates, G. P., Vonsattel, J. P., & Aronin, N. (1997). *Aggregation of Huntingtin in Neuronal Intranuclear Inclusions and Dystrophic Neurites in Brain. Science, 277(5334), 1990–1993.* doi:10.1126/science.277.5334.1990
4. Bhidayasiri, R. (2004). *Chorea and related disorders. Postgraduate Medical Journal, 80(947), 527–534.* doi:10.1136/pgmj.2004.019356
5. Vonsattel, J. P., Myers, R. H., Stevens, T. J., Ferrante, R. J., Bird, E. D., & Richardson, E. P. (1985). Neuropathological classification of Huntington's disease. *Journal of Neuropathology & Experimental Neurology*, *44*(6), 559-577.
6. Harper, P. (1992). The epidemiology of Huntington's disease. Human Genetics, 89(4). doi:10.1007/bf00194305
7. Rothlind, J.C., Bylsma, F.W., Peyser, C., Folstein, S.E. and Brandt, J. (1993) Cognitive and motor correlates of everyday functioning in early Huntington's disease. J. Nerv. Ment. Dis. 181, 194–199.
8. Roulis, E., Hyland, C., Flower, R., Gassner, C., Jung, H. H., & Frey, B. M. (2018). Molecular basis and clinical overview of McLeod syndrome compared with other neuroacanthocytosis syndromes: a review. *Jama Neurology*, *75*(12), 1554-1562.
9. Jung, H. H., Danek, A., & Walker, R. H. (2011). *Neuroacanthocytosis Syndromes. Orphanet Journal of Rare Diseases, 6(1), 68.* doi:10.1186/1750-1172-6-68
10. Jung, H. H., Danek, A., & Frey, B. M. (2007). *McLeod syndrome: a neurohaematological disorder. Vox Sanguinis, 93(2), 112–121.* doi:10.1111/j.1423-0410.2007.00949.x
11. Redman, C. M., Russo, D., & Lee, S. (1999). *Kell, Kx and the McLeod syndrome. Best Practice & Research Clinical Haematology, 12(4), 621–635.* doi:10.1053/beha.1999.0045
12. Dobson-Stone C, Danek A, Rampoldi L, et al. (November 2002). "Mutational spectrum of the CHAC gene in patients with chorea-acanthocytosis". *Eur. J. Hum. Genet.* 10 (11): 773–81. doi:10.1038/sj.ejhg.5200866. PMID 12404112
13. Park, J.-S., & Neiman, A. M. (2020). XK is a partner for VPS13A: A molecular link between Chorea-Acanthocytosis and McLeod syndrome. Molecular Biology of the Cell, mbc.E19–08–0439. doi:10.1091/mbc.e19-08-0439-t
14. Da Silva, N. A., & de Faria Pereira, B. A. (1997). *ACUTE RHEUMATIC FEVER. Rheumatic Disease Clinics of North America, 23(3), 545–568.* doi:10.1016/s0889-857x(05)70347-1
15. Bessen, D. E., Veasy, L. G., Hill, H. R., Augustine, N. H., & Fischetti, V. A. (1995). Serologic evidence for a class I group A streptococcal infection among rheumatic fever patients. *Journal of Infectious Diseases*, *172*(6), 1608-1611.
16. Kaplan, M. H. (1963). Immunologic relation of streptococcal and tissue antigens: I. Properties of an antigen in certain strains of group A streptococci exhibiting an immunologic cross-reaction with human heart tissue. *The Journal of Immunology*, *90*(4), 595-606.
17. Nausieda, P. A., Grossman, B. J., Koller, W. C., Weiner, W. J., & Klawans, H. L. (1980). Sydenham chorea: an update. *Neurology*, *30*(3), 331-331.
18. Church, A. J., Cardoso, F., Dale, R. C., Lees, A. J., Thompson, E. J., & Giovannoni, G. (2002). Anti–basal ganglia antibodies in acute and persistent Sydenham's chorea. *Neurology*, *59*(2), 227-231.
19. Gurkas, E., Karalok, Z. S., Taskin, B. D., Aydogmus, U., Guven, A., Degerliyurt, A., ... & Yilmaz, C. (2016). Predictors of recurrence in Sydenham's chorea: clinical observation from a single center. *Brain and Development*, *38*(9), 827-834.
20. Lue, H. C., Wu, M. H., Wang, J. K., Wu, F. F., & Wu, Y. N. (1994). Long-term outcome of patients with rheumatic fever receiving benzathine penicillin G prophylaxis every three weeks versus every four weeks. *The Journal of pediatrics*, *125*(5), 812-816.
21. Baizabal-Carvallo, J. F., & Jankovic, J. (2012). *Movement disorders in autoimmune diseases. Movement Disorders, 27(8), 935–946.* doi:10.1002/mds.25011
22. Asherson, R. A., Derksen, R. H. W. M., Harris, E. N., Bouma, B. N., Gharavi, A. E., Kater, L., & Hughes, G. R. V. (1987). *Chorea in systemic lupus erythematosus and "lupus-like" disease: Association with antiphospholipid antibodies. Seminars in Arthritis and Rheumatism, 16(4), 253–259.* doi:10.1016/0049-0172(87)90003-5
23. Bruyn, G. W., & Padberg, G. (1984). *Chorea and Systemic Lupus erythematosus. European Neurology, 23(6), 435–448.* doi:10.1159/000115726
24. Baizabal-Carvallo, J. F., & Cardoso, F. (2020). *Chorea in children: etiology, diagnostic approach and management. Journal of Neural Transmission.* doi:10.1007/s00702-020-02238-3
25. Cardoso, F., Seppi, K., Mair, K. J., Wenning, G. K., & Poewe, W. (2006). *Seminar on choreas. The Lancet Neurology, 5(7), 589–602.* doi:10.1016/s1474-4422(06)70494-x

26. Cardoso, F. (2017). *Chorea, Ballism, and Athetosis. Movement Disorders Curricula, 275–282*. doi:10.1007/978-3-7091-1628-9_26
27. Fahn, S. (2000). The spectrum of levodopa-induced dyskinesias. *Annals of neurology*.
28. Pulsinelli, W. A., & Hamill, R. W. (1978). *Chorea complicating oral contraceptive therapy. The American Journal of Medicine, 65(3), 557–559*. doi:10.1016/0002-9343(78)90785-4
29. Hamani, C., Saint-Cyr, J. A., Fraser, J., Kaplitt, M., & Lozano, A. M. (2004). The subthalamic nucleus in the context of movement disorders. *Brain*, *127*(1), 4-20.
30. Przekop, A., & Sanger, T. D. (2011). *Birth-related syndromes of athetosis and kernicterus. Hyperkinetic Movement Disorders, 387–395*. doi:10.1016/b978-0-444-52014-2.00030-6
31. Novak, M. J. U., & Tabrizi, S. J. (2011). *Huntington's Disease: Clinical Presentation and Treatment. Pathophysiology, Pharmacology, and Biochemistry of Dyskinesia, 297–323*. doi:10.1016/b978-0-12-381328-2.00013-4
32. H. Bashir & J. Jankovic (2018) Treatment options for chorea, Expert Review of Neurotherapeutics, 18:1, 51-63, DOI: 10.1080/14737175.2018.1403899
33. Kremer, B., Weber, B., & Hayden, M. R. (1992). *New Insights Into the Clinical Features, Pathogenesis and Molecular Genetics of Huntington Disease. Brain Pathology, 2(4), 321–335*. doi:10.1111/j.1750-3639.1992.tb00709.x
34. Stevenson, V. L., & Hardie, R. J. (2001). Acanthocytosis and neurological disorders. *Journal of neurology*, *248*(2), 87-94.
35. Oechslin, E., Kaup, D., Jenni, R., & Jung, H. H. (2009). *Cardiac abnormalities in McLeod syndrome. International Journal of Cardiology, 132(1), 130–132*. doi:10.1016/j.ijcard.2007.07.167
36. Symmans, W. A., Shepherd, C. S., Marsh, W. L., Øyen, R., Shohet, S. B., & Linehan, B. J. (1979). Hereditary acanthocytosis associated with the McLeod phenotype of the Kell blood group system. *British journal of haematology*, *42*(4), 575-583.
37. Schneider, S. A., Lang, A. E., Moro, E., Bader, B., Danek, A., & Bhatia, K. P. (2010). Characteristic head drops and axial extension in advanced chorea-acanthocytosis. Movement Disorders, 25(10), 1487–1491. doi:10.1002/mds.23052
38. Gewitz, M. H., Baltimore, R. S., Tani, L. Y., Sable, C. A., Shulman, S. T., Carapetis, J., ... & Kaplan, E. L. (2015). Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*, *131*(20), 1806-1818.
39. Dajani, A. S., Ayoub, E., Bierman, F. Z., Bisno, A. L., Denny, F. W., Durack, D. T., ... & Wilson, W. (1993). Guidelines for the diagnosis of rheumatic fever: Jones criteria, updated 1992: special writing group of the committee on rheumatic fever, endocarditis, and Kawasaki disease of the council on cardiovascular disease in the young, American Heart Association. *Circulation*, *87*(1).
40. Bader, B., Walker, R. H., Vogel, M., Prosiegel, M., McIntosh, J., & Danek, A. (2010). Tongue protrusion and feeding dystonia: A hallmark of chorea-acanthocytosis. *Movement Disorders*, *25*(1), 127-129.
41. Dean, S. L., & Singer, H. S. (2017). Treatment of Sydenham's chorea: a review of the current evidence. *Tremor and Other Hyperkinetic Movements*, *7*.
42. Miyakawa, M., Ohkubo, O., Fuchigami, T., Fujita, Y., Moriuchi, R., Hiyoshi, K., ... & Harada, K. (1995). Effectiveness of haloperidol in the treatment of chorea minor. *No to Hattatsu= Brain and Development*, *27*(3), 191-196.
43. Faustino, P. C., Terreri, M. T. R., da Rocha, A. J., Zappitelli, M. C., Lederman, H. M., & Hilário, M. O. E. (2003). Clinical, laboratory, psychiatric and magnetic resonance findings in patients with Sydenham chorea. *Neuroradiology*, *45*(7), 456-462.
44. Hewer, E; Danek, A; Schoser, B. G.; Miranda, M; Reichard, R; Castiglioni, C; Oechsner, M; Goebel, H. H.; Heppner, F. L.; Jung, H. H. (2007). "*McLeod* myopathy revisited: More neurogenic and less benign". *Brain*. 130 (Pt 12): 3285–96. doi:10.1093/brain/awm269
45. Nakano, N., Miyauchi, M., Nakanishi, K., Saigoh, K., Mitsui, Y., & Kato, A. (2015). Successful combination of pallidal and thalamic stimulation for intractable involuntary movements in patients with neuroacanthocytosis. *World Neurosurgery*, *84*(4), 1177-e1.
46. Coppen, E. M., & Roos, R. A. C. (2016). *Current Pharmacological Approaches to Reduce Chorea in Huntington's Disease. Drugs, 77(1), 29–46*. doi:10.1007/s40265-016-0670-4

Article topic: McArdle's Disease.

Author: Shahd Aktham Etoom.

Editor: Ahmad Abuaisheh.

Reviewer: Ethar Hazaimeh.

Keywords: McArdle disease (MD), glycogen storage disease type V (GSDV), glycogen phosphorylase (PYGM), creatine kinase (CK).

Synonyms*: Glycogenosis Type V (GSDV), McArdle Disease, Muscle Glycogen Phosphorylase Deficiency, Myophosphorylase Deficiency, PYGM Deficiency.*

Abstract

Glycogen storage diseases (*GSDs*) are faulty hereditary glycogen metabolism conditions, characterized by deposits or atypical forms of glycogen in the liver, muscle, and brain tissues. This inborn metabolic mistake offers a model for understanding the significance of glycogen in muscle function and the compensatory adaptations that arise in response to decreased glycogenolysis since muscle glycogen is an essential fuel for muscle during exercise. They are regarded as uncommon diseases because of their extremely low frequency.

Exercise intolerance, the second wind phenomenon, and elevated serum creatine kinase activity are the hallmarks of *glycogen storage disease type V (GSDV*), also known as *McArdle disease*. In the population that is affected by this disease, we recapitulate *PYGM* mutations. It has long been believed that McArdle's illness is a metabolic myopathy brought on by a loss of expression of the muscle isoform of *glycogen phosphorylase (PYGM)*.

Overview

The kind of glucose that is stored in the body, called glycogen, is mostly produced from consumed carbs. Multiple enzymes must work in concert to break down glycogen for energy; GSDs are caused by a flaw in one of these enzymes.

Depending on the type of cell, phosphorylase is an enzyme that is encoded by one of three genes: muscle (PYGM gene), liver (PYGL gene), or brain (PYGB gene). The most prevalent muscle GSD, GSDV, is caused by a lack of the muscle-specific isoform of glycogen phosphorylase (myophosphorylase)[1].

A lack of this enzyme prevents the conversion of muscle glycogen into glucose-1-phosphate, preventing glycogenolysis from proceeding. However, due to the ability of muscle fibers to absorb blood glucose and convert it to glucose-6-phosphate after the metabolic block, glycolysis is only partially inhibited in GSDV.[2]

Individuals with GSDV experience muscle fatigue and pain, tachypnea, and tachycardia very soon after beginning physical activity and throughout all intense activities because skeletal muscle uses anaerobic energy for the first few minutes as it transitions from rest to activity, as well as throughout more intense activities. If these warning symptoms go unnoticed, muscular contracture could develop very quickly and cause rhabdomyolysis.

A condition known as "second wind", specific to GSDV, often happens 6 to 10 minutes into physical exertion, Pearson first recognized it et al. (1961) and signifies a noticeably increased capacity for physical exertion, such that formerly exhausting exercise is now more easily endured.[3]

Second wind is characterized by a sharp decline in heart rate, typically by 20 to 50 beats per minute, a marked improvement in the ability to work the muscle to extract oxygen and substrates from arterial blood, a significant drop in perceived exertion, and often a reduction in ventilation and breathing effort.[4]

Clinical overview

The key characteristic of GSDV is "intolerance to physical exercise". Exercise, a type of physical activity, is planned and regulated, making it simpler to control. Activities of daily living (ADL) on the other hand, are frequently spontaneous, and symptoms might appear seconds to minutes after initiating them. Many people only obtain a diagnosis because of an incidental discovery of high serum creatine kinase (CK), despite having a long history of activity restrictions. Muscular tiredness and exercise-induced muscle pain are the predominant symptoms of pain and premature physical activity intolerance, and 30% of GSDV patients experience chronic pain.[16]

Epidemiology

The difference between the prevalence calculated using genetic information and the prevalence calculated using diagnosed cases may be caused by the typical delay in accurate diagnosis. Based on genetic data, the prevalence of GSDV in the Dallas/Fort Worth region of the USA is predicted to be 1/100,000.[17]

GSDV has an autosomal recessive inheritance pattern. The following gender ratios of males to females have been noted in the GSDV cohorts: Italy 65:35, Spain 55:45, and the UK 50:50.

In an autosomal recessive disease, equality is predicted. Given that men are more likely to engage in physically demanding leisure and employment activities, areas where affected men predominate may reflect gender-related reporting bias.[18]

Pathogenesis

Adenosine triphosphate (ATP), which is produced by skeletal muscles, is produced by three main metabolic processes:

(1) Oxidative phosphorylation
(2) Glycolysis
(3) Adenylate kinase and *creatine kinase (CK)* reactions.

The rate of ATP resynthesis must properly match the rate of consumption since the amount of ATP stored in skeletal muscle is limited and would be exhausted in a few seconds of sprinting if not renewed. Compared to glycolysis and adenylate kinase/*CK* activities, oxidative phosphorylation (aerobic ATP generation) produces more energy, although these anaerobic mechanisms can be engaged more quickly.[19]

The two types of exercise:

Aerobic exercise

It includes walking, gentle swimming, cycling, and jogging. Skeletal muscle used different types of fuel during aerobic activity depending on the type, intensity, and duration of the exercise, physical condition, and dietary habits. Since *GSDV* patients may tolerate aerobic exercise better and it favors the consumption of blood-borne substrates like fatty acids, it is useful as a treatment regimen.[20]

"Anaerobic" exercise

It is intense and cannot be continued (e.g., weightlifting or 100-meter dash). Normally, myophosphorylase converts glycogen to glucose during anaerobic exercise, which enters the glycolytic pathway and creates ATP "anaerobically" (or with no need for oxygen).[20]

Any workout has an anaerobic phase that lasts for the first few minutes. Muscle employs a variety of fuel sources, including anaerobic glycolysis, blood glucose, muscle glycogen, and aerobic glycolysis, followed by fatty acid oxidation, depending on the extent and duration of the exercise.[20]

Blood-free fatty acids are the body's main source of energy when at rest. In the mitochondrial beta-oxidation route, these molecules are oxidized to create acetyl-CoA,

which is then processed through the citric acid cycle and mitochondrial respiratory chain to produce ATP.[20]

Clinical Presentation and Complications

A metabolic myopathy known as *McArdle's disease* typically shows exercise intolerance as rapid onset tiredness, myalgia, and cramping in working muscles. [20] Some older patients experience muscle atrophy and weakness.[15]

Although this clinical picture is typically conventional, some patients may show mild or severe manifestations. For instance, in certain cases, the disease manifests at a very young age with hypotonia, generalized muscle weakness, and progressive respiratory failure.[22]

85% of patients experience symptoms before the age of 10, however, the intensity of the symptoms varies, and about 50% of those people were diagnosed for the first time after the age of 30.[21] These symptoms are frequently brought on by persistent, powerful "aerobic" exercise (such as jogging or climbing stairs) or isometric exercise (such as hauling weights), and are typically eased by rest, it can happen to any skeletal muscle.[21]

Additionally, atypical manifestations have been reported, including issues with mastication, dysphagia, oral motor function (which are more common in younger individuals)[23], spontaneous compartment syndrome,[24, 25,] and acute contracture of the posterior neck muscles.[26]

Continuing to work out while experiencing intense discomfort, however, could lead to myoglobinuria and muscle damage (rhabdomyolysis). About 50% of people get myoglobinuria from rhabdomyolysis after vigorous exercise; few people really experience acute renal failure, despite the danger. Even though renal failure is always treatable, it needs to be treated at once.[29] It is clear that having a history of dark urine may prevent *GSDV* misdiagnosis and consequences. [26, 30]

Diagnosis/Workup

GSDV's clinical symptoms often appear in childhood.[29, 31] In GSDV, basal CK is frequently elevated. In young toddlers, the 'second wind' phenomena might not be as obvious.[32]

In short, it is difficult for clinical care experts to diagnose these individuals because the differential diagnosis for this disease is overly complex. Pediatricians should explore these pathologies even though they are rare disorders because the initial presentation typically occurs before the age of 10, and today the first line of defense is frequently

genetic testing. When making a differential diagnosis for adults, the patient's self-report of "second wind" or a flat lactate response with an increase in ammonia levels following a non-ischemic forearm exercise test may be helpful.[33]

The first presentation of symptoms to a general practitioner (GP) often occurs before the age of 10 years; nevertheless, the median age of a correct diagnosis is 33 years old. Children are frequently misdiagnosed by GPs as being "lazy or unfit" (51% of patients) or experiencing "growing pains" (44%), two of the most often reported misdiagnoses.[33]

Males and females are misdiagnosed equally, except for psychological problems, when females are misdiagnosed six times more often than males.[33] With the increasing use of genetic testing, the misdiagnosis of neuromuscular illnesses is projected to decline.[34]

Clinical symptoms, high serum creatine kinase levels, and a lack of lactate rising during anaerobic activity are used to make the diagnosis, which is supported by genetic testing and/or muscle biopsy.[35] A blood test to assess basal CK in GSDV is helpful as a screening test because it is nearly certain to be highly elevated indicating the need for additional investigations.[33]

The absence of genotype-phenotype association in GSDV is explained by a recent article. Regardless of the kind of mutation (missense, nonsense, deletion, insertion, splicing, etc.), most of the research participants lacked myophosphorylase function.[34] Clinical severity, PYGM genotype, and muscle biochemical tests do not appear to be significantly correlated.[35]

After taking a careful clinical history, seeing elevated serum CK levels, and employing minimally invasive techniques based on molecular analysis of the PYGM gene on deoxyribonucleic acid (DNA) isolated from peripheral blood samples, the diagnosis of GSD V can be made. Clinical molecular genetic testing is provided through whole exome sequencing, NGS panels with PYGM (for all GSDs or for rhabdomyolysis, for example), and Sanger sequencing of PYGM (WES). For a diagnosis to be confirmed, two pathogenic mutations must be found in suspected patients.

Single-gene Sanger sequencing, myopathy or rhabdomyolysis gene panels, or WES with peripheral blood samples can all be used for genetic testing.[36,37] Targeted mutation analysis can be used when a proband has known disease-causing familial mutations.[21, 38, 39, 40]

When variations of uncertain significance (VUS) are found, functional exercise tests like the cycle test, non-ischemic forearm tests, and muscle biopsies for the activity of the muscle phosphorylase enzyme may be helpful.[36, 37] Exercise tests may not be definitive when VUS is present, but a biochemical or histochemical analysis of the muscle biopsy tissue may reveal an enzymatic abnormality.[21,41,42] Muscle biopsy samples from people

with GSDV typically exhibit abnormally elevated amounts of subsarcolemmal glycogen buildup (3 to 5 times the normal range).[40]

Enzymatic analysis of skeletal muscle biopsies, which reveals undetectable or extremely low levels of myophosphorylase activity, confirms the diagnosis of GSDV.[38,39] In GSDV samples, myosin-heavy-chain labeling did not reveal any distinctive muscle fiber type distribution patterns.[43]

With the help of both cycle ergometry and walking tests, the value of the "second wind" as a diagnostic sign has been investigated.[44,45] By monitoring heart rate and subjective muscular discomfort every minute, the 12-minute walk test can be administered with ease in a clinical setting. It's vital to keep in mind that in very young patients with GSDV, the "second wind" phenomena might not be readily apparent,[32] and some people could need aid to recognize the "second wind"[46, 47, 48, 49].

Forearm exercise test

Patients with muscle GSD have done a forearm exercise test. A non-ischemic variant of the test is preferable, according to studies in GSDV, as ischemia in many individuals causes cramping and agony along with the possibility of rhabdomyolysis.[50]

Patients with GSDV exhibit a flat lactate response even when forearm muscles are not ischemic due to cuff pressure. As a result, a non-ischemic test is advocated for the diagnosis of GSDV, and patients should be told to cease the test if they feel any pain in their muscles.[51,52]

Workup and Imaging

In a group of 256 people with GSDV, the median basal CK elevation was 2643 IU/L, and just 18 people (7%) had normal values (200 IU/L) reported.[49] CK levels can be very high during episodes of rhabdomyolysis, sometimes exceeding 100,000 IU/L. When starting new medications or testing without an accident, it's crucial to establish a baseline CK level. Patients will be better able to control their disease and avert dangerous episodes thanks to this.

The liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are virtually invariably high when CK levels are over the thousands. This is a normal dispersion of sarcoplasmic muscle transaminases brought on by fiber damage rather than a symptom of liver disease. Further research may be necessary if ALT and AST levels are markedly high compared to the hyperCKemia, or if bilirubin or alkaline phosphatase (ALP) levels are markedly elevated. Myoglobin may be present if pee test strips reveal blood (hemoglobin) or protein. Urate levels are frequently elevated in GSDV because of excessive rises in blood ammonia, inosine, and hypoxanthine brought

on by the rapid breakdown of muscle purine nucleotides, which act as building blocks for uric acid synthesis. This could result in the emergence of hyperuricemia and gout.

Additionally, kidney stones might form because ofbecause of elevated urate levels. Due to the higher frequency of diabetes and coronary artery disease in this population, routine HbA1c testing, and lipid profile analysis are recommended [Quinlivan, R; unpublished data].[73]

Standard muscle MRI evaluation often reveals no fatty infiltration or muscular edema. The lower leg and shoulder girdle muscles may become fatty throughout a long-term illness course. Therefore, illness distinction or therapy monitoring is not possible with routine clinical MRI. Only C13 and P31 magnetic resonance spectroscopy has been able to non-invasively demonstrate abnormal glycogen buildup and metabolism in *McArdle disease* to date.[60, 61, 62, 63, 64]

New (quantitative) MR imaging techniques must be examined to take part in an early disease evaluation. Muscle diffusion tensor imaging (mDTI) can assess the diffusion characteristics of water molecules in muscle tissue to reveal information about muscular microstructure.[65, 66, 67]

Management & Treatment

The aim of treatment should be to lessen episodes of muscular breakdown, which may lead to hospital admissions for serious and fatal conditions such as rhabdomyolysis, ARF, and ACS.

Patients who present for the first time later in life are also more likely to have adopted unhealthy lifestyles and lost fitness. They may find it difficult to find their "second wind" as a result, and they may experience chronic discomfort and weariness as well as a low quality of life.[68]

Most patients should have their annual assessment. To prove physical fitness/functional capacity and the ability of patients with GSD V to use the "second wind," an assessment may include a functional exercise test. This might either be a 12-minute walk test[68] or a 12-minute cycle test[46]. A blood draw to evaluate basal CK, urate, HbA1c, and lipid profiles is advised once a year because of the greater prevalence of GSD V compared to the general population of gout (8.5: 5%), diabetes (6.7: 4.8%), and myocardial infarction (11: 4%) .[49]

Guidance of day-to-day management

To increase physical activity tolerance and lessen muscle injury, patients must be aware of how to get a "second wind." The muscles that are being worked on are what cause the

"second wind" phenomenon. Patients with GSD V must move slowly and be aware of the following symptoms while beginning an activity: muscle tiredness or pain, rate of perceived exertion, increased heart rate, and increased breathing effort. Patients are recommended to slow down (lower exertion) or stop until symptoms go away if any of these signals appear.[69]

The largest amount of oxygen that can be used during physical exercise "VO2 max" is the best indicator of aerobic conditioning. Exercise that is "appropriate" for you can raise your VO2 max. Only low to moderate-intensity work, ideally lasting at least 20 minutes, can be performed by people with muscle GSDs 2-4 times per week. Strength training can increase muscle mass, reduce the severity class, lower the baseline CK, and prevent fixed muscle weakness in the case of GSDV. It is crucial to follow the rules exactly to reduce the chance of contractures. The basic idea is to warm up all your muscles to get them into a "second wind", then perform sets of few repetitions using a circuit training framework, rotating on different machines to allow at least three minutes between bouts of rest.[70, 44, 71, 72]

A revised and updated systematic review of dietary and pharmaceutical interventions for *GSDV* published in the Cochrane Database found no benefit from high-dose oral ribose, a fat-rich diet, glucagon, verapamil, vitamin B6, a high-protein diet, branched-chain amino acid supplementation, dantrolene sodium, a high-dose of creatine, an intravenous course of gentamicin, a ketogenic diet, or intralipid Oral sucrose, a diet high in carbohydrates, ramipril, and low-dose creatine were treatments that provided some improvement.[75]

Surgery

The primary common factor is the generalized or focal failure of blood glucose, the easily accessible energy source that is given to skeletal muscle, whether due to inadequate supply or excessive consumption. Thus, it is advised that patients consult with the anesthetist in person before significant surgeries to go over the safety measures.

Prognosis

In general, this condition does not affect the affected person's life expectancy.[22]

Conclusion

Future treatment trials must work with several centers and utilize consistent assessment techniques due to the rarity of *GSDV*.[20]

There is currently no known cure for *McArdle disease*, although treatments often focus on managing the disease's symptoms and avoiding strenuous exertion. Adjuvant therapy is based on executing a controlled physical activity to increase glucose intake relative to the exercise periods and muscle mitochondrial oxidation capacities.[21,76,2]

Affected people benefit from moderate-intensity aerobic exercise to improve their cardiorespiratory fitness and muscle oxidative capacity. Examples of such exercise are biking, strolling, and brisk walking. Pre-exercise consumption of sports drinks with simple carbohydrates increases exercise tolerance and may prevent rhabdomyolysis brought on by exercise.[20]

References

1. Llavero F, Arrazola Sastre A, Luque Montoro M, et al. McArdle Disease: New Insights into Its Underlying Molecular Mechanisms. *Int J Mol Sci*. 2019;20(23). doi:10.3390/ijms20235919
2. Santalla A, Nogales-Gadea G, Ørtenblad N, et al. McArdle disease: a unique study model in sports medicine. *Sports Med*. 2014;44(11):1531-1544. doi:10.1007/s40279-014-0223-5
3. PEARSON CM, RIMER DG, MOMMAERTS WF. A metabolic myopathy due to absence of muscle phosphorylase. *Am J Med*. 1961;30:502-517. doi:10.1016/0002-9343(61)90075-4
4. DiMauro S, Miranda AF, Sakoda S, et al. Metabolic myopathies. *Am J Med Genet*. 1986;25(4):635-651. doi:10.1002/ajmg.1320250406
5. Hargreaves M, Spriet LL. Skeletal muscle energy metabolism during exercise. *Nat Metab*. 2020;2(9):817-828. doi:10.1038/s42255-020-0251-4
6. Chin ER, Allen DG. Effects of reduced muscle glycogen concentration on force, Ca2+ release and contractile protein function in intact mouse skeletal muscle. *J Physiol*. 1997;498 (Pt 1(Pt 1):17-29. doi:10.1113/jphysiol.1997.sp021838
7. Helander I, Westerblad H, Katz A. Effects of glucose on contractile function, [Ca2+]i, and glycogen in isolated mouse skeletal muscle. *Am J Physiol Cell Physiol*. 2002;282(6):C1306-12. doi:10.1152/ajpcell.00490.2001
8. Bergström J, Hultman E. Muscle glycogen synthesis after exercise: an enhancing factor localized to the muscle cells in man. *Nature*. 1966;210(5033):309-310. doi:10.1038/210309a0
9. Bergström J, Hultman E. A study of the glycogen metabolism during exercise in man. *Scand J Clin Lab Invest*. 1967;19(3):218-228. doi:10.3109/00365516709090629
10. Jiao Y, Shashkina E, Shashkin P, Hansson A, Katz A. Manganese sulfate-dependent glycosylation of endogenous glycoproteins in human skeletal muscle is catalyzed by a nonglucose 6-P-dependent glycogen synthase and not glycogenin. *Biochim Biophys Acta*. 1999;1427(1):1-12. doi:10.1016/s0304-4165(98)00142-1
11. Preisler N, Haller RG, Vissing J. Exercise in muscle glycogen storage diseases. *J Inherit Metab Dis*. 2015;38(3):551-563. doi:10.1007/s10545-014-9771-y
12. Godfrey R, Quinlivan R. Skeletal muscle disorders of glycogenolysis and glycolysis. *Nat Rev Neurol*. 2016;12(7):393-402. doi:10.1038/nrneurol.2016.75
13. SCHMID R, MAHLER R. Chronic progressive myopathy with myoglobinuria: demonstration of a glycogenolytic defect in the muscle. *J Clin Invest*. 1959;38(11):2044-2058. doi:10.1172/JCI103983
14. Mommaerts WF, Illingworth B, Pearson CM, Guillory RJ, Seraydarian K. A FUNCTIONAL DISORDER OF MUSCLE ASSOCIATED WITH THE ABSENCE OF PHOSPHORYLASE. *Proc Natl Acad Sci U S A*. 1959;45(6):791-797. doi:10.1073/pnas.45.6.791
15. Nadaj-Pakleza AA, Vincitorio CM, Laforêt P, et al. Permanent muscle weakness in McArdle disease. *Muscle Nerve*. 2009;40(3):350-357. doi:10.1002/mus.21351
16. Rommel O, Kley RA, Dekomien G, Epplen JT, Vorgerd M, Hasenbring M. Muscle pain in myophosphorylase deficiency (McArdle's disease): The role of gender, genotype, and pain-related coping. *Pain*. 2006;124(3):295-304. doi:10.1016/j.pain.2006.04.017
17. Haller RG. Treatment of McArdle disease. *Arch Neurol*. 2000;57(7):923-924. doi:10.1001/archneur.57.7.923
18. Lucia A, Martinuzzi A, Nogales-Gadea G, et al. Clinical practice guidelines for glycogen storage disease V & VII (McArdle disease and Tarui disease) from an international study group. *Neuromuscul Disord*. 2021;31(12):1296-1310. doi:10.1016/j.nmd.2021.10.006
19. Kitaoka Y. McArdle disease and exercise physiology. *Biology (Basel)*. 2014;3(1):157-166. doi:10.3390/biology3010157
20. Martín MA, Lucia A, Arenas J, Andreu AL. Glycogen Storage Disease Type V. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. ; 1993.
21. Santalla A, Nogales-Gadea G, Encinar AB, et al. Genotypic and phenotypic features of all Spanish patients with McArdle disease: a 2016 update. *BMC Genomics*. 2017;18(Suppl 8):819. doi:10.1186/s12864-017-4188-2

22. Quinlivan R, Buckley J, James M, et al. McArdle disease: a clinical review. *J Neurol Neurosurg Psychiatry*. 2010;81(11):1182-1188. doi:10.1136/jnnp.2009.195040
23. Kouwenberg C V, Voermans NC, Quinlivan R, van den Engel-Hoek L. Mastication and Oral Motor Function in McArdle Disease: Patient Reported Complaints. *J Neuromuscul Dis*. 2018;5(3):353-357. doi:10.3233/JND-180320
24. Mull AB, Wagner JI, Myckatyn TM, Kells AF. Recurrent Compartment Syndrome Leading to the Diagnosis of McArdle Disease: Case Report. *J Hand Surg Am*. 2015;40(12):2377-2379. doi:10.1016/j.jhsa.2015.09.015
25. Triplet JJ, Goss DAJ, Taylor B. Spontaneous Compartment Syndrome in a Patient with McArdle Disease: A Case Report and Review of the Literature. *JBJS case Connect*. 2017;7(3):e49. doi:10.2106/JBJS.CC.16.00196
26. Scalco RS, Chatfield S, Junejo MH, et al. McArdle Disease Misdiagnosed as Meningitis. *Am J Case Rep*. 2016;17:905-908. doi:10.12659/ajcr.900967
27. Witting N, Duno M, Piraud M, Vissing J. Severe axial myopathy in McArdle disease. *JAMA Neurol*. 2014;71(1):88-90. doi:10.1001/jamaneurol.2013.3209
28. Moustafa S, Patton DJ, Connelly MS. Unforeseen cardiac involvement in McArdle's disease. *Heart Lung Circ*. 2013;22(9):769-771. doi:10.1016/j.hlc.2012.12.004
29. Lucia A, Ruiz JR, Santalla A, et al. Genotypic and phenotypic features of McArdle disease: insights from the Spanish national registry. *J Neurol Neurosurg Psychiatry*. 2012;83(3):322-328. doi:10.1136/jnnp-2011-301593
30. Martinez-Thompson JM, Pittock SJ, Milone M. PRES leading to the diagnosis of McArdle disease. *J Clin Neurosci Off J Neurosurg Soc Australas*. 2017;46:62-64. doi:10.1016/j.jocn.2017.08.013
31. Raben N, Sherman JB. Mutations in muscle phosphofructokinase gene. *Hum Mutat*. 1995;6(1):1-6. doi:10.1002/humu.1380060102
32. Pérez M, Ruiz JR, Fernández del Valle M, et al. The second wind phenomenon in very young McArdle's patients. *Neuromuscul Disord*. 2009;19(6):403-405. doi:10.1016/j.nmd.2009.04.010
33. Scalco RS, Morrow JM, Booth S, Chatfield S, Godfrey R, Quinlivan R. Misdiagnosis is an important factor for diagnostic delay in McArdle disease. *Neuromuscul Disord*. 2017;27(9):852-855. doi:10.1016/j.nmd.2017.04.013
34. García-Consuegra I, Asensio-Peña S, Ballester-Lopez A, et al. Missense mutations have unexpected consequences: The McArdle disease paradigm. *Hum Mutat*. 2018;39(10):1338-1343. doi:10.1002/humu.23591
35. Martinuzzi A, Sartori E, Fanin M, et al. Phenotype modulators in myophosphorylase deficiency. *Ann Neurol*. 2003;53(4):497-502. doi:10.1002/ana.10499
36. Nakajima H, Kono N, Yamasaki T, et al. Genetic defect in muscle phosphofructokinase deficiency. Abnormal splicing of the muscle phosphofructokinase gene due to a point mutation at the 5'-splice site. *J Biol Chem*. 1990;265(16):9392-9395. doi:10.1016/s0021-9258(19)38861-1
37. Background H, Specificity S, Mechanism TR, Phosphofructokinase E, Phosphofructokinase AM, Phosphofructokinase K. PHOSPHOFRUCTOKINASE. 1979;46.
38. Shanske S, Nonaka I, Dmauro S. Tsujino1995. Published online 1995:23-27.
39. El-Schahawi M, Tsujino S, Shanske S, DiMauro S. Diagnosis of McArdle's disease by molecular genetic analysis of blood. *Neurology*. 1996;47(2):579-580. doi:10.1212/WNL.47.2.579
40. Hurst C Lawrence B. The New England Journal of Medicine Downloaded from nejm.org on June 3, 2020. For personal use only. No other uses without permission. Copyright © 2009 Massachusetts Medical Society. All rights reserved. Published online 2009:2022.
41. Garcia-Consuegra I, Blázquez A, Rubio JC, et al. Taking advantage of an old concept, "illegitimate transcription", for a proposed novel method of genetic diagnosis of McArdle disease. *Genet Med*. 2016;18(11):1128-1135. doi:10.1038/gim.2015.219
42. Olpin SE, Murphy E, Kirk RJ, Taylor RW, Quinlivan R. The investigation and management of metabolic myopathies. *J Clin Pathol*. 2015;68(6):410-417. doi:10.1136/jclinpath-2014-202808
43. Kohn TA, Noakes TD, Rae DE, et al. McArdle disease does not affect skeletal muscle fibre type profiles in humans. *Biol Open*. 2014;3(12):1224-1227. doi:10.1242/bio.20149548
44. O'Reilly DSJ. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. *Ann Clin Biochem*. 2004;41(Pt 3):255. doi:10.1056/nejmoa031836
45. Buckley JP, Quinlivan RM, Sim J, Eston RG, Short DS. Heart rate and perceived muscle pain responses to a functional walking test in McArdle disease. *J Sports Sci*. 2014;32(16):1561-1569. doi:10.1080/02640414.2014.906045
46. Scalco RS, Chatfield S, Godfrey R, et al. From exercise intolerance to functional improvement: The second wind phenomenon in the identification of McArdle disease. *Arq Neuropsiquiatr*. 2014;72(7):538-541. doi:10.1590/0004-282X20140062
47. Løkken N, Hansen KK, Storgaard JH, Ørngreen MC, Quinlivan R, Vissing J. Titrating a modified ketogenic diet for patients with McArdle disease: A pilot study. *J Inherit Metab Dis*. 2020;43(4):778-786. doi:10.1002/jimd.12223
48. Madsen KL, Laforêt P, Buch AE, et al. No effect of triheptanoin on exercise performance in McArdle disease. *Ann Clin Transl Neurol*. 2019;6(10):1949-1960. doi:10.1002/acn3.50863
49. Scalco RS, Lucia A, Santalla A, et al. Data from the European registry for patients with McArdle disease and other muscle glycogenoses (EUROMAC). *Orphanet J Rare Dis*. 2020;15(1):1-8. doi:10.1186/s13023-020-01562-x
50. Hogrel JY, Laforêt P, Ben Yaou R, Chevrot M, Eymard B, Lombès A. A non-ischemic forearm exercise test for the screening of patients with exercise intolerance. *Neurology*. 2001;56(12):1733-1738. doi:10.1212/WNL.56.12.1733
51. Drouet A, Zagnoli F, Fassier T, et al. Intolérance musculaire à l'effort par déficit en phosphofructokinase: apport au diagnostic du bilan métabolique musculaire (tests d'effort, spectroscopie RMN du P31). *Rev Neurol (Paris)*. 2013;169(8-9):613-624. doi:10.1016/j.neurol.2013.02.006

52. Aasly J, Van Diggelen OP, Boer AM, Brønstad G. Phosphoglycerate kinase deficiency in two brothers with McArdle-like clinical symptoms. *Eur J Neurol*. 2000;7(1):111-113. doi:10.1046/j.1468-1331.2000.00012.x
53. Leite A, Oliveira N, Rocha M. McArdle disease: a case report and review. *Int Med Case Rep J*. 2012;5:1-4. doi:10.2147/IMCRJ.S28664
54. Hogrel JY, van den Bogaart F, Ledoux I, et al. Diagnostic power of the non-ischaemic forearm exercise test in detecting glycogenosis type V. *Eur J Neurol*. 2015;22(6):933-940. doi:10.1111/ene.12685
55. Molares-Vila A, Corbalán-Rivas A, Carnero-Gregorio M, González-Cespón JL, Rodríguez-Cerdeira C. Biomarkers in Glycogen Storage Diseases: An Update. *Int J Mol Sci*. 2021;22(9). doi:10.3390/ijms22094381
56. de Luna N, Brull A, Lucia A, et al. PYGM expression analysis in white blood cells: a complementary tool for diagnosing McArdle disease? *Neuromuscul Disord*. 2014;24(12):1079-1086. doi:10.1016/j.nmd.2014.08.002
57. García-Consuegra I, Rubio JC, Nogales-Gadea G, et al. Novel mutations in patients with McArdle disease by analysis of skeletal muscle mRNA. *J Med Genet*. 2009;46(3):198-202. doi:10.1136/jmg.2008.059469
58. Garcia-Consuegra I, Blázquez A, Rubio JC, et al. Taking advantage of an old concept, "illegitimate transcription", for a proposed novel method of genetic diagnosis of McArdle disease. *Genet Med Off J Am Coll Med Genet*. 2016;18(11):1128-1135. doi:10.1038/gim.2015.219
59. Walters WD, Garnica AD, Schaefer GB. McArdle Disease Presenting With Muscle Pain in a Teenage Girl: The Role of Whole-Exome Sequencing in Neurogenetic Disorders. *Semin Pediatr Neurol*. 2018;26:50-51. doi:10.1016/j.spen.2017.03.004
60. Zange J, Grehl T, Disselhorst-Klug C, et al. Breakdown of adenine nucleotide pool in fatiguing skeletal muscle in McArdle's disease: a noninvasive 31P-MRS and EMG study. *Muscle Nerve*. 2003;27(6):728-736. doi:10.1002/mus.10377
61. Heinicke K, Dimitrov IE, Romain N, et al. Reproducibility and absolute quantification of muscle glycogen in patients with glycogen storage disease by 13C NMR spectroscopy at 7 Tesla. *PLoS One*. 2014;9(10):e108706. doi:10.1371/journal.pone.0108706
62. Lewis SF, Haller RG, Cook JD, Nunnally RL. Muscle fatigue in McArdle's disease studied by 31P-NMR: effect of glucose infusion. *J Appl Physiol*. 1985;59(6):1991-1994. doi:10.1152/jappl.1985.59.6.1991
63. Gruetter R, Kaelin P, Boesch C, Martin E, Werner B. Non-invasive 31P magnetic resonance spectroscopy revealed McArdle disease in an asymptomatic child. *Eur J Pediatr*. 1990;149(7):483-486. doi:10.1007/BF01959400
64. de Kerviler E, Leroy-Willig A, Jehenson P, Duboc D, Eymard B, Syrota A. Exercise-induced muscle modifications: study of healthy subjects and patients with metabolic myopathies with MR imaging and P-31 spectroscopy. *Radiology*. 1991;181(1):259-264. doi:10.1148/radiology.181.1.1887044
65. Ai T, Yu K, Gao L, et al. Diffusion tensor imaging in evaluation of thigh muscles in patients with polymyositis and dermatomyositis. *Br J Radiol*. 2014;87(1043):20140261. doi:10.1259/bjr.20140261
66. Budzik JF, Balbi V, Verclytte S, Pansini V, Le Thuc V, Cotten A. Diffusion tensor imaging in musculoskeletal disorders. *Radiogr a Rev Publ Radiol Soc North Am Inc*. 2014;34(3):E56-72. doi:10.1148/rg.343125062
67. Damon BM, Froeling M, Buck AKW, et al. Skeletal muscle diffusion tensor-MRI fiber tracking: rationale, data acquisition and analysis methods, applications and future directions. *NMR Biomed*. 2017;30(3). doi:10.1002/nbm.3563
68. Buckley NA, Chiew AL. Re: External validation of the paracetamol-aminotransferase multiplication product to predict hepatotoxicity from paracetamol overdose. *Clin Toxicol*. 2015;53(10):1152-1153. doi:10.3109/15563650.2015.1096367
69. Haller RG, Vissing J. No spontaneous second wind in muscle phosphofructokinase deficiency. *Neurology*. 2004;62(1):82-86. doi:10.1212/WNL.62.1.82
70. Pearson CM, Rimer DG, Mommaerts WFHM. A metabolic myopathy due to absence of muscle phosphorylase. *Am J Med*. 1961;30(4):502-517. doi:10.1016/0002-9343(61)90075-4
71. Andersen ST, Haller RG, Vissing J. Effect of oral sucrose shortly before exercise on work capacity in McArdle disease. *Arch Neurol*. 2008;65(6):786-789. doi:10.1001/archneur.65.6.786
72. Mechanisms O. Spontaneous "Second Wind" and Glucose-Induced Second "Second Wind" in McArdle Disease. 2016;59.
73. Nakajima H, Hamaguchi T, Yamasaki T, Tarui S. Phosphofructokinase deficiency: Recent advances in molecular biology. *Muscle Nerve*. 1995;18(14 S):S28-S34. doi:10.1002/mus.880181408
74. Nogales-Gadea G, Santalla A, Ballester-Lopez A, et al. Exercise and Preexercise Nutrition as Treatment for McArdle Disease. *Med Sci Sports Exerc*. 2016;48(4):673-679. doi:10.1249/MSS.0000000000000812
75. Quinlivan R, Martinuzzi A, Schoser B. Pharmacological and nutritional treatment for McArdle disease (Glycogen Storage Disease type V). *Cochrane database Syst Rev*. 2014;2014(11):CD003458. doi:10.1002/14651858.CD003458.pub5
76. Santalla A, Munguía-Izquierdo D, Brea-Alejo L, et al. Feasibility of resistance training in adult McArdle patients: clinical outcomes and muscle strength and mass benefits. *Front Aging Neurosci*. 2014;6:334. doi:10.3389/fnagi.2014.00334

Article topic: Chronic Migraine.

Author: Abdallah Alshloul.

Editor: Ahmad Abuaisheh.

Reviewer: Ethar Hazaimeh.

Keywords: Chronic migraine, Etiology, Pathophysiology, Genetics and Epigenetics, Treatment.

Abbreviations: CM= chronic migraine, EM= episodic migraine, CDH= chronic daily headache.

Abstract

Chronic migraine is the type in which a person has at least 15 headache days a month, involving at least eight days a month with fully developed migraines [1]. CM is a common and disabling neurological disorder. Patients with less frequent migraines (episodic migraine) should be counseled on avoiding risk factors associated with transformation to chronic migraine. The treatment of (CM) involves avoidance of risk factors for (CM), avoidance of migraine attack triggers, use of prophylactic and abortive drugs, and non-drug treatment. The knowing and management of disorders that are comorbid with CM improves patient outcomes.

Overview

Migraine is a headache that often affects one side of the head and can be extremely painful or have a pulsating feeling. Extreme light and sound sensitivity, along with nausea and vomiting, are common side effects. A migraine episode might be so intense that it keeps a patient away from working for hours or even days.

Chronic migraine (CM), one of the most prevalent chronic daily headaches (CDH) illnesses, is characterized by recurrent headache episodes and at least 15 headache days per month. People who experience chronic migraine (CM) frequently experience episodic migraine (EM), and their frequency of headaches rises over time.[2]

With the increasing headache frequency, CM becomes less severe and more tranquil but is associated with worse treatment responses. The under-treated headache and associated comorbidities cause a high disease burden for CM compared with EM.[2]

CM patients have worse socioeconomic status and health-related quality of life. Many studies show that patients with chronic daily headaches have lower levels of education

and household income. In addition, epidemiological profiles show that CM sufferers tend to be older and have a higher body mass index (BMI).[10]

The switch from EM to CM is usually a gradual step, and some patients oscillate between EM and CM. The cause of migraine chronification is not fully clear. The pathogenesis has been postulated to include the development of central sensitization or increased excitability of the trigeminal nociceptive pathways.

The reason only a minority of EM patients are chronic while the vast majority do not is still not fully understood. Although there are some recognized environmental causes, such as drug usage, a genetic predisposition is still a very real potential.

Epidemiology

Approximately 12% of the population suffers from migraine, affecting significantly more women than men. Compared with the overall prevalence of migraine, chronic migraine is not as common as episodic migraine; prevalence is estimated at 0.9% to 2.2% among the general population.

It is estimated that 3% of EM patients evolve to CM per year, and a similar result was obtained in a three-month follow-up. Besides, this transformation is bidirectional with about 26% of CM patients remitting to EM in a two-year follow-up, which makes it difficult to confirm the exact prevalence of CM. However, chronic migraine is often seen in headache centers. Worldwide, up to 45% of patients presenting to headache clinics have daily or near-daily headaches. Therefore, chronic migraine should be understood as a disabling, under-diagnosed, and under-treated disorder.[11]

Clinical Features

Migraine-related disability, fatigue, daily sleepiness, subjective sleep quality, anxiety, and depressive symptoms.[5]

Pain location is equal in unilateral and bilateral sides, pain side is equal in right and left, in most CM with pulsating and may with pressing/tightening and both in sometimes. CM may be associated with allodynia, cephalalgiophobia. In half of the patients, CM occurs with current medication and with acute treatment overuses.[15]

Symptoms of EM and CM are the same. The difference is simply the increase in the frequency of the number of headaches. Typical migraine symptoms include headache, that is moderate to severe in intensity, worsened by physical activity/movement; pain on one or both sides of the head; throbbing pain or pressure-like pain; sensitivity to light, sound, and smells; nausea, vomiting, and Dizziness.[13]

Signs of an episodic migraine transforming into a chronic migraine include having a growing number of migraine attacks and taking more medication because of the growing number of attacks.[13]

Risk Factors

Psychiatric Problems

Psychiatric disorders are quite common comorbidities of migraine patients. Chronic daily headache (CDH) patients had three times the risk of anxiety disorder, depression, bipolar disorder, and panic disorder than non-migraines and they had about double the risk of psychiatric disorders than other migraines.[8]

Sleep-Related Problems

People with CDH/CM frequently exhibit sleep-related problems. Daytime drowsiness, sleep bruxism, insomnia, and frequent snoring are all thought to be risk factors for CH/CM.[8]

Caffeine Overuse

Caffeine can be both beneficial and detrimental for migraine patients. It is a potent vasoconstrictor, so it is used as a component in some acute abortive medication for migraine. In contrast, a delay in the intake of caffeine can cause weak headaches. Abrupt withdrawal of caffeine evokes headaches in more than half of people who usually consume low or moderate amounts of caffeine.[8]

Obesity

In a longitudinal population-based study, the influence of obesity was clearer for new onset CDH/CM, and the relative odds of CDH were three to five times higher in overweight or obese people than in people of normal weight in the USA.[8]

Overuse of acute migraine medication

The most important risk factor for CM is the overuse of acute migraine medication, defined as intake of analgesics on >15 days per month or triptans on >10 days per month. Regular intake of acute migraine medication leads to an increasing headache frequency, which facilitates migraine progression.[9]

Ineffective treatment of acute migraine

One of the main causes of CM is inadequate acute migraine management. This fact, which could be so easily avoided, cannot be emphasized enough: recent data from the American Migraine Prevalence and Prevention Study, which included over 5,000 migraine patients, showed that ineffective acute treatment doubled the risk for migraine chronification compared to effective acute treatment.[9]

Etiology

Migraines are not well understood. Probable causes have been identified, but final answers have not been discovered yet. Some hypotheses about migraine's root cause include:

(CNS) disorder: an underlying neurological condition that might trigger chronic migraines.

Chemical imbalances: *For* the brain to operate at its best, all chemicals must be balanced, and all neural pathways must be free of obstructions. Migraines may develop if any of these processes are disturbed.

Genetic factors: if a family member, such as a parent or brother, has experienced migraine headaches, your chances of having migraines increases.

Vascular irregularities: problems with the shape, size, or blood flow in vessels to or inside your brain may cause migraine.

In some cases, (CM) may be an underlying symptom of another serious condition. Conditions that could cause (CM) include traumatic brain injury; inflammation or other problems with blood vessels in the brain, including stroke; infections such as meningitis, and endocarditis; brain tumors; and intracranial pressure that is low or high.

Pathophysiology

The pathophysiology of (CM) and the mechanisms that result in transformation are not fully cleared. However, the effects of atypical pain processing, central sensitization, cortical hyperexcitability, and neurogenic inflammation have been studied. Atypical modulation of pain might lead to transformation. Decreased inhibition of pain by regions of the descending pain modulatory pathway has been identified in (CM).

In migraines, pain-induced functional activation of pain-inhibiting brainstem regions and the functional connectivity of brainstem pain modulatory regions are atypical. Furthermore, the extent of these abnormalities correlates with the presence of cutaneous allodynia, a symptom of central sensitization.

It is postulated that recurrent migraine attacks lead to sensitization of the trigeminal system, which results in a reduced threshold for activation of this system, more frequent migraine attacks, and transformation to chronic migraine. Cortical hyperexcitability might also contribute to transformation.

Transcranial magnetic stimulation studies (figure 1) of patients with chronic migraine suggest that the occipital cortex of these patients is hyperexcitable, even more so than in patients with (EM).[3] The extent to which lack of cortical inhibition versus intrinsic cortical excitability contributes to this state is not clear.

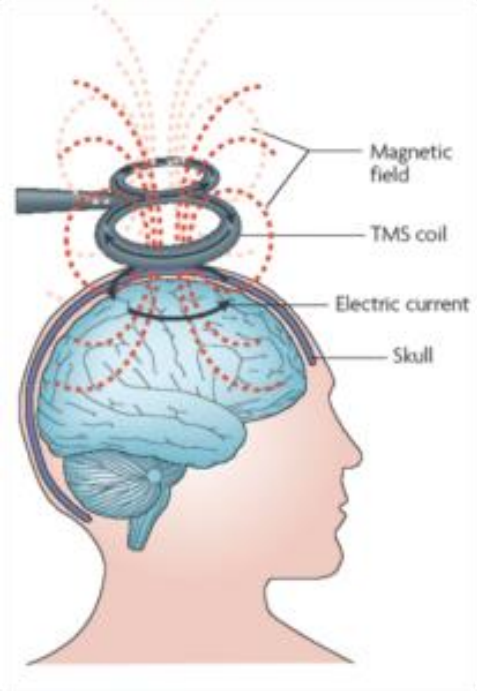


Figure 1: Transcranial magnetic stimulation. 12

There is evidence that the structure and function of other pain-processing regions in the brains of patients with migraine—for example, regions that participate in sensory discriminative, affective, and cognitive pain processing—are also atypical.

Several studies have found positive correlations between the extent of these abnormalities and the increasing frequency of headaches, suggesting that they are precursors to or biomarkers of transformation to chronic migraine.

Neuroimaging studies that have specifically studied patients with (CM) have found atypical pain processing and atypical structure of pain-processing brain regions in this status. Exuberant release of vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP) and the resultant neurogenic inflammation might also contribute to the pathophysiology of chronic migraine.[14]

A recent study found increased plasma concentrations of (CGRP) in migraines through the interictal phase of migraine compared with participants without migraine. In addition, CGRP concentrations were raised in patients with chronic migraine than in those with episodic migraine. It is not known whether high CGRP concentrations are the result of more frequent migraine attacks, thus serving as a potential biomarker of (CM), or whether they are part of the process that leads to more frequent migraine attacks.[14]

Genetics

Genetic factors are a part of deciding the risk of developing EM with and without aura. However, the role of a genetic influence on the progression of EM into CM remains to be cleared. The number of studies that specifically assess genetics in CM is extremely low and the relevance of their findings must be interpreted with caution.

According to the rare studies published on the possible genetic link to CM, three groups of genes have been proposed:

1. Genes are potentially linked to migraine or pain progression.
2. Genes potentially linked to addiction and analgesic overuse.
3. Other genes are involved in neuronal hyperexcitability or oxidative stress.

Catechol-O-methyltransferase (COMT) polymorphisms could be related to the predisposition to chronic pain conditions. Previous reports indicate that (COMT) forms are associated with susceptibility to EM, but no specific studies in CM have been conducted.

Numerous potential genes for drug addiction have been implicated in migraine chronification, particularly in individuals who abuse analgesics. It is remarkable that some of these three genes, which are implicated in the dopaminergic and serotonergic pathways, have also been identified as having a part to play in the pathophysiology of migraines.

Oxidative stress is a topic that is increasing in popularity regarding its relation to the pathophysiology of migraine. However, a study that scrupulous 10 polymorphisms in 8 oxidative stress-related genes in a few populations of CM patients did not detect a relationship with CM.

However, as migraine is considered a complex disease with multifactorial inheritance, Genome-Wide Association Study (GWAS) seems a more proper approach to studying migraine genetic background. To date, 4 (GWAS) studies and 3 meta-analyses have been performed in EM patients leading to the identification of (44) single nucleotide polymorphisms (SNPs) on 38 distinct genomic loci associated with migraine, involved in vascular natural function. Although the number of (SNPs) identified as associated with (EM) has steadily increased, our information on (CM) genetics remains poor.

Studies on the genetic association of several SNP tests did not give significant genetic risk factors for the development of CM. In 1019 individuals with CM or high-frequency migraine, the first in-depth investigation on the genetic relationship between (CM) and high-frequency migraine evaluated (144) SNPs from 48 genes but did not detect any meaningful correlations.

Given the complexity of CM and its potential polygenic origin, additional genetic variations are expected to contribute to the disease's susceptibility, showing that a large sample size of patients and controls is required to discover a genetic relationship with proper accuracy.

The importance of epigenetic processes in a wide range of multifactorial disorders, including migraine, has become abundantly obvious in recent years. There are some indications that neuronal activity during cortical spreading depression may result in epigenetic modifications related to neuronal plasticity, neuroprotection, and control of basal synaptic activity, even though there have been no particular investigations in CM patients yet.

It is therefore conceivable that increased neuronal activity in patients with high-frequency migraine may change the cerebral epigenome, thereby promoting subsequent attacks of migraine and creating a cycle in which the epigenetic programming of genes and pathways underlying excitability is changed towards a more sensitive baseline.

Genes involved in epigenetic processes and the epigenetic regulation of the Calcitonin Gene-Related Peptide (CGRP) gene are some of the (SNPs) linked to migraine. This data has highlighted the significance of epigenetic mechanisms in the pathogenesis and chronicity of migraines.[4]

Treatment

Some people with low frequency (EM) can be treated well with acute therapy (i.e., medications administered during the early symptom or the migraine attack to stop it), whereas those with (CM) always require prophylactic therapy.

The purpose of acute treatment is to stop a migraine attack once it has begun, while the purpose of prophylactic therapy is to prevent attacks from occurring. This reduces the frequency, severity, and associated disability of headaches and lessens the need for acute therapy, which may help prevent concurrent medication overuse headaches (MOH). Preventing the progression of (EM) to (CM) in patients with high-frequency EM may be another goal.[6] Patients with EM can be treated with recommended prophylactic therapy based on the number of attacks more than four and the degree of disability.

Analgesics, non-steroidal anti-inflammatory medications, and triptans should only be used as acute therapy options for headaches in individuals with (CM). Medications having barbiturates and opioids should also be avoided due to their strong associations with (MOH).

Triptans, which are drugs specifically designed to treat migraines, activate presynaptic (5HT1) receptors to prevent the production of (CGRP). Triptans, however, should only be taken two to three days a week at most by patients to prevent MOH, making them unsuitable for the treatment of (CM).

Effective acute treatment of migraine attacks with triptans may assist to halt the transition from EM to CM, but the goal of therapy for CM should be migraine attack prevention rather than depending on medication to stop migraine episodes once they have begun.

Conclusion

Chronic migraine is characterized by at least 15 headache days per month, with at least 8 of those days exhibiting migraine-like symptoms, for a period of time longer than three months. Less frequent headache episodes give way to a trend of increasingly regular headaches as the chronic headache progresses.

Chronic migraine develops over time due to several factors including increased numbers of episodic headaches over time and medications that were once used to treat episodes of headaches became overused to keep the increased number of headaches under control.

References

1 Schwedt, T. J. Chronic migraine. *BMJ: British Medical Journal* **348** (2014).

2 Su, M. & Yu, S. Chronic migraine: A process of demodulation and sensitization. *Mol Pain* **14**, 1744806918767697, doi:10.1177/1744806918767697 (2018).

3 Calabrò, R. S., Billeri, L., Manuli, A., Iacono, A. & Naro, A. Applications of transcranial magnetic stimulation in migraine: evidence from a scoping review. *J Integr Neurosci* **21**, 110, doi:10.31083/j.jin2104110 (2022).

4 Torres-Ferrús, M. *et al.* From transformation to chronification of migraine: pathophysiological and clinical aspects. *J Headache Pain* **21**, 42, doi:10.1186/s10194-020-01111-8 (2020).

5 Lucchesi, C. *et al.* Fatigue, sleep-wake pattern, depressive and anxiety symptoms, and body-mass index: analysis in a sample of episodic and chronic migraine patients. *Neurol Sci* **37**, 987-989, doi:10.1007/s10072-016-2505-1 (2016).
6 Bigal, M. E., Serrano, D., Reed, M. & Lipton, R. B. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. *Neurology* **71**, 559-566, doi:10.1212/01.wnl.0000323925.29520.e7 (2008).
7 Agostoni, E. C. *et al.* Current and emerging evidence-based treatment options in chronic migraine: a narrative review. *The Journal of Headache and Pain* **20**, 92, doi:10.1186/s10194-019-1038-4 (2019).
8 Cho, S.-J. & Chu, M. K. Risk Factors of Chronic Daily Headache or Chronic Migraine. *Current Pain and Headache Reports* **19**, 465, doi:10.1007/s11916-014-0465-9 (2014).

9 May, A. & Schulte, L. H. Chronic migraine: risk factors, mechanisms, and treatment. *Nature Reviews Neurology* **12**, 455-464 (2016).

10 Lipton, R. B. Tracing transformation. *Chronic migraine classification, progression, and epidemiology* **72**, S3-S7, doi:10.1212/WNL.0b013e3181974b19 (2009).

11 Diener, H. C., Solbach, K., Holle, D. & Gaul, C. Integrated care for chronic migraine patients: epidemiology, burden, diagnosis and treatment options. *Clin Med (Lond)* **15**, 344-350, doi:10.7861/clinmedicine.15-4-344 (2015).
12 https://www.walnutmedical.in/post/medstim-repetitive-trans-cranial-magnetic-stimulation-rtms
13 Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. Curr Pain Headache Rep. 2012 Feb;16(1):86-92. doi: 10.1007/s11916-011-0233-z. PMID: 22083262; PMCID: PMC3258393.
14 Lin, Y.-K., Tsai, C.-L., Lin, G.-Y., Chou, C.-H. & Yang, F.-C. Pathophysiology of Chronic Migraine: Insights from Recent Neuroimaging Research. Current Pain and Headache Reports 26, 843-854, doi:10.1007/s11916-022-01087-x (2022).
15 Barbanti, P. et al. Clinical features, disease progression, and use of healthcare resources in a large sample of 866 patients from 24 headache centers: A real-life perspective from the Italian chROnic migraiNe (IRON) project. Headache 61, 936-950, doi:10.1111/head.14123 (2021).

Article title: Hereditary spastic paraplegia.

Author: Tala Mohammad.

Editors: Haneen Al-Abdallat, Haneen A. Banihani.

Reviewer: Ethar Hazaimeh.

Keywords: Hereditary, Ataxia, Spastic, Motor, Neurodegenerative.

Overview and epidemiology

Hereditary spastic paraplegias (HSPs) are a group of neurodegenerative disorders characterized by motor neuron degeneration in the lower extremities,[1] with relative sparing of the rest of the body.[2] It is also known as Strumpell-Lorrain syndrome. HSPs are considered non-life-threatening but are linked with an inadequate quality of life.[3] They can be classified as pure or complex,[4] the latter associated with added neurological features.[2]

HSP is further divided according to the mode of inheritance, phenotype, and pathophysiology.[5] The disease may be autosomal dominant, recessive, X-linked, or a mitochondrial trait.[2] Moreover, the familial form is twice as widespread as the sporadic form in 70% of autosomal dominant HSP.[1] Almost 80 spastic paraplegia genes (SPGs) are present, with an incidence of up to 5 to 100,000 individuals worldwide.[1]

Criteria for Classification	Types
Symptoms and signs (Harding's classification)	Pure HSP Complex HSP
Age and onset of spasticity (Harding's classification)	Type I HSP (Early onset < 35 years) Type II HSP (Classical/late onset > 35 years)
Inheritance pattern	Autosomal dominant HSP Autosomal recessive HSP X-linked HSP Mitochondrial HSP *De Novo*
Intracellular involvement	Membrane/organelle trafficking Axonal transport Dysfunction of mitochondria Defective lipid metabolism Abnormalities in the myelination process

Table 1- HSP Classification [5].

Pathogenesis and etiology

In HSP, motor neurons are the most affected, and their degeneration results in most of the clinical signs.[6] Mutations often affect multiple pathways, ranging from the microtubule cytoskeleton to the mitochondrial compartment.[6] Furthermore, two groups of structures are more commonly implicated following gene mutations; kinesin, spastin, and paraplegin.

Kinesin and spastin are associated with microtubule function, while others, such as paraplegin and HSP60, are implicated in mitochondrial function.[7] Frequently, HSPs result from the degeneration of the longest neurons present in the pyramidal tract and dorsal columns.[1] Hence, patients present with motor symptoms and ataxia. Currently, approximately 60 genetic types have been isolated.[2] The nomenclature of HSP genotypes is grouped as SPGs, which stands for Spastic Paraplegia Genes, followed by the number of gene discoveries.[8] Studies have shown that SPG11 is the most common autosomal recessive HSP genetic type.[8] On another note, ataxia was a common presenting symptom in SPG7, SPG8, SPG20, SPG46, SPG58.[9] In addition, most SPG subtypes, particularly X-linked SPG2, are linked with thinning of the spinal cord.[1]

Clinical Presentation and Complications

Due to the diverse genetic markers that lead to HSP, many clinical manifestations exist.[1] Age of onset of HSP varies significantly, from as young as a couple of months up to 70 years of age.[4] Patients predominantly present with gait impairment resulting from lower extremity weakness and spasticity,[10] a feature which may only be evident while walking.[9]

According to a meta-analysis, gait disturbance was the patients' most common initial presentation.[9] Other presenting features include hyperreflexia and extensor plantar responses.[2] In most of the time, spasticity is more apparent than weakness.[11] Another critical presenting symptom is urinary urgency.[10] In a cross-sectional report survey, HSP patients reported polyuria and nocturia more often than controls. [12] Not to mention, HSP patients commonly complained of constipation, or alternating constipation and diahrrea.[12] Many individuals experience rapid progression of symptoms, such as worsening of gait impairment, in a uniform or nonuniform manner.[10] Moreover, early signs of HSP include mild stiffness, which may be accompanied by loss of muscle tone in the lower extremities.[1]

Workup and Diagnosis

Diagnosis depends on an extensive history and physical exam, considering the absence of family history should not rule out HSP.[2] Usually, HSP is diagnosed by exclusion, specifically in the absence of family history.[2]

Diagnostic differentials include multiple sclerosis and cerebral palsy. Following a comprehensive history, MRI findings may aid in diagnosis. A study reported significant cortical and subcortical atrophy in an Antero-caudal pattern in patients diagnosed with HSP.[13] Along the lines of another study, MRIs in known cases of autosomal dominant HSP indicate evident spinal cord atrophy.[14]

Management and prognosis

No studies have claimed an exact cure or prevention for HSP, and most management is directed toward improving quality of life. Management of HSP focuses mainly on symptoms such as stiffness and spasms,[1] for which oral anti-spastic medications, such as baclofen, can be used.[2] A study exploring possible HSP management showed that using botulinum toxin injections type A (Btx-A) effectively treats lower limb spasticity.[15] Similarly, a different study reported that Btx-A led to variable degrees of improvement in spasticity and gait velocity.[15] Not to mention the improvement of non-motor manifestations such as fatigue.[15]

Patients may also turn to physical therapy including exercise regimes and electrical stimulation.[1] It has been shown that a combination of both physiotherapy and medications provides a good outcome for patients[1] although no clear indications exist on the type and timing for best results.[16] Physiotherapy also shows extreme benefits towards healthy cardiovascular conditioning.[10]

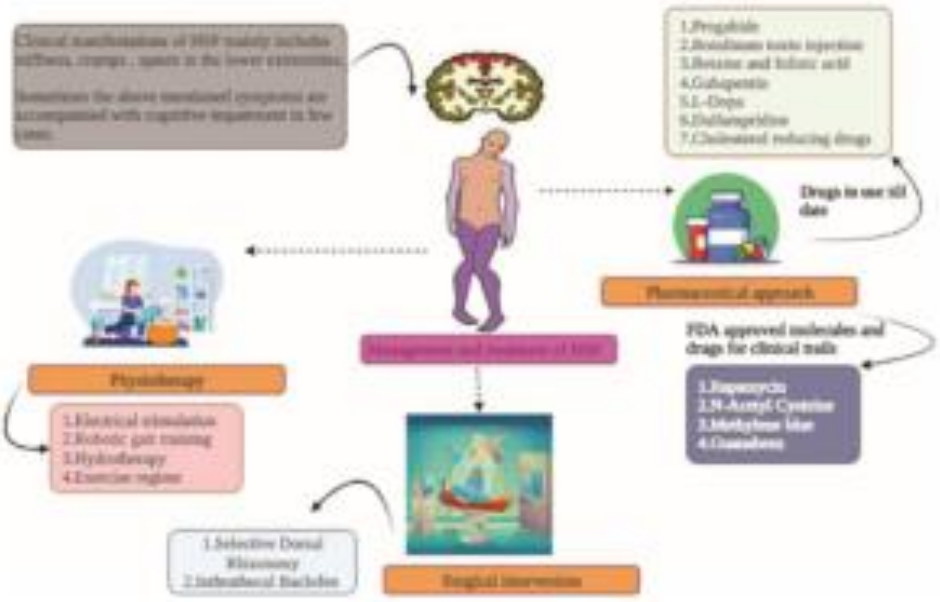


Figure 1- Overview of HSP management and treatment [1].

Surgical intervention may be opted for as a final resort. However, not many studies have been conducted to prove its efficacy. A case report outlined decreased spasticity and improved gait following intrathecal baclofen delivery.[17] Other studies shown that

selective dorsal rhizotomy (SDR), a procedure widely used to relieve spasticity related to cerebral palsy, has led to a significant decrease in spasms and spasticity.[16]

Patients' outcomes are highly variable and dependent on the associated genotype.[2] Generally, patients with pure-type HSP have an average life expectancy and do not suffer many complications.[10] Hence, the prognosis is variable and dependent on the patients themselves.

Recent updates[6]

Drugs have been tested on zebrafish; animal models of HSP, including dorsomorphin and miglustat. These drugs showed significant preservation of the motor phenotype. However, no clinical trials have been conducted yet.

References

1. Meyyazhagan A, Bhotla HK, Pappuswamy M. The Puzzle of Hereditary Spastic Paraplegia : From Epidemiology to Treatment. Published online 2022.
2. Faber I, Servelhere KR, Martinez ARM, Abreu AD, Lopes-cendes I, França-jr MC. Clinical features and management of hereditary spastic paraplegia. 2013;(November):219-226. doi:10.1590/0004-282X20130248
3. Article O. Hereditary Spastic Paraplegia in Koreans : Clinical. 2022;18(3):343-350.
4. Kara E, Tucci A, Manzoni C, et al. Genetic and phenotypic characterization of complex hereditary spastic paraplegia. Brain. 2016;139(7):1904-1918. doi:10.1093/brain/aww111
5. Meyyazhagan A, Orlacchio A. Hereditary Spastic Paraplegia : An Update. Published online 2022.
6. Marchesi T, Leblanc M, Stevanin G. Current Knowledge of Endolysosomal and Autophagy Defects in Hereditary Spastic Paraplegia. Published online 2021:1-24.
7. Watanabe F, Arnold WD, Hammer RE, et al. Pathogenesis of autosomal dominant hereditary spastic paraplegia (SPG6) revealed by a rat model. J Neuropathol Exp Neurol. 2013;72(11):1016-1028. doi:10.1097/NEN.0000000000000000
8. Wagner F, Titelbaum DS, Engisch R, Coskun EK, Waugh JL. Subtle Imaging Findings Aid the Diagnosis of Adolescent Hereditary Spastic Paraplegia and Ataxia. Clin Neuroradiol. 2019;29(2):215-221. doi:10.1007/s00062-018-0665-5
9. Fereshtehnejad SM, Saleh PA, Oliveira LM, et al. Movement disorders in hereditary spastic paraplegia (HSP): a systematic review and individual participant data meta-analysis. Neurol Sci. Published online 2022:947-959. doi:10.1007/s10072-022-06516-8
10. n, Eunsung Mouradian MM. 基因的改变NIH Public Access. Bone. 2008;23(1):1-7. doi:10.1038/nature08365.Reconstructing
11. Hecht MJ, Stolze H, dem Brinke MA, et al. Botulinum neurotoxin type A injections reduce spasticity in mild to moderate hereditary spastic paraplegia-report of 19 cases. Mov Disord. 2008;23(2):228-233. doi:10.1002/mds.21809
12. Kanavin ØJ, Fjermestad KW. Gastrointestinal and urinary complaints in adults with hereditary spastic paraparesis. Orphanet J Rare Dis. 2018;13(1):1-6. doi:10.1186/s13023-018-0804-8
13. Utz KS, Kohl Z, Marterstock DC, et al. Neuropsychology and MRI correlates of neurodegeneration in SPG11 hereditary spastic paraplegia. Orphanet J Rare Dis. Published online 2022:1-11. doi:10.1186/s13023-022-02451-1
14. Hedera P, Eldevik OP, Maly P, Rainier S, Fink JK. Spinal cord magnetic resonance imaging in autosomal dominant hereditary spastic paraplegia. Neuroradiology. 2005;47(10):730-734. doi:10.1007/s00234-005-1415-3
15. Servelhere KR, Faber I, Martinez A, et al. Botulinum toxin for hereditary spastic paraplegia: Effects on motor and non-motor manifestations. Arq Neuropsiquiatr. 2018;76(3):183-188. doi:10.1590/0004-282x20180013
16. Bellofatto M, De Michele G, Iovino A, Filla A, Santorelli FM. Management of hereditary spastic paraplegia: A systematic review of the literature. Front Neurol. 2019;10(JAN):1-10. doi:10.3389/fneur.2019.00003
17. Heetla HW, Halbertsma JP, Dekker R, Staal MJ, Van Laar T. Improved gait performance in a patient with hereditary spastic paraplegia after a continuous intrathecal baclofen test infusion and subsequent pump implantation: A case report. Arch Phys Med Rehabil. 2015;96(6):1166-1169. doi:10.1016/j.apmr.2015.01.012

Article topic: Charles Bonnet syndrome.

Author: Sarkis Gerges.

Editor: Lubna AL-Rawabdeh.

Reviewer: Ethar Hazaimeh.

Keywords: Charles Bonnet syndrome, visual hallucinations, visual impairment

Introduction

Charles Bonnet Syndrome (CBS), also called " phantom vision," is an illness where cognitively normal people experience simple or complex and consistent visual hallucinations, due to damage along the visual pathway.[1]This condition was named after the 18th-century botanist and philosopher, Charles Bonnet recounted the complex visual hallucinations experienced by his grandfather, Charles Lullin, in his work "Analytical Essay on the Faculties of the Soul."[2]

Depending on the study, the prevalence of CBS might range from 0.4% to 30% [1]. Differential CBS prevalence rates exist for a variety of reasons. First, no single definition of CBS has been endorsed by all medical professionals. Second, ophthalmology, geriatric medicine, and neurology are among the fields in which CBS is diagnosed. Third, many people are hesitant to admit that they have visual hallucinations out of concern that they will be branded as mentally ill [3,4,5].

Etiology and pathogenesis:

Many studies show no positive correlation between the risk of CBS and increased age [6,7]. Even though CBS affects geriatric populations because of the increased incidence of eye disease in the elderly, it can affect all ages suffering from visual impairment [8].

CBS can be caused by any factor affecting the visual pathway, extending from the visual cortex down to the eyes [9]. The most common etiologies include Figure (1):

- Age-related macular degeneration
- Diabetic retinopathy
- Cataract
- High Myopia
- Retinal vein occlusion

In addition to these etiologies, subjective feelings of loneliness, low extroversion, and shyness may contribute to an increased risk of being affected by CBS. [10]

The precise pathogenesis of CBS is still unknown. However, 2 main theories are suggested to explain the visual hallucinations experienced during CBS:

- The **deprivation theory** suggests that diminution in sensory input leads to the production of spontaneous images from the visual association cortex, resulting in visual hallucinations [12].
- The **'release theory'** suggests that a lesion of the visual pathway causes abnormal signals to be sent to the visual cortex. The hallucinations result from a combination of normal and abnormal signals at the level of the visual association cortex [12].

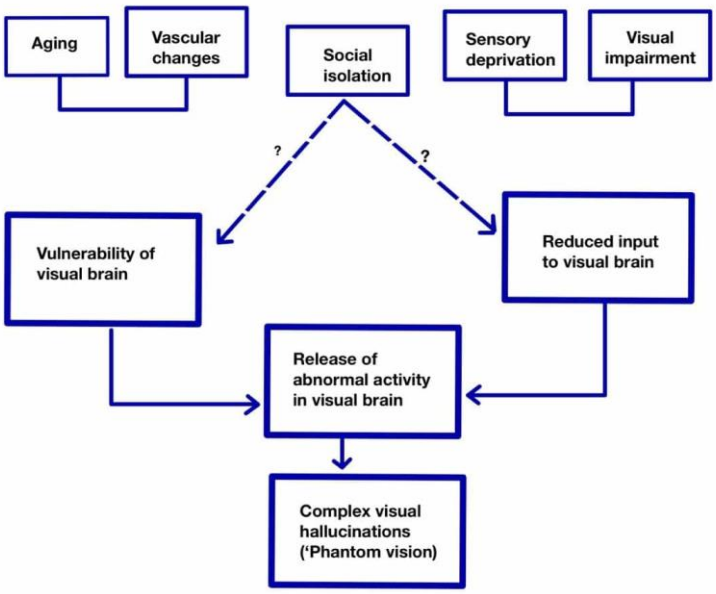


Figure (1): Factors contributing to CBS pathogenesis Charles Bonnet syndrome

Clinical presentation

Clinical case

A 91-year-old patient suffers from age-related macular degeneration and chronic diseases such as hypertension and has geographic atrophy in both eyes. This patient was diagnosed with CBS after seeing many complex images several times over 2 weeks. In addition, The hallucinations lasted for only a minute, and were not scary to the patient, as he was able to know they were not there.[11] The following 2 figures (Figures 2 and 3) show the patient's posterior pole of both eyes where we can notice a large geographic atrophy.[11]

Figure 2: Posterior Pole O.D.

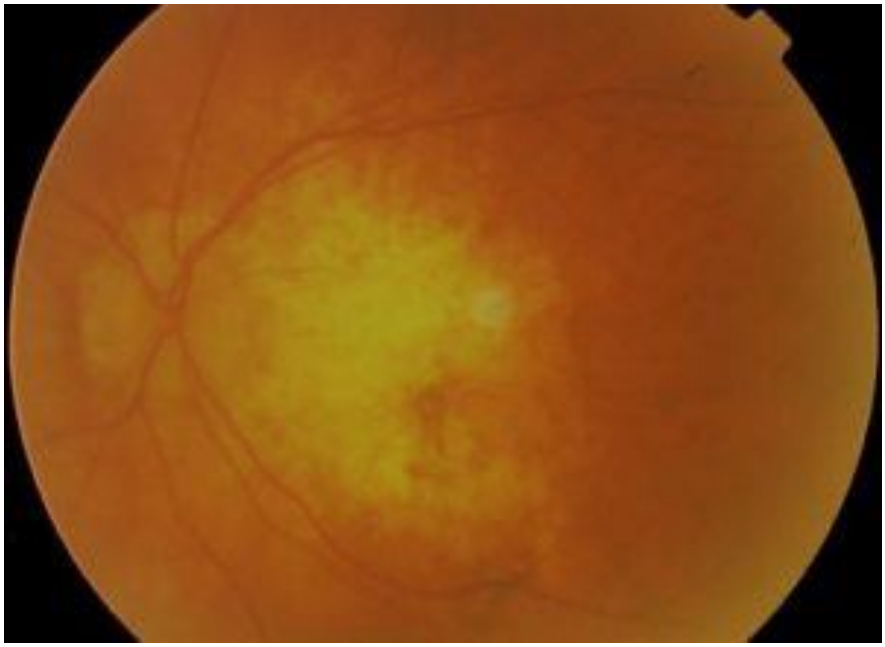


Figure 3: Posterior Pole O.S.

Clinical Characteristics

The frequency and timing of the hallucinations can vary widely among patients with Charles Bonnet Syndrome. Hallucinations can be episodic, periodic, or chronic. The hallucinations are usually daily (like in the presented case), but they may be weekly and tend to occur upon awakening [6,14].

Furthermore, patients who have recently begun hallucinations hallucinate more frequently than those who suffer from chronic hallucinations. In addition, the hallucinations tend to last for several minutes (70%), but in some cases, the duration of hallucinations can be seconds or hours [14].

Unfamiliar or familiar images may be seen during hallucinations. Hallucinations may occur in color or in black and white, they could be motionless or not. In addition, hallucinations could be less clear in comparison to reality. Usually, patients hallucinate only with their eyes open [9]. Finally, patients suffering from CBS are mentally and cognitively normal.

Complications

CBS is described as a temporary condition not associated with significant adverse complications outside of aggravating illusions. However, approximately 32% of CBS patients suffer from psychological problems such as anxiety and emotional distress due to hallucinations, thus, a continuous psychological follow-up is required. [15,16]

Workup and Diagnosis

In addition to CBS, visual hallucinations can be caused by different neurological, psychiatric, and metabolic disorders (Table 1). Hence, these etiologies must be ruled out to diagnose CBS by performing psychological and neurological tests such as MMSE and CT scans. CBS is considered a diagnosis of exclusion, but the diagnosis can be more difficult because of the comorbidities, especially in the elderly. [17,18]

Neurologic disorders	Hemispheric lesions Parkinson's disease Lewy-body dementia Brain-stem lesions Epilepsy Migraine Narcolepsy-cataplexy syndrome
Psychiatric disorders	Acute psychosis Delirium Schizophrenia Affective disorder Conversion reactions

Toxic and metabolic disorders	Metabolic encephalopathies are caused by cardiopulmonary insufficiency, uremia, hepatic disease, endocrine disturbances, and vitamin deficiency states. inflammatory and infectious diseases Hallucinogenic agents Drug and alcohol withdrawal syndromes Medications or toxin side effects
Miscellaneous conditions	Sensory and sleep deprivation Hypnopompic or hypnagogic states Intense emotional experiences (stress, grief) Charles Bonnet syndrome

Table (1): Causes of visual hallucinations [17]

Treatment and management:

Management of CBS can vary depending on the severity of symptoms. In mild symptoms, reassurance is sufficient in 94% of the cases. However, in more severe symptoms, CBS can be managed by medications and behavioral techniques, such as blinking during a hallucination, rapid eye movement from one object to another, or improved lightning. [12,19]. In addition to these techniques, many other types of treatments could be given

Pharmacotherapy

Used to treat patients who suffer from continuous and disturbing hallucinations. In such cases, physicians may prescribe low doses of atypical antipsychotics such as olanzapine and quetiapine or cholinesterase inhibitors such as donepezil, since these drugs show good efficacy and minimal side effects. [19,20,21].

Psychological therapy

Psychological therapy techniques such as hypnosis, relaxation, and cognitive remodeling have been advocated to minimize visual hallucinations' disturbing effects.[22]

Optimizing Visual Function

Hallucinations may disappear through optical correction, although visual deficit correction may not always be possible [1]. Removal of a cataract, treatment of diabetic retinopathy, and laser photocoagulation of a subretinal hemorrhage (all with resultant improvement in vision) have been associated with the alleviation of illusions.[17]

Prevention

There is no concrete way to prevent CBS, but preserving the vision can reduce the risks. Therefore, people, especially the elderly, must have regular eye exams. [24]

Prognosis

Recent studies suggest that CBS takes more than 8 years to be resolved, in other words, hallucinations' frequency tends to decrease after a prolonged period. However, an old study shows that Charles Bonnet syndrome tends to resolve spontaneously within a year, as was the case for Charles Lullin. [25,26,27]

References

1. Linda Pang, Hallucinations Experienced by Visually Impaired: Charles Bonnet Syndrome, 2016 Dec;93(12):1466-1478.
2. Lee Jones, Lara Ditzel-Finn, Jamie Enoch, Mariya Moosajee An overview of psychological and social factors in Charles Bonnet syndrome, 2021 Jul 30;13:25158414211034715
3. Wilkinson F. Auras and other hallucinations: windows on the visual brain. Prog Brain Res 2004; 144:305Y20.
4. Eperjesi F, Akbarali N. Rehabilitation in Charles Bonnet Syndrome: a review of treatment options. Clin Exp Optom 2004; 87:149 Y52.
5. Chen CS, Lin SF, Chong MY. Charles Bonnet syndrome and multiple sclerosis. Am J Psychiatry 2001; 158:1158Y9
6. Khan JC, Shahid H, Thurlby DA, Yates JRW, Moore AT. Charles Bonnet Syndrome in age-related macular degeneration: the nature and frequency of images in subjects with end-stage disease. Ophthalmic Epidemiol 2008;15:202Y8.
7. Menon GJ. Complex visual hallucinations in the visually impaired: a structured history-taking approach. Arch Ophthalmol 2005;123: 349Y55.
8. Wilkinson F. Auras and other hallucinations: windows on the visual brain. Prog Brain Res 2004;144:305Y20.
9. Teunisse RJ, Cruysberg JR, Hoefnagels WH, Verbeek AL, Zitman FG. Visual hallucinations in psychologically normal people: Charles Bonnet's syndrome. Lancet. 1996 Mar 23;347(9004):794-7.
10. Teunisse RJ, Cruysberg JR, Hoefnagels WH, et al. Social and psychological characteristics of elderly visually handicapped patients with Charles Bonnet syndrome. Compr Psychiatry 1999;40:315-9.
11. Kilda Carpenter, Jasleen K Jolly, Holly Bridge: The elephant in the room: understanding the pathogenesis of Charles Bonnet syndrome, 2019 Nov;39(6):414-421.
12. Anita P Schadlu, Ramin Schadlu, J Banks Shepherd 3rd: Charles Bonnet syndrome: a review. Curr Opin Ophthalmol: 2009 May;20(3):219-22
13. Yaacoub, S.Ferucci, Charles Bonnet syndrome. 2011 Jul;82(7):421-7.
14. Vukicevic M, Fitzmaurice K. Butterflies, and black lacy patterns: the prevalence and characteristics of Charles Bonnet hallucinations in an Australian population. Clin Experiment Ophthalmol 2008; 36:659–665
15. R Bou Khalil, S Richa: Psychiatric, psychological comorbidities of typical and atypical Charles-Bonnet syndrome 2011 Dec;37(6):473-80
16. Cox TM, ffytche DH. Negative outcome Charles Bonnet syndrome. Br J Ophthalmol. 2014 Sep;98(9):1236-9.
17. Elizabeth M Kester. Charles Bonnet syndrome: case presentation and literature review. 2009 Jul;80(7):360-6.
18. Ali G Hamedani, Victoria S Pelak The Charles Bonnet Syndrome: a Systematic Review of Diagnostic Criteria: 2019 Jul 25;21(9):41

19. Vaphiades MS, Celesia GG, Brigell MG. Positive spontaneous visual phenomena are limited to the hemianopic field in lesions of central visual pathways. Neurology. 1996 Aug;47(2):408-17.
20. Alao AO, Hanrahan B. Charles Bonnet syndrome: visual hallucination and multiple sclerosis. Int J Psychiatry Med. 2003;33(2):195-9.
21. Coletti Moja M, Milano E, Gasverde S, et al. Olanzapine therapy in hallucinatory visions related to Bonnet syndrome. Neurol Sci 2005; 26:168–170
22. Ukai S, Yamamoto M, Tanaka M, Takeda M. Treatment of typical Charles Bonnet syndrome with donepezil. Int Clin Psychopharmacol. 2004 Nov;19(6):355-7.
23. Norelli SK, Long A, Krepps JM. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Aug 29, 2022. Relaxation Techniques.
24. Charles Bonnet Syndrome, Cleveland Clinic : https://my.clevelandclinic.org/health/diseases/24403-charles-bonnet-syndrome
25. Gold K & Rabins PV. Isolated visual hallucinations and the Charles Bonnet syndrome: A review of the literature and presentation of six cases. Compr Psychiatry 1989; 30: 90–98.
26. Khan J, Shahid H, Thurlby D, Yates J & Moore A. Charles Bonnet syndrome in age-related macular degeneration: the nature and frequency of images in subjects with end-stage disease. Ophthalmic Epidemiol 2008; 15: 202–208.
27. Santhouse AM, Howard RJ & Ffytche DH. Visual hallucinatory syndromes and the anatomy of the visual brain. Brain 2000; 123: 2055–2064.

Article topic: Dystonia.

Author: Amr Atef Hassan.

Editor: Ahmad Abuaisheh, Rahmeh Abdullah.

Reviewer: Ethar Hazaimeh.

Keywords**: **Dystonia, Etiology, Wilson's disease, Botulinum toxin

Abstract

Dystonia is a neurological disorder that manifests as abnormal, involuntary movements or positions due to ongoing or intermittent muscle contractions. In a recent consensus, dystonia is now classified into two axes to define its clinical features and underlying causes. This classification system enables exact recognition of both isolated and combined forms of dystonia while still incorporating the descriptions of generalized and focal dystonia, which prove valuable in planning investigations and treatment strategies. This article explores the characterization of dystonia for improved identification and provides a concise overview of its management. Treatment options for dystonia encompass medications, botulinum toxin, and deep brain stimulation.

Overview

Dystonia is recognized as the third most prevalent movement disorder, following Parkinson's disease and essential tremor (1). A definition for dystonia was established by a committee of the Dystonia Medical Research Foundation's Scientific Advisory Board in February 1984, which remained valid until 2013 when an international committee developed a new concept (2). This neurological disorder is characterized by abnormal and involuntary muscle contractions, leading to sustained abnormal postures, twisting, or both, as well as repetitive movements of body parts (3).

Dystonia can be a significant or presenting feature in many neurodegenerative diseases (4). In most cases, dystonia is a combination of abnormal movements and postures. However, some types, such as blepharospasm and laryngeal dystonia, are not associated with postures but instead involve focal involuntary contractions that interfere with the physiological opening or closing of the eyelids or larynx (5). Dystonia may occur alone or in combination with other clinical issues (6).

The prevalence of dystonia has been reported to be around 164 per million, with focal cervical dystonia [CD] being the most common type (7). Prevalence estimates also depend on age, with early-onset dystonia (<20 years) estimated to be between 0.3 and 5

cases per 100,000, while adult-onset (>20 years) dystonia is between 0.3 and 732 cases per 100,000 (8). The aim of this article is to shed light on dystonia, with a focus on its definition, etiology, clinical classification, and management.

Etiology

Over the years, the genetics of dystonia have been extensively studied, resulting in the identification of a multitude of genes that can cause this movement disorder (9). Despite the advancements in our understanding of dystonia's etiology, the underlying cause of most forms remains unclear (table 1). As new clinical, genetic, and basic science information appears, the classification of dystonia based on etiology will need to be continually updated (1).

Nervous system pathology	Inherited	Acquired	Unknown
Nervous system pathology with degeneration (or heredodegenerative)	Autosomal dominant	Perinatal brain injury	Sporadic
Neurodegeneration with brain iron accumulation	Autosomal recessive	Infection/ inflammation	Familial

Wilson's disease	X-linked Recessive Exposure to a neurotoxic agent	Toxic
	Mitochondrial	Drug Vascular Brain injury Neoplastic Functional

Table (1): The etiology of dystonia (1,10)

Inherited dystonia

Inherited forms of dystonia are confirmed to have a genetic basis and can be further divided into multiple subgroups based on their pattern of inheritance (1):

Autosomal dominant dystonia encompasses several forms, including DYT-TOR1A, DYT/PARK-GCH1, DYT-THAP1, DYT-SGCE, and DYT/PARK-ATP1A3.

Autosomal recessive dystonia includes several forms, such as DYT-ATP7B (also known as Wilson disease), NBIA/DYT-PANK2 (pantothenate kinase-associated neurodegeneration), NBIA/DYT/PARKa-PLA2G6 (PLA2G6-associated neurodegeneration), and multiple metabolic disorders.

X-linked recessive dystonia consists of disorders such as DYT/PARK-TAF1, DYT/CHOR-HPRT (Lesch-Nyhan syndrome), and DYT-TIMM8A (Mohr-Tranebjaerg syndrome).

Mitochondrial dystonia is caused by mutations in the mitochondrial genome and includes forms such as Leigh syndrome or DYT-mt-ND6 (Leber optic atrophy and dystonia). It is worth noting that a significant number of recessive forms (autosomal and X-linked) and mitochondrial forms are classified as complex dystonia forms, while all isolated dystonia with a known genetic cause are inherited in an autosomal dominant fashion.

Nervous system pathology

Dystonia can be caused by various inherited degenerative diseases, including autosomal-dominant and autosomal-recessive conditions, X-linked dominant and recessive conditions, and mitochondrial defects. The neurodegenerative process can manifest in additional symptoms and signs, and dystonia may be observed.

Wilson's disease is a common cause of dystonia and can present as generalized, segmental, or multifocal dystonia, with cranial involvement being characteristic. Other common signs include the "sardonic" smile, wing-beating tremor, dysarthria, dysphagia, drooling, ataxia, and dementia. The disease can affect the brain, liver (cirrhosis, acute hepatitis), eyes (Keyser-Fleischer rings), heart, kidneys, bones, joints, glands, and muscles. As the condition is potentially treatable, it should be considered when observing any patient with movement disorders (10).

The pathologic changes in Wilson's disease are typically observed in central gray matter nuclei and white matter tracts in the brainstem, with the underlying cause of the high susceptibility of these brain regions to copper toxicity unknown (11,12). Most severe abnormalities are present in the putamen, which is typically shrunken, soft, and brown-yellowish discolored. In severe cases, putaminal necrosis with iron-laden macrophages surrounding the necrotic cavity may occur (13), and cavitation can be rarely found in the thalamus, dentate nucleus, or white matter (14,15).

Cellular alterations have been identified in specific forms of dystonia, such as neuronal inclusions in brainstem nuclei in patients with DYT-TOR1A, showing abnormalities on the cellular level. These findings require further replication and extension, as is true for another line of research linking dystonia to cerebellar dysfunction based on Purkinje cell loss and axonal swelling in the cerebellum of patients suffering from cervical dystonia (1).

Acquired dystonia

Acquired dystonia can occur secondary to a precipitating event. About half of the children with dystonia have an acquired cause for their condition, which can include hypoxic brain injury at birth, preterm delivery, and kernicterus. The timing of dystonia onset can vary after a causal event. For example, in drug-induced dystonia, acute reactions can be seen hours after the administration of antidopaminergic medications (e.g., metoclopramide, and prochlorperazine). One of the most common presentations is an oculogyric crisis, where the patient has an upward, conjugate, tonic deviation of the eye (16). Other causes of acquired dystonia can include perinatal injury, stroke, head trauma or peripheral trauma, brain tumor, exposure to neurotoxic agents, Japanese B encephalitis, encephalitis lethargica, brain abscesses (mostly involving the basal ganglia), cerebellum, and thalamus (10).

Functional dystonia should be considered in patients with dystonia who display atypical patterns of muscle movement, fixed dystonia, or experience a reduction in symptoms when distracted. This condition is often understood through a biopsychosocial framework that takes into account factors that contribute to abnormal brain processing of sensory and motor signaling. Identifying functional dystonia and providing a mechanistic explanation for the patient's symptoms can lead to significant improvement in their condition. It is important to note that functional dystonia should not be excluded as a diagnosis and should be actively considered alongside other probable causes of dystonia.

Unknown dystonia

Dystonia can be categorized as either sporadic or familial, with the latter indicating a possible genetic contribution. The identification of new dystonia-related genes, including GNAL, ANO3, KCTD17, and KMT2B, has allowed these subtypes to be classified as inherited forms of dystonia (1).

Classification of dystonia

Once a movement disorder is identified as dystonic in nature, it should be further characterized according to the current classification system, which was established by the Movement Disorder Society in 2013 (17).

This classification system includes Axis I Clinical Characteristics and Axis II Etiology. Clinical characteristics of dystonia include age of onset, body distribution, and temporal pattern, as shown in Table (2). Associated features include whether the dystonia is isolated or combined with another movement disorder and any accompanying neurological or systemic symptoms (18).

Age at onset	Body distribution	Temporal pattern	Associated features
Infancy (birth to 2 years)	Focal	Disease course: - Static - Progressive	Isolated (no other feature)
Childhood (3-12 years)	Multifocal	Variability : 1- Persistent 2- Paroxysmal 3- Diurnal 4- Action- specific	Combined (+ Another movement disorder)
Adolescence (13-20 years)	Segmental		Complex (+ other manifestation, may include non-neurological)
Early adulthood (21-40 years) Late adulthood (>40 years)	Generalized +/- leg involvement Hemidystonia		

Table (2): Clinical characteristics of dystonia. (1)

Age at onset

According to research, dystonia that begins in childhood is more likely to have an identifiable acquired cause and may progress from focal to generalized, while typical adult-onset focal dystonia is more likely to be a subtype of isolated dystonia and usually

does not spread (19). This classification follows established neurological disorder classifications and informs prognosis and diagnosis (17).

Childhood dystonia is a heterogeneous condition in terms of its clinical presentation and genetics. Emerging evidence indicates that mutations in genes associated with neurodevelopmental disorders may play a role in the development of dystonia that appears early in life (20).

Body distribution

Dystonic signs can occur in any part of the body, but commonly affect the cranial and cervical regions, larynx, trunk, and limbs, either individually or in combination (1). Dystonia can be categorized based on how it affects different parts of the body, including:

- Focal dystonia, which affects only one specific region of the body.
- Segmental dystonia, which affects two or more adjacent regions of the body.
- Multifocal dystonia, which affects two or more non-adjacent regions of the body.
- Hemidystonia, which affects one-half of the body.
- Generalized dystonia, which affects the trunk and at least three other areas of the body.

Temporal pattern

The time course of the disease is a crucial clinical feature that aids in diagnosis and treatment decisions. The disease course distinguishes static forms from progressive forms and is an essential temporal characteristic (5). Pediatric neurologists commonly use this terminology, but it is also applicable to adult cases.

Diurnal variability is used to differentiate dystonia that consistently occurs under the same conditions from variable forms, including task-specific, action-specific, and spontaneous dystonia.

Paroxysmal dystonia is distinct from dystonia which is always triggered by the same action or activity (task-specific dystonia). In paroxysmal dystonia, the same trigger may or may not cause an attack, while in action dystonia, the same motor activity will predictably induce dystonia (5).

Paroxysmal dystonia typically lasts after the trigger has ended, while action (or task-specific) dystonia is only present during the inducing action.

Dystonia variability can have four different patterns:

- Persistent dystonia, which persists to approximately the same extent throughout the day.
- Diurnal fluctuations, where dystonia varies during the day and has recognizable circadian variations in occurrence, severity, and phenomenology.
- Paroxysmal dystonia, a sudden self-limited episode of dystonia typically induced by a trigger with a return to the pre-existing neurological condition.
- Action-specific dystonia, which only occurs during a particular activity or task.

Associated features

Associated features are divided into:

- Isolated dystonia
- Combined dystonia
- Complex dystonia

According to research (1), various syndromes may arise from dystonia, including isolated dystonia or dystonia combined with myoclonus, parkinsonism, or other movement disorders. The term "primary" was coined to describe syndromes in which dystonia is the only phenotypic manifestation (with or without dystonic tremor).

Primary dystonia is characterized by dystonia being the sole clinical sign, and typically, there are no identifiable secondary causes or consistently associated brain pathology. Dystonia can emerge at any age, and age at onset is an important variable that affects clinical presentation and prognosis. Some cases of isolated dystonia have a genetic basis, with three genes currently known to cause the condition: TOR1A, THAP1, and GNAL. Additionally, three other genes (CIZ1, ANO3, and TUBB4) have recently been implicated and require further confirmation (22).

Combined dystonia, on the other hand, refers to cases in which dystonia is combined with other movement disorders, such as myoclonus or parkinsonism (5).

Diagnosis of dystonia

Currently, the diagnosis of dystonia is primarily based on physical examination and pattern recognition by an experienced clinician. This can be challenging due to the wide range of dystonia phenotypes and etiologies, as well as dystonia mimics like functional dystonia. Dystonia can present with distinctive characteristics, including as the only

symptom or part of a mixed neurological or systemic disorder. Childhood-onset dystonia can be particularly difficult to classify both etiologically and clinically (23).

Patients with isolated dystonia may require a laboratory workup depending on their age at onset, body distribution, and the presence of affected family members. Adults with focal or segmental dystonia may not require any diagnostic tests as they are often unrevealing. However, in adults with hemidystonia or generalized dystonia, neuroimaging may be useful as there is a higher likelihood of finding a structural cause.

Genetic testing may not be cost-effective for sporadic adult-onset isolated dystonia unless other family members are affected. Younger individuals with isolated dystonia require a different diagnostic approach as there is a higher likelihood of finding a cause. Neuroimaging is important for all early-onset cases, and genetic testing should target specific genes for early-onset isolated dystonia (6).

For patients with combined dystonia, an additional workup is warranted regardless of age at onset or body distribution, depending on the nature of associated features. Neuroimaging is useful in all combined dystonia, as it can provide important diagnostic clues. Genetic testing for DYT1 and DYT6 dystonia is not useful in combined dystonia syndromes, but laboratory testing is driven by the syndromic pattern. For example, dystonia combined with Parkinsonism may lead to a relatively small list of disorders for more targeted diagnostic testing (6).

Management of dystonia

Patients with suspected dystonia should be referred to a specialist in movement disorders for further evaluation and access to proper treatment. Blood tests, including a full blood count, urea and electrolytes, liver function tests, and caeruloplasmin, can be conducted at this stage. Brain imaging is often reserved for neurological review since imaging protocols are tailored to the patient's clinical features. Treatment for dystonia depends on the underlying cause. In general, botulinum toxin injections are the first-line treatment for focal dystonia, while oral medications and surgery are used to treat generalized dystonia (20).

Treatment of dystonia

There are several treatment options available for dystonia, including counseling and education, oral medications, botulinum neurotoxin injections, physical and occupational therapy, and neurosurgical interventions (6).

Pharmacological treatments may involve dopaminergic, antidopaminergic, and anticholinergic therapies, baclofen, benzodiazepines, muscle relaxants, dopamine

depleters, and other medications (24). Unfortunately, many patients require a combination of treatments, and a considerable number of patients may not respond to medical treatment due to poor tolerability or lack of benefit, especially with high doses of anticholinergic drugs in adults (25).

Anticholinergic Medications

The class of drugs known as anticholinergics is often used to treat dystonia. The most prescribed medication of this class is trihexyphenidyl, but other drugs like benztropine, ethopropazine, procyclidine, and biperiden have also been used. A small trial has even shown that diphenhydramine, which is a histamine H1 antagonist with anticholinergic properties, can be effective in treating dystonia. These drugs are believed to work by reducing the hyperactivity of cholinergic interneurons in the striatum. The choice of which drug to prescribe may depend on factors such as the patient's individual symptoms and medical history (26).

Botulinum toxin (BoNT) is a commonly used first-line therapy for many dystonic syndromes, with a long record of accomplishment of safety and efficacy (27). It is particularly effective in reducing hypertonia, but it does not improve strength or directly improve function (28). BoNT works by blocking the release of acetylcholine into the neuromuscular junction, causing local temporary chemodenervation and muscle paralysis (28). It is important to note that BoNT must be used carefully and in combination with an active program of other rehabilitation techniques, as it only improves function in cases where a few muscles are the major cause of disability (28). Large safety studies have shown that BoNT is safe and effective for clinical use, and its uses have expanded greatly over the past three decades. Dr. Alan Scott, an ophthalmologist, first described the effect of BoNT on extraocular movements in monkeys affected by strabismus in 1981 (27).

Benzodiazepines, such as clonazepam, are often used in dystonia, although their efficacy has not been evaluated in large, controlled studies. Open and retrospective studies have shown efficacy in treating generalized and focal dystonia, particularly in blepharospasm and cervical dystonia with predominant head tremors (29).

Deep brain stimulation (DBS) has become a major therapy option for movement disorders, including dystonia (30). GPi and subthalamic nucleus (STN) are the two main targets for DBS in dystonia treatment (31). Certain types of genetic dystonia, such as TOR1A, KMT2B, TAF1, and SGCE, typically have better responses to DBS than others, such as THAP1, ATP1A3, and GNAL (31).

Posteroventral pallidal deep brain stimulation (DBS) is a highly effective treatment for severe, medication-resistant generalized and segmental dystonia, as well as certain forms of focal dystonia. Studies have demonstrated long-term improvement in motor

symptoms and activities of daily living, with average improvement rates ranging from 50 to 60% depending on various factors. However, as is the case with DBS for Parkinson's disease and essential tremors, while symptoms are often significantly improved, they are rarely eliminated, highlighting the need for continued improvements in the technique (26).

Conclusion

Although dystonia is a common symptom, the number of neuropathologically studied cases of human dystonia remains limited. This can be attributed to several factors, including the rarity of dystonia being the direct cause of death, and cultural barriers in certain populations such as Ashkenazi and Amish peoples, who have a higher incidence of genetic dystonia like DYT1. However, advances in data collection on dystonia patients have allowed for large cross-sectional studies that can identify factors influencing the prevalence and clinical characteristics of dystonia, including tremors.

References

1- Grütz K, Klein C. Dystonia updates: definition, nomenclature, clinical classification, and etiology. J Neural Transm (Vienna). 2021 Apr;128(4):395- 404. doi: 10.1007/s00702-021-02314- 2. Epub 2021 Feb 19. PMID: 33604773; PMCID: PMC8099848.

2- Camargo CH, Teive HA. Evolution of the concept of dystonia. Arq Neuropsiquiatr. 2014 Jul;72(7):559-61. doi: 10.1590/0004-282x20140056. PMID: 25054990.

3- Snaith A, Wade D. Dystonia. BMJ Clin Evid. 2011 Jun 13;2011:1211. PMID: 21663705; PMCID: PMC3275299.

4- LeDoux MS. Dystonia: phenomenology. Parkinsonism Relat Disord. 2012 Jan;18 Suppl 1(Suppl 1):S162-4. doi: 10.1016/S1353-8020(11)70050-5. PMID: 22166421; PMCID: PMC4869992.

5- Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013 Jun 15;28(7):863-73. doi: 10.1002/mds.25475. Epub 2013 May 6. PMID: 23649720; PMCID: PMC3729880.

6- Jinnah HA, Factor SA. Diagnosis and treatment of dystonia. Neurol Clin. 2015 Feb;33(1):77- 100. doi: 10.1016/j.ncl.2014.09.002. PMID: 25432724; PMCID: PMC4248237.

7- Ortiz R, Scheperjans F, Mertsalmi T, Pekkonen E. The prevalence of adult- onset isolated dystonia in Finland 2007-2016. PLoS One. 2018 Nov 20;13(11):e0207729. doi: 10.1371/journal.pone.0207729. PMID: 30458031; PMCID: PMC6245745.

8- Bailey GA, Rawlings A, Torabi F, Pickrell O, Peall KJ. Adult-onset idiopathic dystonia: A national data-linkage study to determine epidemiological, social deprivation, and mortality characteristics. Eur J Neurol. 2022 Jan;29(1):91- 104. doi: 10.1111/ene.15114. Epub 2021 Oct 15. PMID: 34543508; PMCID: PMC9377012.

9- Standaert DG. Update on the pathology of dystonia. Neurobiol Dis. 2011 May;42(2):148-51. doi: 10.1016/j.nbd.2011.01.012. Epub 2011 Jan 8. PMID: 21220015; PMCID: PMC3073692.

10- Batla A. Dystonia: A review. Neurol India. 2018 Mar- Apr;66(Supplement):S48-S58. doi: 10.4103/0028-3886.226439. PMID: 29503327.

11- Poujois A, Mikol J, Woimant F. Wilson disease: brain pathology. Handb Clin Neurol. 2017;142:77-89. doi: 10.1016/B978-0-444-63625-6.00008-2. PMID: 28433113.

12- Horoupian DS, Sternlieb I, Scheinberg IH. Neuropathological findings in penicillamine- treated patients with Wilson's disease. Clin Neuropathol. 1988 Mar-Apr;7(2):62-7. PMID: 3390974.

13- Dusek P, Bahn E, Litwin T, et al. Brain iron accumulation in Wilson disease: a post mortem 7 Tesla MRI - histopathological study. Neuropathol Appl Neurobiol 2017;43:514-32. 10.1111/nan.12341

14- Richter R. The pallial component in hepato-lenticular degeneration. J Neuropathol Exp Neurol 1948;7:1-18. 10.1097/00005072-194801000-00001

15- Mikol J, Vital C, Wassef M, et al. Extensive cortico-subcortical lesions in Wilson's disease: clinico-pathological study of two cases. Acta Neuropathol 2005;110:451-8. 10.1007/s00401- 005-1061-1.

16- Sadnicka A, Meppelink AM, Kalinowski A, Oakeshott P, van den Dool J. Dystonia. BMJ. 2022 Apr 11;377:e062659. doi: 10.1136/bmj-2020-062659. PMID: 35410890; PMCID: PMC9070304.

17- di Biase L, Di Santo A, Caminiti ML, Pecoraro PM, Di Lazzaro V. Classification of Dystonia. Life (Basel). 2022 Jan 29;12(2):206. doi: 10.3390/life12020206. PMID: 35207493; PMCID: PMC8875209.

18- Medina A, Nilles C, Martino D, Pelletier C, Pringsheim T. The Prevalence of Idiopathic or Inherited Isolated Dystonia: A Systematic Review and Meta- Analysis. Mov Disord Clin Pract. 2022 Aug 24;9(7):860-868. doi: 10.1002/mdc3.13524. PMID: 36247920; PMCID: PMC9547134.

19- Sadnicka A, Meppelink AM, Kalinowski A, Oakeshott P, van den Dool J. Dystonia. BMJ. 2022 Apr 11;377:e062659. doi: 10.1136/bmj-2020-062659. PMID: 35410890; PMCID: PMC9070304.

20- Doummar D, Treven M, Qebibo L, Devos D, Ghoumid J, Ravelli C, Kranz G, Krenn M, Demailly D, Cif L, Davion JB, Zimprich F, Burglen L, Zech M. Childhood-onset progressive dystonia associated with pathogenic truncating variants in CHD8. Ann Clin Transl Neurol. 2021 Oct;8(10):1986-1990. doi: 10.1002/acn3.51444. Epub 2021 Aug 20. PMID: 34415117; PMCID: PMC8528468.

21- Titi-Lartey OA, Patel BC. Benign Essential Blepharospasm. 2022 Aug 8. In:

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 32809668.

22- Albanese A, Sorbo FD. Dystonia and Tremor: The Clinical Syndromes with Isolated Tremor. Tremor Other Hyperkinet Mov (N Y). 2016 Apr 5;6:319. doi: 10.7916/D8X34XBM. PMID: 27152246; PMCID: PMC4850743.

23- Smit M, Albanese A, Benson M, Edwards MJ, Graessner H, Hutchinson M, Jech R, Krauss JK, Morgante F, Pérez Dueñas B, Reilly RB, Tinazzi M, Contarino MF, Tijssen MAJ; Collaborative Working Group. Dystonia Management: What to Expect From the Future? The Perspectives of Patients and Clinicians Within DystoniaNet Europe. Front Neurol. 2021 Jun 3;12:646841. doi: 10.3389/fneur.2021.646841. PMID: 34149592; PMCID: PMC8211212.

24- Termsarasab P, Thammongkolchai T, Frucht SJ. Medical treatment of dystonia. J Clin Mov Disord. 2016;3:19.

25- Jankovic J. Medical treatment of dystonia. Mov Disord. 2013 Jun 15;28(7):1001-12. doi: 10.1002/mds.25552. PMID: 23893456.

26- Bledsoe IO, Viser AC, San Luciano M. Treatment of Dystonia: Medications, Neurotoxins, Neuromodulation, and Rehabilitation. Neurotherapeutics. 2020 Oct;17(4):1622-1644. doi: 10.1007/s13311-020-00944-0. Epub 2020 Oct 23. PMID: 33095402; PMCID: PMC7851280.

27- Hassell TJW, Charles D. Treatment of Blepharospasm and Oromandibular Dystonia with Botulinum Toxins. Toxins (Basel). 2020 Apr 22;12(4):269. doi: 10.3390/toxins12040269. PMID: 32331272; PMCID: PMC7232182.

28- Bertucco M, Sanger TD. Current and emerging strategies for treatment of childhood dystonia. J Hand Ther. 2015 Apr-Jun;28(2):185-93; quiz 194. doi: 10.1016/j.jht.2014.11.002. Epub 2014 Nov 15. PMID: 25835254; PMCID: PMC4424089.

29- Cloud LJ, Jinnah HA. Treatment strategies for dystonia. Expert Opin Pharmacother. 2010 Jan;11(1):5-15. doi: 10.1517/14656560903426171. PMID: 20001425; PMCID: PMC3495548.

30- Mehdorn HM. Deep brain stimulation for dystonia: review of the literature. J Neurosurg Sci. 2016 Jun;60(2):199-210. Epub 2016 Mar 15. PMID: 26977634.

31- Bellows S, Jankovic J. Treatment of dystonia and tics. Clin Park Relat Disord. 2019 Dec 4;2:12- 19. doi: 10.1016/j.prdoa.2019.11.005. PMID: 34316614; PMCID: PMC8302199.(3p2)

Article topic: Internuclear Ophthalmoplegia.

Author: Sarah Mahfouz, Ziad Azar.

Editors: Lubna AL-Rawabdeh.

Reviewer: Ethar Hazaimeh.

keywords: Internuclear Ophthalmoplegia, medial longitudinal fasciculus, lateral gaze, multiple sclerosis, brainstem infarction.

Overview

Internuclear Ophthalmoplegia (INO) is a visual disorder most prevalent in the elderly population, often associated with a history of multiple sclerosis (MS) or brainstem infarction.

INO results from damage to the medial longitudinal fasciculus (MFL), a bundle of nerves located in the brainstem, specifically in the paramedian area between the midbrain and pons. This disorder is characterized by a lateral horizontal visual impairment, marked by deficient adduction in one eye, the one next to the lesion, and abducting nystagmus in the other [1]. First described in 1903, INO has since been better defined as a neurological condition and visual phenomenon [1].

In this article, we aim to introduce internuclear ophthalmoplegia, briefly describing its clinical features and etiological process. We will also unfold its relationship with multiple other disorders and syndromes, highlighting its diagnostic and clinical value.

Etiology and Pathogenesis

The medial longitudinal fasciculus (MLF) is a highly specialized and heavily myelinated fiber tract that establishes a crucial connection between the abducens nerve and the paramedian pontine reticular formation (PPRF), linking to the oculomotor nerve nuclei on the contralateral side [3]. This intricate neural pathway serves as the ultimate common denominator for various forms of ocular motility, Figure (1).

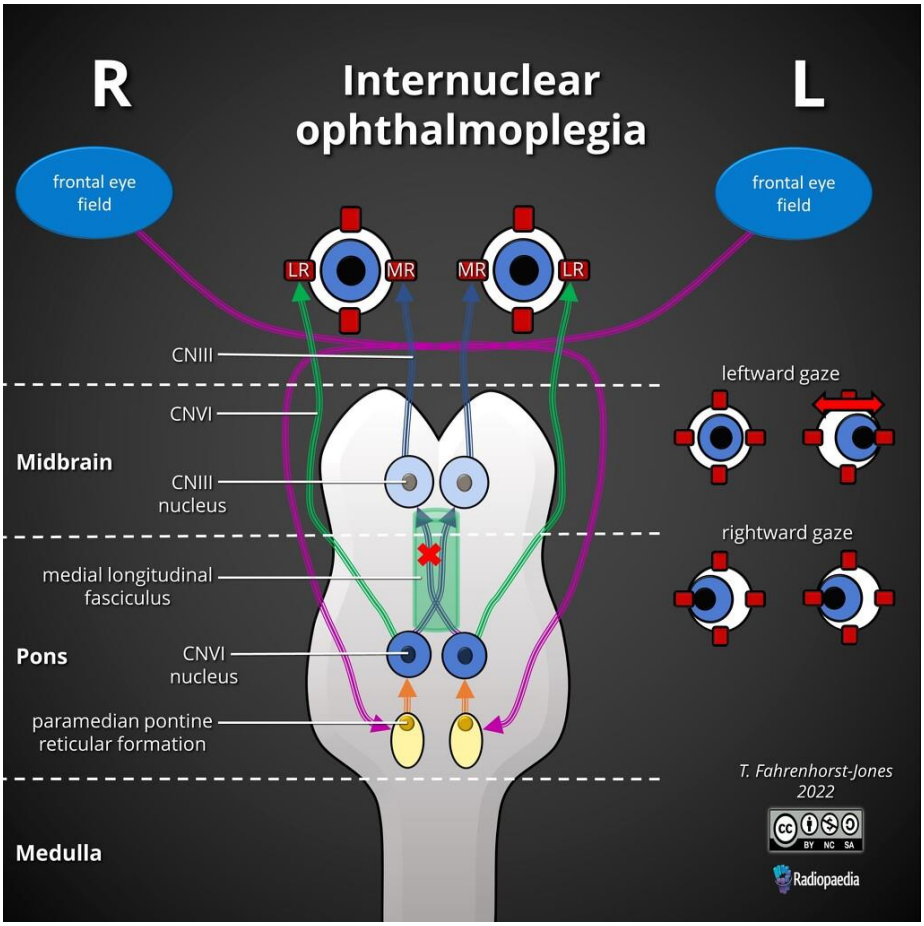


Figure (1): Internuclear ophthalmoplegia. Sharma R, Fahrenhorst-Jones T, Yap J, et al. Figure 1 displays the Internuclear Ophthalmoplegia diagram [2].A lesion affecting the MLF gives rise to a distinct form of ophthalmoplegia and can result in the impairment of horizontal conjugate eye movements, primarily due to the disruption of communication between the oculomotor nerve nuclei (III) and abducens nerve nuclei (VI) [1].

It is imperative to recognize that the MLF is susceptible to damage from a variety of sources: (demyelinating, neoplastic, inflammatory, ischemic ...)

Demyelinating

In younger patients, Internuclear Ophthalmoplegia (INO) typically forms a part of multiple sclerosis (MS) presentations. It may even manifest as the initial symptom, as demyelination can affect various segments of the Medial Longitudinal Fasciculus (MLF), with bilateral INO being the most common outcome.

Additionally, INO may be a feature in other demyelinating syndromes such as Myelin Oligodendrocyte Glycoprotein-IgG-Associated Disorder and Neuromyelitis Optica. In such instances, ophthalmoplegia can occur unilaterally or bilaterally.

Ischemic

In the elderly population, lesions affecting the Medial Longitudinal Fasciculus (MLF) arise because of cerebrovascular accidents.

These incidents typically involve the small perforating paramedian arteries originating from the basilar arteries, responsible for providing blood supply to the region housing the sixth nerve nucleus. Simultaneously, the small perforating branches of the P2 segment of the posterior cerebral artery are responsible for irrigating the midbrain where the third nerve nucleus is situated.

Therefore, occurrences such as small embolic events, hypertensive strokes, vascular dissection, and vasculitis affecting these arteries can give rise to lesions within the MLF and subsequently lead to the manifestation of Internuclear Ophthalmoplegia (INO) [3].

Infections

Infections are a less frequently met etiological factor contributing to Internuclear Ophthalmoplegia (INO), and they can be categorized as follows:

a. Bacterial infections, including conditions such as Syphilis and Lyme disease.
b. Viral infections, encompassing diseases such as HIV and herpes zoster.
c. Fungal infections, exemplified by cryptococcosis.
d. Parasitical infections, with cysticercosis being an illustrative example.

Other conditions

Internuclear Ophthalmoplegia (INO) can be attributed to a spectrum of diverse underlying conditions, including but not limited to:

- Inflammatory disorders, such as Sarcoidosis, Systemic Lupus Erythematosus, Behcet's Disease, and Sjogren's Syndrome.
- Tumorous growths comprise conditions like medulloblastoma, glioma, lymphoma, and metastatic tumors.
- Nutritional disorders, exemplified by Pernicious Anemia and Wernicke Encephalopathy.
- Toxic effects induced by drugs, with substances like lithium, narcotics, phenothiazines, and tricyclic antidepressants implicated.
- Traumatic head injuries.
- Congenital malformations, including the Arnold-Chiari malformation.
- Metabolic conditions, such as Fabry Disease and hepatic encephalopathy.
- Degenerative conditions.
- Iatrogenic causes.

- Subdural hematoma.
- Hydrocephalus.

Saccadic eye movements represent a pivotal ocular function in which the Medial Longitudinal Fasciculus (MLF) plays a substantial role. This intricate process involves the transmission of signals originating from the Frontal Eye Field (FEF) to the contralateral Paramedian Pontine Reticular Formation (PPRF) and the rostral interstitial nucleus of the MLF, specifically for horizontal and vertical saccades, as elucidated in reference [4].

Subsequently, the PPRF serves to stimulate the ipsilateral abducens nucleus, which, in turn, conveys signals to the ipsilateral lateral rectus muscle. Simultaneously, signals are transmitted through the MLF to reach the contralateral medial rectus subnucleus of the third cranial nerve nucleus. This coordinated effort results in the establishment of a horizontal gaze towards the eye opposite the initiating FEF.

As a fundamental diagnostic indicator in cases of Internuclear Ophthalmoplegia (INO), the clinical presentation often includes deceleration or impairment of adduction in the affected eye on the same side as the lesion. In the contralateral eye, a dissociated nystagmus may manifest, believed to be a compensatory mechanism aimed at mitigating the weakness observed in the adducting eye. This phenomenon aligns with Herring's law of equal innervation, which posits that an increase in innervation to a muscle is accompanied by a corresponding increase in innervation to its yoke muscle. In the context of INO, these muscles are the medial rectus muscle and the contralateral lateral rectus muscle, as expounded in reference [1].

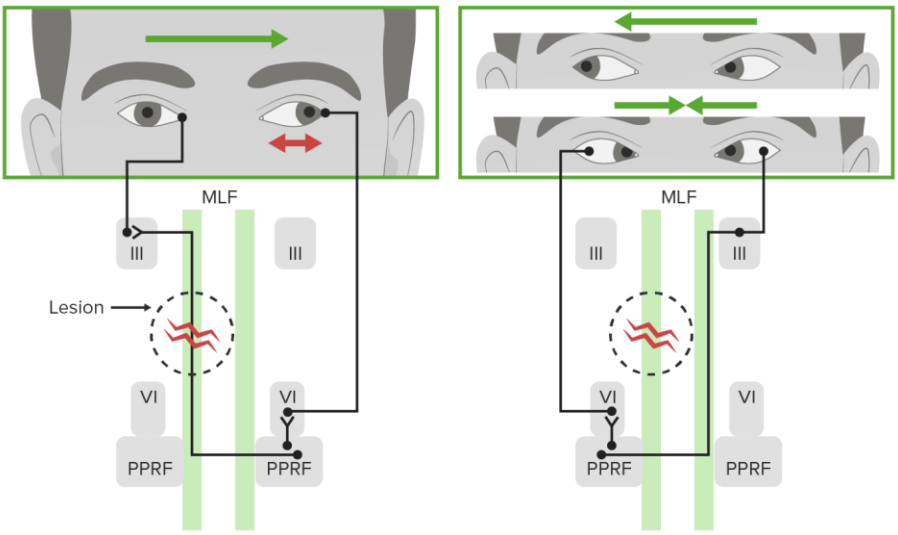


Figure (2): displays Internuclear Ophthalmoplegia [5].

Clinical Presentations and Complications

The principal clinical hallmark characterizing a patient afflicted with internuclear ophthalmoplegia (INO) is the manifestation of either partial or complete ipsilesional impairment of adduction in conjunction with horizontal dissociated saccades and nystagmus directed contralaterally while trying to fixate on an object situated in the direction opposite to the site of the lesion [1]. To illustrate, in the event of a lesion within the left medial longitudinal fasciculus (MLF) and an attempt to direct gaze to the right, one would observe dissociated nystagmus, characterized by an involuntary rhythmic eye movement [6], and/or saccades, which denote rapid eye movements following a sudden shift in the point of fixation [7], in the right eye. Simultaneously, there would be an impaired adduction in the left eye, instead of the expected normal leftward adduction and rightward abduction.

Concomitant symptoms attributed to MLF lesions may encompass a spectrum of manifestations, ranging from mild symptoms like headaches to more intricate complications indicative of brainstem dysfunction, including conditions such as aspiration pneumonia and respiratory failure [1]. Of note are:

- Dizziness ranks among the most frequently reported symptoms associated with MLF impairment, especially when elicited during lateral gaze examination [8].
- Blurred vision [1].
- Difficulty in tracking rapidly moving objects [3].
- Horizontal diplopia, or double vision characterized by the lateral separation of two images, because of impaired ipsilesional adduction [3,9].
- Vertical diplopia, marked by one image appearing higher than the other, typically stemming from skew deviation. Skew deviation arises from asymmetric disruption of supranuclear input from the inner ear, leading to a misalignment of the eyes and prompting the ipsilateral eye to deviate upward (hypertropia) [1,3,9].
- Furthermore, disruptions in the coordinated horizontal eye movements may result in the loss of binocular vision [3].
- This, in turn, engenders visual confusion, wherein two distinct images are perceived as superimposed upon the same spatial plane [3,10]. Additionally, depth perception, as represented by stereopsis, may also be compromised [3].
- Oscillopsia, characterized by unstable vision due to the misperception of a moving environment [3,11], may ensue, alongside symptoms such as reading fatigue, among others [3].

It is important to keep in mind that these symptoms vary in intensity and likelihood depending on several factors, but mostly depending on the specific etiology of the presented INO.

- It is also important to note that visual difficulties looking sideways hampers the ability to drive or even walk properly, which increases the risks of car crashes and falls [3].

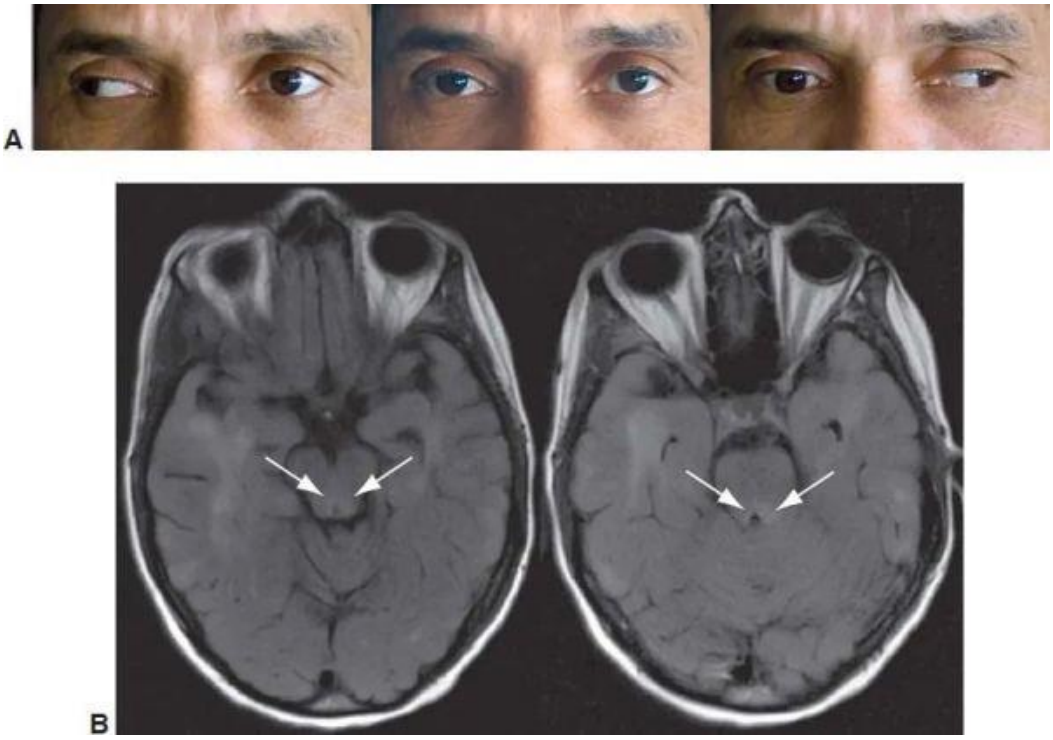


Figure (3): displays Binocular INO [3].

Number	Sex/age	Pathology	Location	Additional lesions	Symptoms/signs
1	M/72	CVA	Right upper pons	Minimal punctate CVA	Diplopia; dizziness; right INO; left nystagmus
2	M/39	Demyelination	Right mid pons	Minimal periventricular plaques	Diplopia; dizziness; bilateral INO
3	M/30	Demyelination	Right mid pons	Minimal periventricular plaques	Diplopia; dizziness
4	F/52	CVA	Right mid pons	None	Diplopia; impaired right eye adduction
5	M/75	CVA	Right upper midbrain	None	Dizziness; right INO; left nystagmus
6	F/54	CVA	Right upper midbrain	None	Dizziness; headache; right INO; left nystagmus
7	M/52	Demyelination	Bilateral inferior midbrain	Moderate periventricular plaques	Weakness; dizziness
8	F/39	Demyelination	Left inferior pons	Moderate periventricular plaques	Gait instability; right leg weakness; right ptosis
9	F/56	Demyelination	Bilateral mid pons	Minimal periventricular plaques	Dizziness; right nystagmus

Table (1) displays the Type of pathology, location, presence of additional lesions, and neurological clinical signs and symptoms recorded for patients with a lesion in the medial longitudinal fasciculus on brain MRI.[1]CVA: cerebrovascular accident, INO: internuclear ophthalmoplegia [12], Fiester P, Rao D, Soule E, Andreou S, Haymes D.

Workup and Diagnosis

The diagnostic process for Internuclear Ophthalmoplegia (INO) involves a thorough medical history and a meticulous physical examination, focusing on the evaluation of eye motion [8]. Clinical tests, such as assessing saccadic velocity and utilizing optokinetic drums or tapes, are essential for detecting subtle disconjugate saccades in the eye [3]. Upon diagnosis, more tests, particularly magnetic resonance imaging (MRI) and computed tomography (CT) scans are invaluable tools for further investigation [3]. In general, MRI is considered superior to CT for evaluating INO, with up to 75% of patients demonstrating visible damage to the Medial Longitudinal Fasciculus (MLF) on MRI scans [9]. Proton density imaging is particularly effective in detecting demyelinating lesions [1]. Less common causes may need supplementary blood and cerebrospinal fluid studies.

Differential Diagnosis

Distinguishing INO from other neurological conditions is crucial. The following differential diagnoses should be considered:

- **Lateral Gaze Palsy:** This condition involves the inability to perform horizontal, conjugate eye movements in one or both directions and can result from lesions affecting the abducens nerve, Paramedian Pontine Reticular Formation (PPRF), or the frontal or parietal eye fields [13].
- **One-and-a-Half Syndrome:** Characterized by a combination of a conjugate horizontal gaze palsy in one direction and INO in the opposite direction, this syndrome results from lesions involving the MLF, PPRF, and/or the abducens nerve [5].
- **Pseudo INO:** Symptoms resembling INO may occur due to peripheral conduction defects, such as Miller Fisher Syndrome and Myasthenia Gravis, rather than MLF lesions [14].
- **Third Nerve Palsy:** This condition, in addition to INO symptoms, presents with pupillary dilation, ptosis, loss of accommodation, absence of abduction nystagmus in the fellow eye, impaired convergence, and limitation of elevation [3].
- **Progressive Supranuclear Palsy:** This brain disorder causes issues with walking, balance, and eye movements similar to bilateral INO [3,15].

Treatment and Management

INO treatment strategies primarily depend on addressing its underlying cause. Treatment options vary accordingly. Symptomatic relief for diplopia can be achieved through botulinum toxin injections and the use of Fresnel Prisms [1]. Surgical intervention may be considered for strabismus correction, especially in cases of wall-eyed bilateral INO [1].

Incidences and Risk Factors

INO is associated with multiple sclerosis (MS), with studies showing its occurrence in 15 to 52% of individuals with MS [16]. The prevalence of INO rises significantly with age, peaking around 52 years, but is rare in pediatrics [1]. Incidence is equal for both genders.

Etiologically, one-third of INO cases result from infarctions, most often presenting unilaterally [1,17]. Another third is associated with multiple sclerosis and other demyelinating disorders, typically affecting younger individuals with a bilateral presentation [1]. The remaining third is attributed to head trauma, infections, brainstem injuries, hemorrhages, vasculitis (e.g., Sjogren Syndrome and Systemic Lupus Erythematosus), and certain tumors (especially pontine gliomas and medulloblastomas) [1]. Additional risk factors, such as vitamin D deficiency and a family history of individuals with MS, are linked to the underlying causes of INO [18].

Prognosis

The prognosis for most INO patients is favorable, with outcomes contingent on the underlying cause and treatment. Rapid recovery is seen when there are no other neurological signs, such as facial palsy, ataxia, hemiparesis, vertigo, pyramidal tract dysfunction, sensory symptoms, dysarthria, and no visible lesions causing INO [3]. Cerebrovascular disorders, brainstem demyelination, and trauma tend to result in a less favorable prognosis [1].

Recent Updates

Recent research has explored innovative treatments for INO. A study demonstrated that a single dose of 20 mg of fampridine significantly improved saccadic eye movement in 23 multiple sclerosis patients with INO, with sustained results for approximately 5 hours [19]. Additionally, stem cell remyelination, facilitated by the accessibility of the medial longitudinal fasciculus around the ventricles, holds promise for neuroprotection and restoration [1].

In terms of diagnosis, emerging techniques like proton density imaging and infrared oculography have shown promise in detecting INO in demyelinated patients, highlighting the potential for enhancing diagnostic precision in the field of neuroimaging [1,16].

References

[1] Feroze KB, Wang J. Internuclear Ophthalmoplegia. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441970/
[2] Sharma R, Fahrenhorst-Jones T, Yap J, et al. Internuclear ophthalmoplegia. Reference article, Radiopaedia.org (Accessed on 16 Jan 2023) https://doi.org/10.53347/rID-54399
[3] Andrew Go Lee, MD, Aswini Kini, MD, Jeremy Swisher,Internuclear Ophthalmoplegia, https://eyewiki.aao.org/Internuclear_Ophthalmoplegia
[4] Frohman TC, Galetta S, Fox R, Solomon D, Straumann D, Filippi M, Zee D, Frohman EM. Pearls & Oy-sters: The medial longitudinal fasciculus in ocular motor physiology. Neurology. 2008 Apr 22;70(17):e57-67. [PubMed]
[5] Internuclear Ophthalmoplegia, October 27, 2022: https://app.lecturio.com/#/article/3179?return=%23%2Fwelcome%3Ffv%3D1
[6] John Hopkins Medicine, Health, Conditions and Diseases, Nystagmus: https://www.hopkinsmedicine.org/health/conditions-and-diseases/nystagmus
[7] Purves D, Augustine GJ, Fitzpatrick D, et al., editors. Neuroscience. 2nd edition. Sunderland (MA): Sinauer Associates; 2001. Types of Eye Movements and Their Functions. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10991/
[8] Fiester P, Rao D, Soule E, et al. (August 23, 2020) The Medial Longitudinal Fasciculus and Internuclear Opthalmoparesis: There's More Than Meets the Eye. Cureus 12(8): e9959. doi:10.7759/cureus.9959
[9] Najem K, Margolin E. Diplopia. [Updated 2022 Feb 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441905/
[10] Economides JR, Adams DL, Horton JC. Perception via the deviated eye in strabismus. J Neurosci. 2012 Jul 25;32(30):10286-95. doi: 10.1523/JNEUROSCI.1435-12.2012. PMID: 22836262; PMCID: PMC3435149.
[11] Tilikete, Carolinea, b, c; Vighetto, Alaina, b, c. Oscillopsia: causes and management. Current Opinion in Neurology 24(1): p 38-43, February 2011. | DOI: 10.1097/WCO.0b013e328341e3b5
[12] Fiester P, Rao D, Soule E, Andreou S, Haymes D. The Medial Longitudinal Fasciculus and Internuclear Opthalmoparesis: There's More Than Meets the Eye. Cureus. 2020 Aug 23;12(8):e9959. doi: 10.7759/cureus.9959. PMID: 32983663; PMCID: PMC7510542.
[13]. Katz, D.I. (2011). Lateral Gaze Palsy. In: Kreutzer, J.S., DeLuca, J., Caplan, B. (eds) Encyclopedia of Clinical Neuropsychology. Springer, New York, NY. https://doi.org/10.1007/978-0-387-79948-3_1923
[14] Ayşe İlksen Çolpak, Tülay Kansu*Hacettepe University Institute of Neurological Sciences and Psychiatry, Ankara, Turkey, Pseudo-Internuclear Ophthalmoplegia https://jag.journalagent.com/tjn/pdfs/TJN_19_1_35%5BA%5D.pdf
[15] Progressive Supranuclear Palsy, Mayo Clinic: https://www.mayoclinic.org/diseases-conditions/progressive-supranuclear-palsy/symptoms-causes/syc-20355659
[16] S.N. Hof, F.C. Loonstra, L.R.J. de Ruiter, L.J. van Rijn, A. Petzold, B.M.J. Uitdehaag, J.A. Nij Bijvank,The prevalence of internuclear ophthalmoparesis in a population-based cohort of individuals with multiple sclerosis, Multiple Sclerosis and Related Disorders, Volume 63,2022,103824, ISSN 2211-0348, https://doi.org/10.1016/j.msard.2022.103824.
[17] Virgo JD, Plant GT. Internuclear ophthalmoplegia. Pract Neurol. 2017 Apr;17(2):149-153. doi: 10.1136/practneurol-2016-001428. Epub 2016 Dec 7. PMID: 27927777.
[18] Oliver Tobin, M.B., B.Ch., B.A.O., Ph.D., Multiple Sclerosis, Mayo Clinic : https://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/symptoms-causes/syc-20350269
[19] Kanhai KMS, Nij Bijvank JA, Wagenaar YL, Klaassen ES, Lim K, Bergheanu SC, Petzold A, Verma A, Hesterman J, Wattjes MP, Uitdehaag BMJ, van Rijn LJ, Groeneveld GJ. Treatment of internuclear ophthalmoparesis in multiple sclerosis with fampridine: A randomized double-blind, placebo-controlled cross-over trial. CNS Neurosci Ther. 2019 Jun;25(6):697-703. doi: 10.1111/cns.13096. Epub 2019 Feb 12. PMID: 30756475; PMCID: PMC6515699.

Article title: Creutzfeldt- Jakob disease (CJD)

Author: Balqees Jboul.

Editor: Lobana Mahdawi.

Reviwer: Ethar Hazaimeh.

Keywords: ***CJD, Neurodegenerative Disease.***

Overview

Creutzfeldt-Jakob disease is a rare and fatal transmissible neurodegenerative disorder that the underlying cause of it is misfolded prion proteins (PrPSc). Effective therapeutics for the disease are not available and the accurate diagnosis of the disease can be challenging, but there is a palliative treatment that tries to keep the person as comfortable as possible and reduce the symptoms, The most common form of human prion disease is sCJD with incidence around 1.5 to 2.0 per million person-years. (1)

Pathogenesis

Several types of CJD may be different with respect to symptoms evolution, neuropathological characteristics, and biomarker profile, they are related to Methionine/Valine(M/V) polymorphism and with a molecular mass of (PrPSc). A definitive diagnosis of CJD needs neuropathological confirmation. There are many types of CJD as Sporadic, iatrogenic, variant, and familial. In the late 1980s to early 1990s, there was high exposure of the UK population to bovine spongiform encephalopathy-contaminated food products, which caused more than 150 deaths from variant type of Creutzfeldt–Jakob disease (vCJD). (1)

Although the pathogenesis is not clearly understood, data from animal models and from patients who have vCJD have shown that oral exposure to BSE is followed by accumulation of (PrPres) in gut-associated lymphoid tissue rapidly, then by hematogenous spread, reaching the lymphoreticular system. Spreading to the central nervous system may not occur for several years, but the blood taken from individuals who were in the pre-clinical phase of their disease appears the ability to transmit the disease. (2)

Clinical presentation and complication

Common clinical manifestations of CJD include a rapid decline in cognitive function, cerebellar dysfunction, behavioral changes, and visual problems. CJD is easily

misdiagnosed as another disorder due to unclear early presentation. Psychiatric symptoms of the disease at the onset, painful sensory symptoms that are persistent, dementia, and development of at least two of the following five neurologic signs: poor coordination, visual signs, chorea, hyperreflexia, or myoclonus after more than 4 months of the onset of the disease should increase the consideration about CJD. Most patients die within 1 year of the onset of the symptoms. The most common complications of Creutzfeldt-Jakob disease are overwhelming infections, respiratory failure, and congestive heart failure (5).

Workup and Diagnosis

The neuropathological investigation and immunostaining of PrPSc allow a clear diagnosis of prion diseases also MRI is an immensely helpful imaging technique for CJD, it usually shows abnormalities of signal in the putamen and head of the caudate (9).

Early presentation of CJD is characterized by an increased diffusion-weighted imaging (DWI) signal in the cortex or deep gray matte, Figure (1). (3). For definite diagnosis, a brain biopsy is required but it has complications such as infections spreading, the possibility of a false negative result due to sample error in which typical pathology and PrPSc may not be present in all cortical regions, and issues about the quality of the tissue, understanding of all of these considerations and that it is very invasive, brain biopsy is usually only considered when the diagnosis is not clear and in treatable conditions such as encephalitis or lymphoma (6).

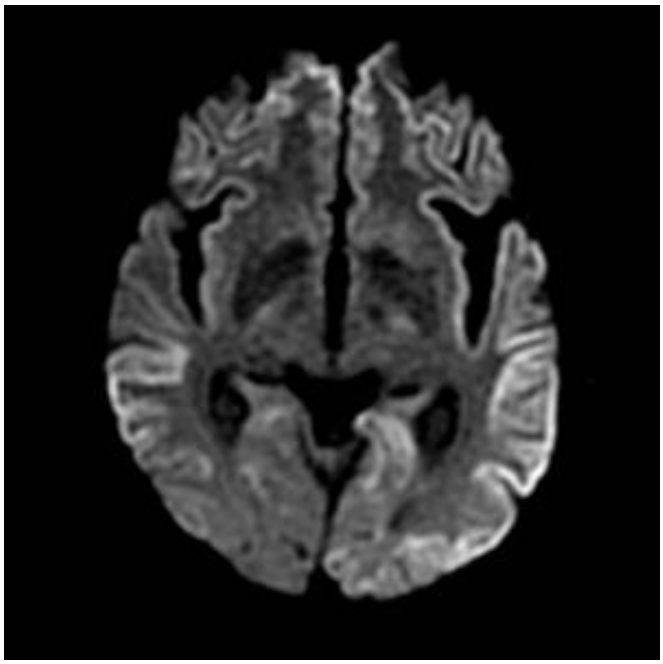


Figure (1): The most sensitive sequence to identify characteristic changes is diffusion-weighted imaging. (10)

A less invasive procedure, tonsillar or even adenoid biopsy, was found helpful in the diagnosis of variant CJD (vCJD) but is not useful for other forms of prion disease. The direct in vivo detection of PrPSc in sCJD employing routinely accessible bio-fluids appears possible but a novel study using urine showed low sensitivity of 40%, there is also Protein Misfolding Cyclic Amplification (PMCA) test that was improved to reproduce and amplify PrPSc in micro-tubes and has an acceptable sensitivity, especially with vCJD but high sensitivity, could not be found in sCJD or other prion diseases(6)

Real-time Quaking Induced Conversion (RT-QuIC) test that depends on energizing" the misfolding of prion protein coupled to a fluorescent readout, recently there is (second generation RT-QuIC) to reduce the assay time and to increase the sensitivity. The diagnostic performance of the improved CSF RT-QuIC is better than surrogate marker tests for prion diseases such as 14-3-3 and tau proteins, and together with PRNP gene sequencing, the test promotes the major prion subtypes to be differentiated in vivo (4)

Management

Until now treatment of prion diseases depends on supportive treatment, and there is no approval-specific therapy that can stop the progression of the disease. Many drugs have been evaluated such as acyclovir, amantadine, antibiotics, antiviral agents, interferon, and steroids but none of these drugs has shown a consistent benefit. (7)

Prevention

vCJD was acquired by food exposure and transmitted through blood transfusion so to reduce any risk of acquiring vCJD from food, travelers to Europe or other areas with indigenous cases of BSE should avoid beef and beef products to reduce the opportunity of contamination with tissues that may have the BSE agent. Conversely, Milk and milk products from cows are not a common risk for transmission of the BSE agent, however, there is no known way to prevent sporadic Creutzfeldt-Jakob disease (CJD). (8)

Patients with a family history of the neurological disease should talk with a genetics counselor so he can help them sort through the risks associated with their situation, while in the cases of iatrogenic CJD, properly cleaning and sterilizing the medical equipment can reduce the incidence of transmission and prevent spreading of the disease. Newer regulations that regulate the feeding of cows may also help prevent the spread of prion diseases. (8)

References

1. Hermann P, Appleby B, Brandel JP, Caughey B, Collins S, Geschwind MD, et al. Biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease. Vol. 20, The Lancet Neurology. Lancet Publishing Group; 2021. p. 235–46.
2. Hilton DA. Pathogenesis and prevalence of variant Creutzfeldt-Jakob disease. Vol. 208, Journal of Pathology. 2006. p. 134–41.
3. Vitali P, Maccagnano E, Caverzasi E, Henry RG, Haman A, Torres-Chae C, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias [Internet]. 2011. Available from: www.neurology.org
4. Foutz A, Appleby BS, Hamlin C, Liu X, Yang S, Cohen Y, et al. Diagnostic and prognostic value of human prion detection in cerebrospinal fluid. Ann Neurol. 2017 Jan 1;81(1):79–92.
5. Wikidoc.org. 2022. Creutzfeldt-Jakob disease natural history, complications and prognosis - wikidoc. [online] Available at: https://www.wikidoc.org/index.php/Creutzfeldt-Jakob_disease_natural_history,_complications_and_prognosis
6.(Hermann P ،Hermann P, Appleby B, Brandel JP, Caughey B, Collins S, Geschwind MD, Green A, Haïk S, Kovacs GG, Ladogana A, Llorens F, Mead S, Nishida N, Pal S, Parchi P, Pocchiari M, Satoh K, Zanusso G, Zerr I. Biomarkers and diagnostic guidelines for sporadic Creutzf)
7. *Creutzfeldt-Jakob disease* (no date) *ucsfhealth.org*. Available at: https://www.ucsfhealth.org/conditions/creutzfeldt-jakob-disease (Accessed: 06 October 2023).
8.Ritchie, D.L., Peden, A.H. and Barria, M.A. (2021) Variant CJD: Reflections a quarter of a century on, MDPI. Available at: https://www.mdpi.com/2076-0817/10/11/1413 (Accessed: 06 October 2023).
9 . Henriette J. Tschampa, Kai Kallenberg, Horst Urbach, Bettina Meissner, Claudia Nicolay, Hans A. Kretzschmar, Michael Knauth, Inga Zerr, MRI in the diagnosis of sporadic Creutzfeldt–Jakob disease: a study on inter-observer agreement, Brain, Volume 128, Issue 9, September 2005, Pages 2026–2033, https://doi.org/10.1093/brain/awh575

10. Case courtesy of Mathieu Deltomme, Radiopaedia.org. From the case rID: 54199

Article topic: Benign paroxysmal positional vertigo (BPPV).

Author: Yasmin Dahabreh.

Editors: Ainaa A.Alzamari, Hamid Ghanem.

Reviewer: Ethar Hazaimeh.

Keywords: Benign paroxysmal positional vertigo (BPPV), Canalolithiasis, Cupulolithiasis, vertigo, nystagmus, torsional nystagmus, repositioning maneuvers, Dix-Hallpike maneuver.

Abstract

Background: vertigo is a sensation when the patient feels that the environment or himself is spinning. There are many subtypes of vertigo that are divided into central and peripheral vertigo. BPPV is considered the most common cause of peripheral. Symptoms such as vertical, torsional, and horizontal nystagmus, nausea, and vomiting typically occur. It is attributed to calcium debris that either floats or attaches to the cupula. There are many types, but the vast majority are the lateral and the posterior-canal types, hence its diagnosis requires which type is affected so the treatment that includes many maneuvers.

Methods: A systematic review search was done which studied primarily Benign Paroxysmal Positional Vertigo (BPPV) through the literature databases.

Conclusion: Vertigo is caused by a type of balance disorder called BPPV, at least 20% of patients will complain of vertigo during a clinic visit. It is usually misdiagnosed with other diseases. It is also diagnosed and treated depending on the type is injury.

Introduction

Benign Paroxysmal Positional Vertigo (BPPV) is a brief episode of mild to severe dizziness that is induced by changes in head positions. It is one of the most common causes of vertigo as it accounts for 14–42% of patients presenting with vertigo (1). A patient with BPPV feels like the surrounding environment is spinning, causing a loss of balance, that may associate with vomiting and nausea (1, 2). It can also be defined as transient position-induced horizontal, vertical, or torsional nystagmus (1). BPPV is explained by the migration of otoliths (calcium debris) freely in the endolymph, or collection in the cupula (2). This disease affects elderly women more than other people (3). This type of disorder is usually misdiagnosed with other benign to life-threatening diseases that can cause vertigo (2), such as Ménière disease, unilateral vestibular loss

(UVL), vascular loop syndrome, and many others (2). Risk factors for BPPV are osteoporosis, vitamin D deficiency, diabetes mellitus, hypertension, and hyperlipidemia (4). Diagnosis for this disorder depends on the type of canal that is affected (5). There are many types of BPPV but the posterior canal type is considered the most common with (80-90%) incidence among patients, then lateral type (10-20%) and other atypical types (2-3%) (6).BPPV is treated by maneuvers that rely on the type of the affected canal; medication is used for BPPV comorbidities, on the other hand, surgical procedures are used as the last option after long-term ineffective treatment(7).

Pathophysiology

There are two attributed hypotheses to BPPV pathophysiology, which are canalolithiasis and cupulolithiasis. In canalolithiasis, the otoliths move freely in the endolymph (fluid in the semicircular canals normally detects angular head acceleration) because of gravity (8). Due to the viscosity of the endolymph, these particles create a current, which will lead to a cupular displacement. The heavy debris in the canal causes inappropriate movement of the fluid with linear accelerations such as gravity and causes an inappropriately spinning sensation when the head shifts with gravity. The other hypothesis (cupulolithiasis) (9) states that deposits of the otoliths or otoconia collect and adhere directly to the cupula and settle there, making it more responsive to gravity (10). These two mechanisms either increase or decrease the depolarization rate and change the angular head acceleration, which is not supposed to occur in an average person. Canololithiasis occurs more commonly than the other hypothesis (10).

Clinicopathologic studies showed that canalolthiasis appeared to be more common in typical BPPV. Other studies have demonstrated that otoconia may be the source of the canaliths by floating in the lumen with and without linking filaments and attached to a gel matrix. Age-related destruction of the gel matrix and the filaments or the otoconia themselves can create an idiopathic BPPV (3). Other theories have been published that suggest bone loss could be the source of otoconia (the calcium deposits). In one study, patients with BPPV had low bone density, and the rates of osteopenia and osteoporosis were higher compared to the control group (11). Therefore, osteoporosis and vitamin D deficiency may increase the risk of BPPV (4,12).

BPPV can be due to a secondary cause such as head injury or inner ear disease that causes a detachment of the otoconia from the utricle or degeneration and uncoupling of otoconia such as sudden sensorineural hearing loss, Meniere's disease or vestibular neuritis, ear surgery, herpes zoster oticus, and inner ear ischemia (10,13,14). BPPV has the possibility to show during surgeries such as elevating the floor of the maxillary sinus. In rare situations, decompression sickness can be caused due to nitrogen bubbles in the canals. Moreover, it could show in giant cell arteritis (GCA) (15). A survey revealed that BPPV is independently associated with age, hypertension, hyperlipidemia, and stroke (3)

Clinical manifestations

BPPV is divided into many subtypes; these subtypes are further divided into typical and atypical types (9). The typical types consist of the posterior-canal-type (canalolithiasis), lateral-canal-type BPPV (canalolithiasis), and lateral-canal-type BPPV (cupulolithiasis) all of them meet specific criteria according to specific symptoms and signs. On the other hand, the atypical BPPV does not meet the criteria, such as the anterior-canal-type of BPPV (canalolithiasis), the posterior-canal-type of BPPV (cupulolithiasis), and the multiple-canals-type of BPPV (9).

Patients with BPPV usually present with multiple vertigo episodes, which are described as dizziness, passing out, ringing in the ear, and torsional, vertical, or horizontal nystagmus that last for one minute or less, depending on the type of BPPV which can happen more than once in weeks or months. It can be provoked by changing head positions, such as looking upward while standing, sitting, or in a supine position. These episodes may be associated with vomiting or nausea. Most importantly, it is important to mention that there is no neurological or hearing loss in this type of disorder. Some have reported the presence of inner ear damage before BPPV. Fifty percent of the patients complain of imbalance between attacks even after treatment. Clinicians can see gait disturbances and the appearance of nystagmus (10,16).

Latency: a brief period of 1-5 seconds between assuming provocative head position and onset of nystagmus
Reversibility: nystagmus reverses direction when the head is returned to the erect position
Crescendo: nystagmus intensity increases quickly to a peak and then slowly subsides
Transience: nystagmus and vertigo subside within 5-30 seconds
Fatigability: with repeated head positioning, nystagmus and vertigo are no longer elicited

Table (1): Definitions of Findings supporting the Diagnosis of Benign Paroxysmal Positional Vertigo (10).

Diagnosis

A detailed history should be taken to diagnose BPPV. Provoking maneuvers are being used in the physical examination with a typical history of BPPV. These maneuvers can help by triggering nystagmus to occur thus it can manifest the canal in which the ear is affected (17).

Dix-Hallpike is the diagnostic maneuver for some types of BPPV; this maneuver has around 55 to 80% effectiveness and sensitivity in diagnosing BPPV (18). When performing this maneuver, the patient should be seated so that their head would be over the edge of the table when they reclined back to supine. They should then perform a 45-degree cervical rotation toward the test side, lie down, and allow their head to move 30 degrees off the edge of the table while being watched for nystagmus. Nystagmus can have latency and not be present immediately so the physician should assess the nystagmus for at least 30 after finishing the test (19).

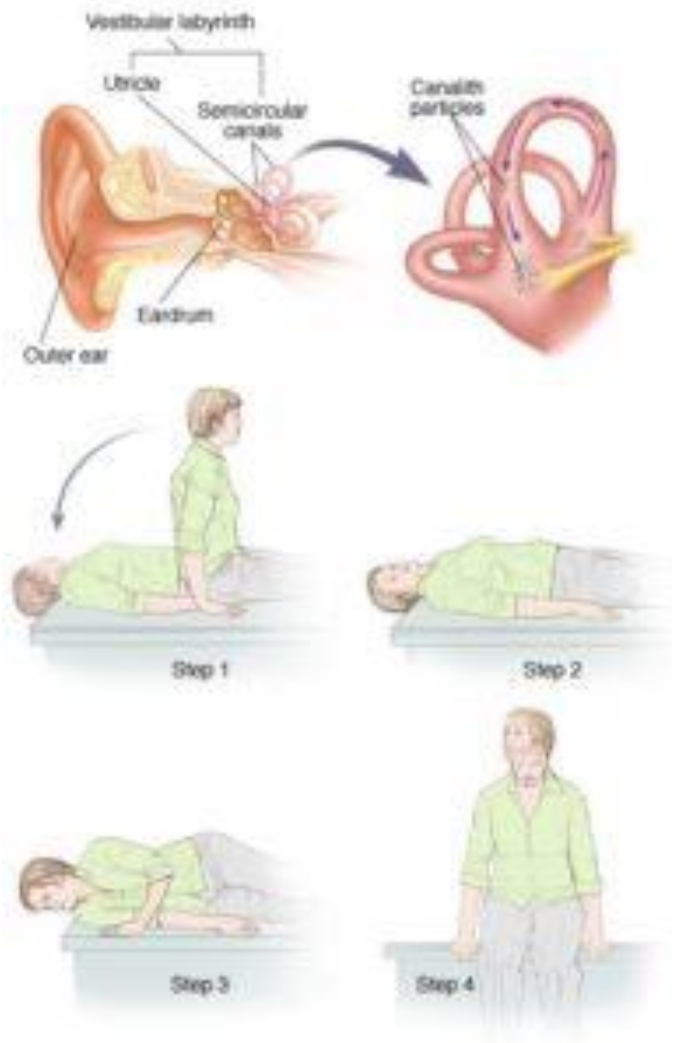


Fig1. Dix-Hallpike maneuver, the physician stands the patient to the right side and rotates his head 45 degrees to the right, Then the patient moves from the sitting to the supine position where the right ear position and the patient's neck are slightly upward. The latency, duration, and direction for both nystagmus and vertigo should be noted. The free-floating debris is thought to cause this type of disorder.

In typical posterior-canal BPPV, the nystagmus will be upward vertical or torsional nystagmus, in which the eye rotates in the direction of the affected ear. Torsional

nystagmus where the eyes can rotate to the unaffected ear can be induced by the reverse Dix-Hallpike maneuver where the patient is brought back to the upright position (9). This nystagmus lasts less than one minute, is characterized by an increase then decrease in intensity, and is diminished after repeated head positioning (9,20).

A typical posterior type BPPV has the same diagnostic features it has a longer duration of vertigo that lasts for more than a minute (21). On the other hand, the atypical anterior canal BPPV is different from the typical BPPV by having downward vertical and torsional nystagmus (22).

If this maneuver was ineffective, meaning there was no nystagmus, or it showed horizontal nystagmus, that may indicate another type of BPPV, such as lateral type BPPV (23); in this situation, another maneuver should be applied (23). The most known one is the horizontal roll maneuver, when performing this maneuver; the patient will be lying on their back with their neck flexed by 30 degrees and their head rotated to the left or right by around 90 degrees. A positive Horizontal roll maneuver is dizziness or rotatory vertigo due to changes in head positions relative to gravity (9). This vertigo has a short duration of less than one minute, described as an increase and then decrease in intensity, which can still decrease after multiple head positions (9).

This type is characterized by a geotropic nystagmus where the nystagmus is beating fast toward the ground and slow beating when it returns after eight seconds of turning to the affected ear. In geotropic nystagmus, the affected side is the side where it has severe symptoms, for example, rightward horizontal nystagmus is induced by turning the head to the right ear if the right ear is the affected one (24,25). The nystagmus consists of major horizontal and minor torsional components (26).

If the patient has the atypical lateral BPPV, the previously mentioned maneuver will provoke a vertigo attack by specific head positions, this attack will last for more than one-minute duration (21). The intensity is not decreased during the attack (21). This vertigo is not associated with cochlear or other neurological symptoms. During the procedure by apogeotropic positional nystagmus, the pupils move against the ground (toward the ceiling) in fast beating and return to the original position by slow beat (27). It differs from the typical type that the nystagmus is induced toward the less harmful or more severe: leftward horizontal nystagmus indicates that the right ear is affected. The nystagmus consists of minor and major torsional components. They don't appear with latency and last for more than one minute. Peripheral and central vestibular diseases that cause vertigo are ruled out (26).

There is a better way to diagnose lateral type by bow and lean, where the patient flexes his neck and then tilts the head backward, in this test, the horizontal canal will first align with the gravity before turning 180 degrees horizontally. Hence, the right nystagmus has a right beat toward the bow, and the left beats toward the lean (28).

Differential diagnosis

According to a study, 36 causes of nystagmus of the BPPV type were found to be due to other causes rather than the presence of canalolithiasis /cupulthiasis (10).

Table (2). The cases where the BPPV-type positional nystagmus and vertigo were caused by other disorders (Pseudo-BPPV) (10).

Disorder Causing BPPV-Type Nystagmus	NUMBER OF CASES
Meniere's disease	26
Cerebellopontine angle tumor	3
Stroke	3
Labyrinthine fistula.	3
Multiple sclerosis	3
	TOTAL CASES = 36

Table (2). The cases where the BPPV-type positional nystagmus and vertigo were caused by other disorders (Pseudo-BPPV) (10).

As the table demonstrated these cases were not reported as BPPV. For example, in cases where the positional nystagmus showed during or shortly after Meniere's disease, it indicates they are a manifestation of Meniere's disease (10). Cases of stroke and cerebellopontine angle tumor are considered pseudo-BPPV, or diseases associated with BPPV (true BPPV) diseases could be similar to BPPV, such as postural or orthostatic hypotension, because both can cause dizziness that is stimulated by changing positions (29, 30). However, patients with orthostatic hypotension describe their dizziness as faint rather than vertigo, while 90% of BPPV patients have these symptoms. In addition, this kind of hypotension is not provoked by rolling down or BPPV maneuvers (29, 30).

Chronic unilateral vestibular hypofunction or unilateral vestibular loss (UVL) is where there is a loss in the vestibular function of the ear. This disease is associated with transient dizziness after rapid head turns, but this vertigo lasts only for two seconds, in the BPPV case, it lasts from 30 to 60 sec and does not require rapidity of head turns. Also, BPPV maneuvers are not a problem for UVL patients (31).

Labyrinthitis or vestibular neuritis, where there is an inflammation of the labyrinth or vestibular nerve, respectively, can also present with a nystagmus that is similar to BPPV (32-35). Other brain lesions such as stroke, Arnold-Chiari malformation, multiple sclerosis, cerebellar degeneration, ischemia, intoxication, Acoustic neuroma, and meningioma, can induce the appearance of nystagmus (32-35).

Meniere's disease is a rare inner ear disorder. A report was published and believed that it is one of the other disorders that can cause BPPV-Type Positional Nystagmus and Vertigo. The distinction between Meniere and BPPV is based on history, vertigo, and symptomatology (10).

Vestibular migraine is a type of migraine where people experience a combination of vertigo and dizziness, and it can present as isolated positional vertigo, such as BPPV. Symptoms duration can be used as a distinctive feature because it usually lasts for hours, but in rare cases, it could last for a few seconds to a few minutes (36). retrospective review of 362 patients with positional vertigo where 10 patients were identified by vestibular migraine and distinguished from BPPV by having a shorter recurrence time (it is more likely to happen over hours to days rather than weeks to months (37). It targets younger patients usually (37). Moreover, its symptoms are often difficult to describe during vertigo episodes (37). Finally, positional nystagmus is atypical for BPPV.

Treatment

Treatment of BPPV relies on repositioning maneuvers, and it is crucial to not delay the treatment because the quality of life would be significantly affected (38). Repositioning maneuvers are the best evidence-based method for treating BPPV. Making the correct diagnosis and determining the affected side and the canal are especially important in the treatment process (38, 39).

A typical posterior canal type is treated by physical theory. Its advantages are clearing the posterior canal of the floating debris and encouraging migration to the utricle, where otoconia are typically reabsorbed (40). Semont's Liberatory Maneuver and Epley's Canalith repositioning maneuver have good results and efficacy based on trials with a 90% success rate. Also, it is not dependent on the patient's age and pre-existing neurological disorders (39, 40).

The Modified Epley Maneuver, also known as the Canalith Repositioning Maneuver (CRM), forms five phases, each lasting three minutes, designed to transfer the otoconia sequentially from the posterior canal to the common crus and finally to the vestibule (41). It starts with a patient on the bed with the head rotated to the left for the left posterior canal about 45 degrees, then quickly moved to the Dix-Hallpike position with the affected ear downward, then the head is rotated 90 degrees toward the unaffected side, causing the movement of the debris in an ampullofugal stimulus and keeps rotating the head with 90 degrees toward the right causing the otoliths to exit the canal. Finally, the patient is slowly moved to the sitting position. An upward nystagmus with a torsional part toward the affected ear shows that the maneuver worked successfully because it shows that the particles have left the posterior canal through the common crus (42).

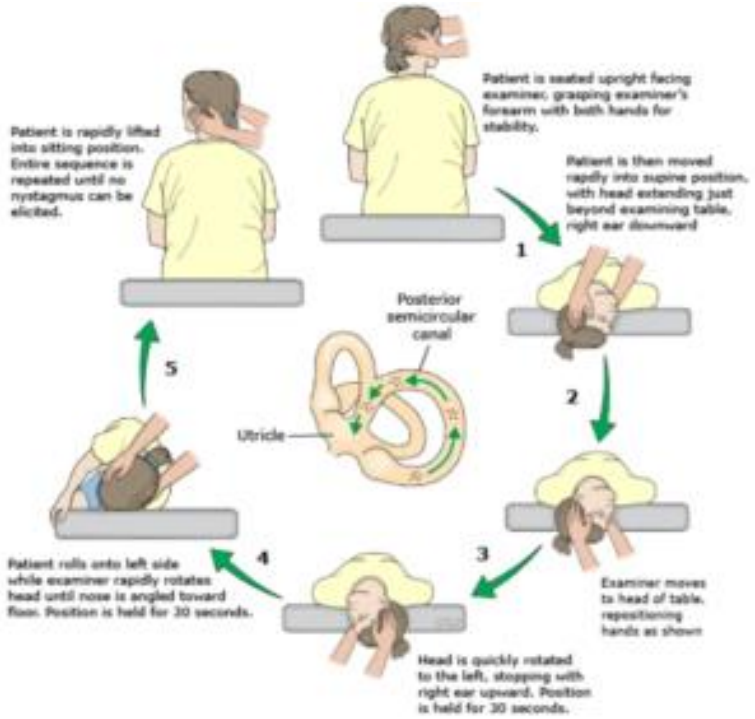


Figure (2). Epley's maneuver for left posterior canal BPPV. 1 the patient is on the bed with the head rotated 45° to the left side. 2. The patient is then moved quickly into the Dix-Hallpike provoking position with the affected ear downwards. 3. Slowly rotate the head 90 degrees toward the unaffected side. 4. the head and the trunk are moved 90 degrees to the right causing movement of debris and exit Canal, finally the patient is slowly moved into a sitting position (not represented in this fig).

The other maneuver that treats atypical type of posterior canal is the Liberatory or Modified Semont Maneuver where a rapid tilt of 180 degrees to the posterior canal plane emits the otoconia from the posterior canal by centrifugal force. For a left posterior canal BPPV, the patient should swiftly lean to the side that is affected while rotating their head 45 degrees to the right and hold that position for one minute (43). Free-floating otoconia moves toward the lower portion of the canal, causing an ampullofugal flow that, after a little latency, a typical positional nystagmus is triggered. The patient is then immediately (within 1.5 s) rotated into a right side-lying position with the nose down, creating an endolymphatic flow and a rotatory nystagmus beating towards the highest right ear. A reversed nystagmus indicated that this maneuver failed as a prognostic factor (44). In addition, the speed of rotation is critical to get the best results of this procedure because if it was performed slowly, it could be ineffective because the debris can fall back into the canal (45).

In clinical practice, results have shown that Epley and Semont's maneuvers have the same efficacy (46). Attacks tend to recur 10–20% of the time in the first two weeks, requiring one to three repetitions of the same treatment or choosing a different

repositioning strategy (46). Other shorter maneuvers are proposed now to treat this type, such as the “Chair-based Abbreviated Reposi- toning Maneuver (ChARM) (47).

Horizontal type (HC) BPPV is classified into two subtypes that can be identified by their specific positional nystagmus. The more common is characterized by geotropic nystagmus, and the less common presenting apogeotropic nystagmus (48). This type is treated by modified Gufoni’s maneuver which is performed on the affected ear with the patient’s head turned 45° upward, then swiftly positioned it from sitting position to the affected side. The head is then turned 90 degrees toward the healthy ear (nose up). After that, the head should roll to the unaffected side once the entire body is placed in the supine posture. The patient is then returned to a sitting position with the head tilted slightly forward. The head is then rolled to the unaffected side once the entire body is placed in the supine posture. The patient is then returned to a sitting position with the head tilted slightly forward. Each position should be held for three minutes (49).

On the other hand, the geotropic nystagmus (canalithiasis) is treated by the barbecue rotation maneuver (BBQ) (50). This maneuver is aimed to remove free otoconia from the HC by using centrifugal force; the patient is rotated 90 degrees in the direction of the healthy ear at a time. The procedure is not comfortable for obese, elderly, or motion-restricted patients (50). Gufoni’s maneuver can also be used, which allows the otoconial debris to exit the canal under the centrifugal force created by the rapid deceleration. An alternative maneuver is the forced Prolonged Position (FPP) which is recommended for obese, elderly, and patients with restricted movement. In this way, otoconial debris can leave the canal under gravity (51, 52).

Anterior BPPV is treated by reverse Epley/Epley, and Yacovino maneuvers are the most widely used treatments for acBPPV with the advantage that Yacovina does not require the affected side to be known (53). It consists of four movements separated by 30-s intervals: the patient is moved first from sitting to a supine head-hanging position, then the head is tilted where the chin is the chest, and last, the patient sits up. The outcome of Yacovian depends on the duration of the downward nystagmus beat. Patients with nystagmus that lasts for less than one minute have better effects (54). Self-administered treatment is not recommended because the recurrence may not arise in the same canal (55).

Vestibular suppressant medications, such as antihistamines and benzodiazepines are not recommended treatments in acute BPPV (39). Otherwise, medication is helpful for comorbidities that may have developed before or after BPPV that decrease the quality of life, such as anxiety/depression and residual dizziness are frequent findings in BPPV patients. Hence Anti-vertiginous, anti-anxiety, and antiemetic drugs may be used (55).

In some cases, a normalized vitamin D serum is used to treat patients susceptible to detachment of otoconia from the utricular macula with low serum vitamin D levels and disorders of bone metabolism (56,57).

In severe cases, continuous BPPV may be treated by surgical procedures that can be safe and effective, but it should be recommended after a thorough follow-up when there have been no recurrences in other canals or when both sides are affected (58).

Conclusion

Benign positional paroxysmal vertigo is an inner ear disorder. Symptoms are characterized by a repeated brief attack of vertigo or dizziness that differs according to which type the patients have. There are many diseases that are like BPPV in presentation, such as Meniere's disease. The diagnosis and treatment rely on the repositioning maneuver, which varies depending on the affected side.

References

1.Ibekwe T, Rogers C. Clinical evaluation of posterior canal benign paroxysmal positional vertigo. Nigerian Medical Journal. 2012;53(2):94.
2.Kerber KA, Newman-Toker DE. Misdiagnosing Dizzy Patients. Neurologic Clinics. 2015 Aug;33(3):565–75.
3.von Brevern M, Radtke A, Lezius F, et al. Epidemiology of benign paroxysmal positional vertigo: a population based study. J Neurol Neurosurg Psychiatry. 2007;78:710–5.
4.Chen J, Zhang S, Cui K, Liu C. Risk factors for benign paroxysmal positional vertigo recurrence: a systematic review and meta-analysis. Journal of Neurology. 2020 Aug 24;
5.Ulytė A, Valančius D, Masiliūnas R, Paškonienė A, Lesinskas E, Kaski D, et al. Diagnosis and treatment choices of suspected benign paroxysmal positional vertigo: current approach of general practitioners, neurologists, and ENT physicians. European Archives of Oto-Rhino-Laryngology. 2019 Jan 29;276(4):985–91.
6.Hornibrook J. Benign Paroxysmal Positional Vertigo (BPPV): History, Pathophysiology, Office Treatment and Future Directions. International Journal of Otolaryngology. 2011;2011:1–13.
7.Corvera Behar G, García de la Cruz MA. Surgical treat- ment for recurrent benign paroxysmal positional ver- tigo. Int Arch Otorhinolaryngol. 2017;21:191–4.
8.overview of nystagmus",section on"basic clinical vestibular physiology"
9.Imai T, Inohara H. Benign paroxysmal positional vertigo. Auris Nasus Larynx [Internet]. 2022 Apr 3;
10.Hughes CA, Proctor L. Benign Paroxysmal Positional Vertigo. The Laryngoscope. 1997 May;107(5):607–13.
11.Jeong SH, Choi SH, Kim JY, et al. Osteopenia and osteoporosis in idiopathic benign positional vertigo. Neurology 2009; 72:1069.
12.Sfakianaki I, Binos P, Karkos P, et al. Risk Factors for Recurrence of Benign Paroxysmal Positional Vertigo. A Clinical Review. J Clin Med 2021; 10.
13.Lee NH, Ban JH, Lee KC, Kim SM. Benign paroxysmal positional vertigo secondary to inner ear disease. Otolaryngology–Head and Neck Surgery. 2010 Sep;143(3):413–7.
14.Kim MB, Ban JH. Benign paroxysmal positional vertigo accompanied by sudden sensorineural hearing loss: A comparative study with idiopathic benign paroxysmal positional vertigo. The Laryngoscope. 2012 Aug 22;122(12):2832–6.
15.Amor-Dorado JC, Llorca J, Costa-Ribas C, Garcia-Porrua C, Gonzalez-Gay MA. Giant Cell Arteritis: A New Association with Benign Paroxysmal Positional Vertigo. The Laryngoscope. 2004 Aug;114(8):1420–5
16.Lim YH, Kang K, Lee HW, et al. Gait in Benign Paroxysmal Positional Vertigo. Front Neurol 2021; 12:633393.
17.Palmeri R, Kumar A. Benign Paroxysmal Positional Vertigo [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2022
18.Hoffman RM, Einstadter D, Kroenke K. Evaluating dizziness. The American Journal of Medicine. 1999 Nov;107(5):468–78.
19.Furman JM, Cass SP. Benign paroxysmal positional vertigo. The New England Journal of Medicine [Internet]. 1999 Nov 18;341(21):1590–6.
20-21.Watanabe Y, Ishikawa K, Yamamoto M, Nakamura T, Shineno K, Asai M, et al. Japanese practical guideline of BPPV. Equilib Res 2009;68: 218–225.
22. Califano L, Salafia F, Mazzone S, Melillo MG, Califano M. Anterior canal BPPV and apogeotropic posterior canal BPPV: two rare forms of vertical canalolithiasis. Acta Otorhinolaryngol Ital. 2014;34:189–97
23.Uno A, Moriwaki K, Kato T, Nagai M, Sakata Y. [Clinical features of benign paroxysmal positional vertigo]. *Nippon Jibiinkoka Gakkai Kaiho* 2001;104:9-16. [PubMed]
24.De la Meilleure G, Dehaene I, Depondt M, Damman W, Crevits L, Vanhooren G. Benign paroxysmal positional vertigo of the horizontal canal. Journal of Neurology, Neurosurgery & Psychiatry. 1996 Jan 1;60(1):68–71.
25.Han BI, Oh HJ, Kim JS. Nystagmus while recumbent in horizontal canal benign paroxysmal positional vertigo. Neurology. 2006 Mar 13;66(5):706–10.

26.Imai T, Takeda N, Ito M, Sekine K, Sato G, Midoh Y, et al. 3D analysis of benign positional nystagmus due to cupulolithiasis in posterior semicircular canal. Acta Otolaryngol 2009;129:1044–9
27.Parnes LS, Agrawal SK, Atlas J. Diagnosis and management of benign paroxysmal positional vertigo (BPPV). CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne [Internet]. 2003;169(7):681–93.
28. Choung YH, Shin YR, Kahng H, Park K, Choi SJ. ???Bow and Lean Test??? to Determine the Affected Ear of Horizontal Canal Benign Paroxysmal Positional Vertigo. The Laryngoscope. 2006 Oct;116(10):1776–81
29.Pezzoli M, Garzaro M, Pecorari G, Cena M, Giordano C, Albera R. Benign paroxysmal positional vertigo and orthostatic hypotension. Clinical Autonomic Research. 2009 Oct 10;20(1):27–31.
30. "Approach to the patient with dizziness", section on 'Presyncope'
31.Argaet EC, Bradshaw AP, Welgampola MS. Benign Positional Vertigo, its diagnosis, treatment and mimics. Clinical Neurophysiology Practice. 2019 Apr;
32.Barber HO. Positional vertigo and nystagmus. ***Otolaryngol ClinNorthAm*** 1973;6:169-87
33.Spector M. Positional vertigo after stapedectomy. ***Ann Otol*** Rhinol Laryngol 1961;70:251-4
34.McClure JA, Rounthwaite J. Vestibular dysfunction associ-ated with benign paroxysmal vertigo. ***Laryngoscope*** 1977; 87:1434-42.
35. Stahle J, Terins J. Paroxysmal positional nystagmus. ***Ann*** Otol Rhonol Laryngol 1965;74:69-83.
36."Pathophysiology, clinical manifestations, and diagnosis of migraine in adults"
37.von Brevern M, Radtke A, Clarke AH, Lempert T. Migrainous vertigo presenting as episodic positional vertigo. Neurology. 2004 Feb 9;62(3):469–72.
38.von Brevern M, Bertholon P, Brandt T, et al. Benign paroxysmal positional vertigo: diagnostic criteria. J Vestib Res. 2015;25:105–17
39.Bhattacharyya N, Gubbels SP, Schwartz SR, et al. Clinical practice guideline: benign paroxysmal posi- tional vertigo (update). Otolaryngol Head Neck Surg. 2017;156:S1–S47.
40. Chen CC, Cho HS, Lee HH, Hu CJ. Efficacy of reposi- tioning therapy in patients with benign paroxysmal positional vertigo and preexisting central neurologic disorders. Front Neurol. 2018;9:486.
41.Parnes LS, Price-Jones RG. Particle repositioning ma-neuver for benign paroxysmal positional vertigo. Ann Otol Rhinol Laryngol. 1993;102:325–31.
42.Mandalà M, Salerni L, Nuti D. Benign Positional Paroxysmal Vertigo Treatment: a Practical Update. Current Treatment Options in Neurology. 2019 Dec;21(12).
43.Semont A, Freyss G, Vitte E. Curing the BPPV with a liberatory maneuver. Adv Otorhinolaryngol. 1988;42:290–3.
44.Califano L, Melillo MG, Mazzone S, Vassallo A. Converting apogeotropic into geotropic lateral canalolithiasis by head-pitching manoeuvre in the sit- ting position. Acta Otorhinolaryngol Ital. 2008;28:287–91.
45.Kim HJ, Kim JS. The patterns of recurrences in idio- pathic benign paroxysmal positional vertigo and self- treatment evaluation. Front Neurol. 2017;8:690.
46.Herdman SJ, Tusa RJ, Zee DS, Proctor LR, Mattox DE.
Single treatment approaches to benign paroxysmal positional vertigo. Arch Otolaryngol Head Neck Surg. 1993;119:450–4.
47.Califano L, Capparuccia PG, Di Maria D, Melillo MG, Villari D. Treatment of benign paroxysmal positional vertigo of posterior semicircular canal by "Quick Lib- eratory Rotation Manoeuvre". Acta Otorhinolaryngol Ital. 2003;23:161–7
48.Choi S, Choi HR, Nahm H, Han K, Shin JE, Kim CH. Utility of the bow and lean test in predicting subtype of benign paroxysmal positional vertigo. Laryngoscope. 2018;128(11):2600–4.
49.Zuma e Maia F. New treatment strategy for apogeotropic horizontal canal benign paroxysmal po- sitional vertigo. Audiol Res. 2016;6:163
50.Mandalà M, Salerni L, Nuti D. Benign Positional Paroxysmal Vertigo Treatment: a Practical Update. Current Treatment Options in Neurology. 2019 Dec;21(12).
51.Kim JS, Oh S-Y, Lee S-H, et al. Randomized clinical trial for geotropic horizontal canal benign paroxysmal po- sitional vertigo. Neurology. 2012;79:700–7
52.Mandalà M, Pepponi E, Santoro GP, et al. Double- blind randomized trial on the efficacy of the Gufoni maneuver for treatment of lateral canal BPPV. Laryn- goscope. 2013;123:1782–6.
53.Yacovino DA, Hain TC, Gualtieri F. New therapeutic maneuver for anterior canal benign paroxysmal posi- tional vertigo. J Neurol. 2009;256:1851–5.
54.Ling X, Li KZ, Shen B, Si LH, Hong Y, Yang X. Diagnosis and treatment of canal benign paroxysmal positional vertigo. Int J Audiol. 2018;57:673–80.
55.Wei W, Sayyid ZN, Ma X, Wang T, Dong Y. Presence of anxiety and depression symptoms affects the first time treatment efficacy and recurrence of benign paroxys- mal positional vertigo. Front Neurol. 2018;9:178.
56.AlGarni MA, Mirza AA, Althobaiti AA, Al-Nemari HH, Bakhsh LS. Association of benign paroxysmal posi- tional vertigo with vitamin D deficiency: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol. 2018;275:2705–11.
57.Jeong SH, Kim JS. Impaired calcium metabolism in benign paroxysmal positional vertigo: a topical review. J Neurol Phys Ther. 2019;43(Suppl 2 Supplement, Special Supplement: International Conference on Ves- tibular Rehabilitation):S37–41.
58.Corvera Behar G, García de la Cruz MA. Surgical treat- ment for recurrent benign paroxysmal positional ver- tigo. Int Arch Otorhinolaryngol. 2017;21:191–4.

Article topic: Transient Global Amnesia (TGA).

Author: Rama Amourah.

Editor: Haneen Al-Abdallat, Haneen A. Banihani.

Reviewer: Ethar Hazaimeh.

Keywords: ***transient, anterograde amnesia, retrograde amnesia, memory, venous insufficiency***

Overview

To understand memory loss disorders, one must first understand memory itself. In the context of neuropsychiatry, memory is the ability to process, store, and recall or recognize information for next use. [1] There are two large, interconnected categories for the type and longevity of information stored in human memory: short-term (or working) and long-term memory. Short-term memory can have a limited amount of new information that can only be remembered for a brief period, while long-term memory allows an individual to store and retrieve an indefinite amount of information for an indefinite period. Repetition or processing of information in the working or short-term memory facilitates its conversion to long-term memory; conversely, if long-term memories are not retrieved, they may be forgotten.[2]

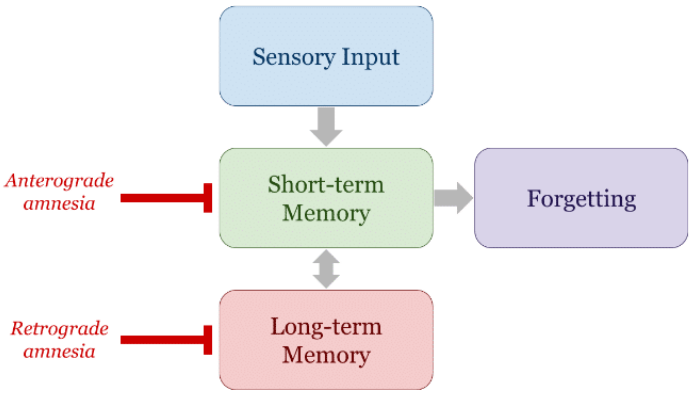


FIGURE 1: Flowchart of memory and amnesia[1, 2]

Amnesia is the transient or permanent loss of memory (the ability to store and recall learned information) without losing other cognitive functions. There are two types of amnesia: anterograde and retrograde. The difference between them is that people

affected by anterograde amnesia cannot form new long-term memories due to an inability to commit information to long-term memory from short-term memory. In contrast, people with retrograde amnesia cannot recall previously formed long-term memories from a variable interval of the person's life. [3] People may acquire amnesia with anterograde and retrograde characteristics, which is described as global. [2]

Introduction

Transient global amnesia (TGA) is an attack of global amnesia that the affected individual fully recovers from within twenty-four hours. The presence of a trigger (such as emotional stress) and the deficit in long-term memory varies between patients, but what all cases of TGA have in common is that there are no other losses in cognitive and neurological function or associated signs and symptoms. [4], [5]

Etiology

The pathophysiology of transient global amnesia is disputed as of the writing of this article. Studies have proposed several different pathological processes which may cause this disease, which can be described as follows:

Vascular

One of the theories is that TGA is caused by venous insufficiency, leading to an episode of venous congestion in the brain, particularly the medial temporal lobes.[5] This could explain why many common triggers of TGA also increase intrathoracic pressure, increasing cerebral venous pressure (Figure 2).[6][7] Several studies found an association between TGA and internal jugular vein (IJV) valve insufficiency or occlusion of the brachiocephalic vein. However, other studies have found that IJV insufficiency does not explain all cases of TGA, and many people with IJV do not experience TGA. [8] Another possible vascular cause for TGA is hypoperfusion due to arteriolar vasoconstriction in response to triggers, including hyperventilation and increased cerebral venous pressure. Several imaging studies have shown that a considerable proportion of TGA patients have imaging findings consistent with transient ischemia[9]; however, not all TGA patients have findings of cerebral hypoperfusion, and whether the ischemia is causative of TGA is unclear. [10]

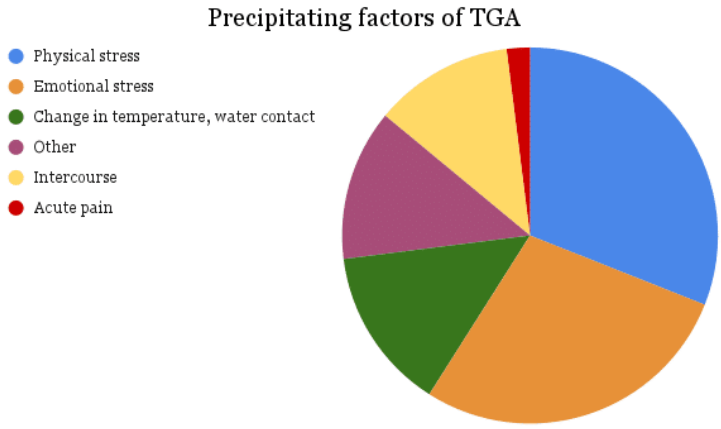


FIGURE 2: Some common TGA triggers, sorted by frequency. [10], [19]

Migraine-related

Migraine is most likely caused by cortical spreading depression: a cortical wave of neuronal hyperactivity followed by hypoactivity.[11] Cortical spreading depression or similar patterns of cortical neuronal polarization and depression have been implicated by some studies to be associated with TGA.[12] This is supported by the fact that people less than fifty-six years old who experienced TGA have a history of migraines.[12], [13]

Epileptic

Some publications guess that the pathophysiology of TGA is epileptic due to its similarity to transient epileptic amnesia (TEA), which is an episode of anterograde amnesia caused by an aware focal seizure of the temporal lobe. However, TGA and TEA are considered separate diagnoses with distinguishing features (Table 1), and studies found that patients with TGA have normal EEG readings. [14]

TABLE 1: Table comparing TGA and TEA. [13]

	TGA	TEA
RISK FACTOR	History of migraine	No
PRECIPITATING FACTOR	Yes	Inconclusive
DURATION	Usually 4-6 hours, <24 hours	<1 hour

ASSOCIATED NEUROLOGICAL SYMPTOMS	None	+/- Oral automatisms, gustatory and olfactory hallucinations
EEG FINDINGS	No abnormalities	Abnormalities in temporal or frontotemporal areas
MRI FINDINGS	Hippocampal DWI hyperdensity which resolves when the attack ends	+/- Hippocampal sclerosis or atrophy
RISK OF RECURRENCE	Low	High
RESPONSE TO ANTISEIZURE DRUGS	Poor response	Responds well

Other

β-amyloid deposits in the CA1 area of the hippocampus have also been found to be associated with TGA. [12]

Clinical Presentation

The typical TGA case is an adult fifty to seventy years old who suddenly becomes disoriented to place and time and is distressed by this change. They often repeat the same questions, trying to orient themselves as to where they are and how they got to be in their situation. TGA patients may also have some degree of retrograde amnesia but are always self-aware and never present with other neurological or cognitive symptoms. The attack always resolves within twenty-four hours, and there is no change in the patient's baseline neurological health. [4], [10]

Diagnosis and Investigations

TGA is a diagnosis based on the patient's history and physical and neurological exam based on a set of criteria (Table 2). Imaging and other investigations are more helpful in ruling out differential diagnoses such as transient ischemic attacks (TIAs) and TEA than they are for identifying TGA. [15]

TGA diagnostic criteria
○ The attack was witnessed by a capable observer and reported as being a definite loss of recent memory (anterograde amnesia). ○ There was an absence of clouding of consciousness or other cognitive impairment other than amnesia. ○ There were no focal neurological signs or deficits during or after the attack. ○ There were no features of epilepsy, or active epilepsy in the past two years, and the patient did not have any recent head injury. ○ The attack was resolved within 24 hours.

TABLE 2: TGA diagnostic criteria. [16]

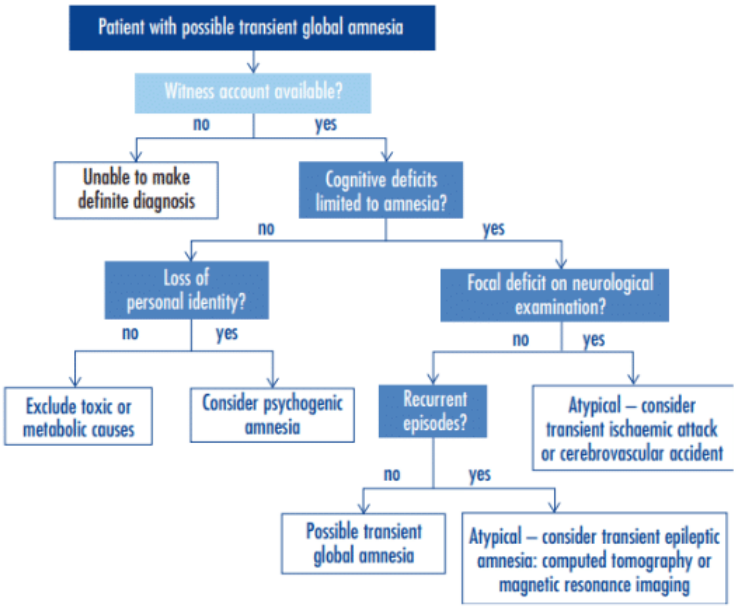


FIGURE 3: Flowchart for diagnosing TGA and its differentials. [17]

Treatment and management

TGA does not need treatment because it resolves entirely within twenty-four hours. [18] It is essential to counsel the patient and their family about what happened and reassure them that TGA is benign.

Prevention

Given the low recurrence, low morbidity, and disputed etiology of pure TGA, there are few publications on preventing it.

Risk factors

People between the ages of fifty-six and seventy-five years old were found to have the highest occurrence of TGA. Most men who experienced TGA reported that it was preceded by physical stress, while women who experienced TGA reported emotional stressors and a history of anxiety, or some personality disorder associated with their attack. People younger than fifty-six years old who had TGA are more likely to have a history of migraines than the general population. [19]

Prognosis

TGA has an excellent prognosis. Only 12.5% of people who experience TGA will have subsequent attacks, and their risk of TIA and dementia are 3% and 6%, respectively. [20] People who had TGA do not have a higher rate of vascular accidents, psychological disturbances, or mortality than a healthy control population, unlike people who experienced a TIA. That said, it is unclear whether TGA patients are at a higher risk of epilepsy and dementia than the general population. [21]

Recent developments

Researchers are exploring the possibility of a relationship between TGA and the SARS-CoV-2, or COVID-19, pandemic. A review of some case reports concluded that there had been an increase in the incidence of TGA since the onset of the pandemic; however, they were unable to conclude if that was due to the virus itself or the psychological stress of the pandemic.[22], [23] Some publications claim that there may be an association between COVID-19 vaccines and TGA, but the link between the two is unclear.[24], [25]

References

1. Daroff RB, Bradley WG. (2012). *Bradley's neurology in clinical practice*. 6th ed. Philadelphia, PA: Elsevier/Saunders.
2. Baddeley, Alan D., et al. (2005). *The essential handbook of memory disorders for clinicians*. J. Wiley.
3. Cifu, David X, & Lew, L. Henry. (2013). *Handbook of Polytrauma Care and Rehabilitation*. Demos medical publishing.
4. Arena, J. E., & Rabinstein, A. A. (2015). *Transient Global Amnesia. Mayo Clinic Proceedings, 90(2), 264–272.*
5. Lewis SL. (1998). *Aetiology of transient global amnesia.* Lancet; 352(9125): 397-399.
6. Cejas, C., Cisneros, L. F., Lagos, R., Zuk, C., & Ameriso, S. F. (2009). *Internal Jugular Vein Valve Incompetence Is Highly Prevalent in Transient Global Amnesia. Stroke, 41(1), 67–71.*
7. Chung CP, Hsu HY, Chao AC, Chang FC, Sheng WY, Hu HH. (2006). Detection of intracranial venous reflux in patients of transient global amnesia. Neurology, 66(12): 1873–77

8. Bettermann K. (2006). *Transient global amnesia: the continuing quest for a source*. Arch Neurol, 63: 1336–38.
9. Di Filippo, M., & Calabresi, P. (2007). Ischemic bilateral hippocampal dysfunction during transient global amnesia. Neurology, 69(5), 493–493.
10. Pantoni, L., Lamassa, M., & Inzitari, D. (2000). *Transient global amnesia: a review emphasizing pathogenic aspects. Acta Neurologica Scandinavica, 102(5), 275–283.*
11. Dodick DW & Gargus JJ (August 2008). "Why migraines strike". *Scientific American.*
12. Bartsch, T., & Deuschl, G. (2010). Transient global amnesia: functional anatomy and clinical implications. *The Lancet Neurology*, *9*(2), 205-214.
13. Butler, C. R., & Zeman, A. (2008). A case of transient epileptic amnesia with radiological localization. Nature Clinical Practice Neurology, 4(9), 516–521.
14. Butler, CR., Graham, K.S., Hodges, J.R., Kapur, N., Wardlaw, J.M., and Zeman, A. (2007). "The Syndrome of Transient Epileptic Amnesia" (PDF). *Annals of Neurology*. 61 (6): 587–598.
15. Spiegel, D. R., Smith, J., Wade, R. R., Cherukuru, N., Ursani, A., Dobruskina, Y., ... Dreyer, N. (2017). *Transient global amnesia: current perspectives. Neuropsychiatric Disease and Treatment, Volume 13, 2691–2703.*
16. Hodges JR, Warlow CP. (1990). Syndromes of transient amnesia: towards a classification. A study of 153 cases. J Neurol Neurosurg Psychiatry. 53(10):834–843.
17. Williamson, J., & Larner, A. J. (2015). Transient global amnesia. *British Journal of Hospital Medicine*, *76*(12), C186-C188.
18. Owen, D., Paranandi, B., Sivakumar, R., & Seevaratnam, M. (2007). *Classical diseases revisited: transient global amnesia. Postgraduate Medical Journal,* 83(978), 236–239.
19. Quinette P, Guillery-Girard B, Dayan J, et al. (2006). What does transient global amnesia really mean? Review of the literature and thorough study of 142 cases. Brain, 129: 1640–58.
20. Nausieda, P. A. (1979). Long-term Prognosis in Transient Global Amnesia. JAMA: The Journal of the American Medical Association, 241(4), 392.
21. B: Liampas, I., Raptopoulou, M., Siokas, V., Tsouris, Z., Brotis, A., Aloizou, A., Dastamani, M. & Dardiotis, E. (2021). The long-term prognosis of Transient Global Amnesia: a systematic review. *Reviews in the Neurosciences*, *32*(5), 531-543.
22. Farjoud-Kouhanjani, M., Shafie'ei, M., Taghrir, M. H., Akbari, Z., Hashemi, S. M. A., Eghlidos, Z., ... & Rahimi-Jaberi, A. (2022). Transient global amnesia after COVID-19: A systematic scoping review of case reports. *Current Journal of Neurology*, 244-250.
23. Nishizawa, T., Kawakami, A., Taguchi, T., & Osugi, Y. (2020). *Transient global amnesia with bilateral hippocampal lesions during the COVID-19 global outbreak. Journal of General and Family Medicine, 22(3), 154–155.*
24. Merino, D., Gérard, A. O., Van Obberghen, E. K., Ben Othman, N., Ettore, E., Giordana, B., Viard, D., Rocher, F., Destere, A., Benoit, M., & Drici, M. D. (2022). COVID-19 Vaccine-Associated Transient Global Amnesia: A Disproportionality Analysis of the WHO Safety Database. *Frontiers in pharmacology*, *13*, 909412.
25. Katsuki, M., Higo, Y., Komagata, S., Kashiwagi, K., & Koh, A. (2022). Transient Global Amnesia Related to the Third Coronavirus Disease-19 (COVID-19) Vaccination. *Cureus*, *14*(7), e27121

Article topic: The Role of Physical Exercise in Neuroplasticity.

Author: Rahaf Al-Awawdeh, Etaf Alajjouri.

Editor: Lubna AL-Rawabdeh.

Reviewer: Ethar Hazaimeh.

Keywords: Mental health, neuroplasticity, Neurorehabilitation, physical exercise, electrical stimulation.

Abstract

The purpose of this review is to discuss various interventions for improving motor function and physical performance in individuals with health conditions such as aging, neurological conditions, and mobility impairments. The research discusses various interventions for improving motor function and physical performance, including resistance training, virtual reality, physiotherapy, physical exercises, balance training, electrical stimulation, and the combination of central and peripheral stimulation. The research also highlights the benefits of each intervention and their effects on cortical plasticity, brain activity, and functional recovery. Additionally, the review emphasizes the importance of exercise, a healthy diet, and cognitive engagement in promoting positive brain health.

Introduction

Neuroplasticity is the nervous system's ability to adjust to intrinsic or external stimuli by readjusting structure, connections, and function [1]. Neuroplasticity refers to the brain's ability to reorganize itself by forming new neural connections throughout life in response to experiences, learning, and environmental factors [2]. It’s the brain's ability to modify its shape and make a new neuronal connection via a new stimulus [3].The principles of neuroplasticity include the importance of feedback and feed-forward connections, the role of neuromodulator processes in controlling plasticity, and the importance of small learning steps and repetition [2].The brain has a special self-organization character, which is the development of an organized system without external factors [3].The neuroplasticity process involves the formation and strengthening of neural connections as well as the pruning of unused connections. This is a fundamental process underlying learning, memory, and recovery from injury or disease. It is driven by the brain's ability to modify the strength of existing connections between neurons and to create new connections in response to new experiences [2]. The brain may learn and adapt to new experiences due to this dynamic process [4].

Studies have shown that the processes in the brain that control fast learning can themselves be upregulated by specific forms of training [2]. Any change in the nervous system can cause changes in the neural network for motor, sensory, and cognitive functions [1]. There are various aspects of biochemical mechanisms supporting neuroplasticity, including the involvement of specific proteins such as protein kinases, proteases, and cytokines in synaptic plasticity. Therefore, biochemical mechanisms are essential for the brain's ability to change and adapt throughout life, which is the essence of neuroplasticity. These therapeutic tools are designed to harness the brain's ability to change and adapt in response to experiences and learning to address specific neurological and psychiatric disorders [2].

Prevention methods

Maintaining a healthier brain can be achieved through modifiable lifestyle factors such as physical activity, cognitive engagement, and diet. Regular physical activity has been shown to reduce the risk of cognitive decline in aging adults [5]. Exercise has the main role of improving physical performance and decreasing a wide range of pathologies, including cardiovascular, metabolic, and neurodegenerative disorders. Endurance exercise is a physical exercise that causes increases in the respiratory rate and heart rate, and it’s called aerobic exercise. Endurance exercise is inexpensive and accessible and has a lot of benefits not only in the physical domain but also in the mental domain. It helps maintain memory and cognition, delay brain aging, and enhance neurodegenerative pathologies symptoms like Parkinson's disease, ALS, and Alzheimer's disease [6]. Endurance exercises are anti-aging therapies that improve neuronal survival, promote synaptic plasticity, and decrease the disease progression of neurodegeneration [6].

The neuroprotective impact of endurance exercise: decreases stress, anxiety, neuro-inflammation, and insulin resistance [6]. Cognitive training and rehabilitation can be used to facilitate the reorganization and proper function of cognitive circuits, enhancing brain reserve and cognitive reserve [5]. Preventive approaches to promote positive health habits such as reading, discussion groups, computer usage, participation in card and board games, solving puzzles, playing musical instruments, and learning a second language can also be beneficial for brain health [5]. Also, the diet plays a significant role in protecting against cognitive decline [5].Diet can affect our brain negatively or positively based on the type of food that we eat. It is one of the modifiable factors that can delay the aging process, such as decreased fat and sugar intake and opioid and alcohol addiction [3]. A review of the literature suggests that a Mediterranean-style diet, which is rich in fruits, vegetables, whole grains, fish, and healthy fats, may be particularly beneficial for brain health [5]. Acute caffeine intake can improve performance on memory tasks, and regular, moderate consumption of coffee, tea, and

cacao can enhance brain health. The neurological effects of caffeine are well-established, and it has been shown to improve cognitive performance for at least 10 hours [7].

Neurological diseases that affect brain function:

Alzheimer Disease

Alzheimer's is one of the most dangerous forms of dementia. It is considered one of the most severe economic, social, and medical diseases. The drugs that are mostly prescribed for Alzheimer's disease are acetylcholinesterase inhibitors (Ach Els) and memantine. These drugs improve some symptoms, but surprisingly, they don't have any effect on decreasing the progression of ADLs, social behaviors, or communication [8].

Studies showed that physical exercises not only have a positive effect on general health but also have other effects on mental health and prevent or decrease the risk of neurodegenerative diseases. Physical exercise has a positive effect on some of the most characteristic signs of Alzheimer's disease, through the regulation of oxidative stress-related mechanisms in the brain, increased blood flow and metabolism, and especially the decrease of cortical formation and accumulation of Aβ. Moreover, some of the mechanisms through which exercise has a positive impact on Alzheimer's disease appear to involve improvements in mitochondrial function. Also, exercise decreases the risk of cognitive impairment, so exercises that induce alterations in cognitive status are necessary for Alzheimer's patients to improve their quality of life [9].

Exercises improve brain structure and function. The adaptation that occurs because of exercise increases hippocampal neurogenesis and volume, increases brain blood flow, increases plasticity, and decreases the brain atrophy that occurs due to aging. Recently, research showed that physical exercise is the most effective strategy to counteract and prevent neurodegenerative diseases like Alzheimer's. Exercise intensity, repetition, and duration are not clear and are still under discussion [9].

Depression

In cases of depression, brain structure changes are always associated with certain areas of the nervous system, including the anterior lobe, cingulate gyrus, hippocampus, striatum, and white matter. Reductions in brain volume (including structural brain changes like neuronal loss and dropped neurotrophic factor) are related to depressive episodes. The hippocampus plays a vital role in cognitive exertion as well as stress and mood regulation in cases of depression. Exercise can play a positive role in preventing and treating depression. Several types of exercise, such as aerobic exercise, resistance exercise, and mind-body exercise, can palliate depressive symptoms and lower

depression levels. Exercise can reshape the brain structure of depression cases, spark the function of affiliated brain areas, and promote behavioral adaptation, which changes the brain's neuroprocessing and delays cognitive decline in depression cases [10]. Aerobic exercise has been shown to result in decreased anxiety and depression in animal models, even in stressful situations. Physical exercise has an action like selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression and anxiety [11]. Exercise has a better antidepressant effect than traditional drugs, and moderate-intensity aerobic exercise for at least 9 weeks, 3–4 days a week, can effectively reduce the threat of depression [10].
Physical exercise is associated with improved psychological well-being and satisfaction with life in humans [11].

Stroke (CVA)

A stroke is a medical contingency that occurs when the blood flow to the brain is cut off or reduced, depriving brain tissue of oxygen and nutrients. This can cause brain cells to die, leading to permanent brain damage, disability, or death. Stroke has two types: ischemic stroke and hemorrhagic stroke.

A stroke can cause abrupt paralysis or numbness in the face, arm, or leg, particularly on one side of the body; unexpected confusion; difficulty speaking or understanding speech; loss of balance or coordination; and a sudden severe headache with no known cause [12].

After a stroke, the brain undergoes neuroplastic changes that can lead to motor impairment. There are various approaches and techniques for stroke rehabilitation that aim to enhance neuroplasticity and improve motor function after stroke, such as:

Physical therapy

This involves exercises and activities that help improve strength, flexibility, and coordination.

Pharmacological interventions

Medications such as antidepressants, anti-spasticity agents, and neuroprotective agents may be used to improve motor function after stroke.

Stem cells

Stem cells may be used to promote neural repair and regeneration after stroke.

Neural growth factors

These are proteins that promote the growth and survival of neurons and may be used to enhance neuroplasticity after stroke.

Exogenous biomaterials

These are materials that can be implanted or injected into the body to promote neural repair and regeneration.

Robot-assisted therapy

This involves the use of robotic devices to assist with movement and improve motor function.

Orthotics

These are devices such as braces or splints that can be worn to support and stabilize the affected limb.

Peripheral nerve/muscle stimulation

Electrical stimulation of the nerves or muscles may be used to improve motor function after stroke.

Transcranial magnetic stimulation

This involves the use of magnetic fields to stimulate the brain and improve motor function.

Occupational therapy and speech [12].

The effect of physical exercises after stroke is described as the first-line intervention strategy to decrease the chronic impairment of sensory and motor function

Physical exercise can be used as a diagnostic, rehabilitation, and preventive tool for stroke patients. For starters, acute exercise could be used as a diagnostic tool to uncover new neural mechanisms underlying stroke pathology. Furthermore, physical exercise training is recommended as a useful rehabilitation tool, it inhibits inflammatory processes and the expression of apoptotic markers in the brain, promotes angiogenesis and the expression of some growth factors in the brain, and improves the activation of affected muscles during exercise. Its depending on the exercise parameters used, exercise training may aggravate sensorimotor deficits and brain injuries. Therefore, it is important to design individualized exercise programs that consider the patient's specific

needs and limitations. Regular physical activity before a stroke may decrease the severity of motor outcomes after having a stroke and help reduce the severity of the motor result.

Therefore, to prevent stroke using physical exercise, it is recommended to engage in regular physical activity, such as walking, jogging, cycling, or swimming, for at least 30 minutes a day, five days a week. Additionally, it is important to maintain a healthy diet, control blood pressure, quit smoking, limit alcohol consumption, and manage diabetes to reduce the risk of developing stroke [13].

Physiotherapy can help patients return to their daily living activities and professional activities, reducing the burden on their caregivers and the healthcare system. Physiotherapy approaches may include exercises to improve strength, balance, and coordination, as well as gait training and functional activities to improve mobility and independence.
Overall, physiotherapy is an essential component of stroke recovery and can significantly improve outcomes for stroke patients [14].

Spinal cord injuries (SCI)

The impact of a spinal cord injury is the sudden loss of movement and function, which can be life changing. Spinal cord injury can affect motor, sensory, and autonomic functions, and result in local and global inflammatory reactions. Motor function loss following SCI, as well as plastic changes in the spinal cord because of the injury, can result in hyperreflexia, spasticity, and spasms. Spinal cord injury can also trigger a loss of downstream activity-dependent processes, producing spinal interneuron degeneration and several activity-dependent maladaptive changes [15].

Activity-dependent neuroplasticity can be used to promote motor recovery after spinal cord injury by promoting the formation of new functional connections and strengthening spared connections in the spinal cord. Motor rehabilitation can also be used to promote motor recovery by training circuits and promoting adaptive plasticity [15].

Parkinson’s disease (PD)

Parkinson's Disease (PD) is a progressive neurodegenerative movement disorder that is characterized by motor symptoms such as resting tremor, rigidity, bradykinesia or akinesia, and postural instability.
It is caused by the loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to motor and cognitive dysfunction as well as mood disorders. Age is the most important risk factor for developing PD, but environmental factors like pesticide exposure, β-adrenergic antagonist use, and male gender also increase PD risk. Exercise

has been shown to modify dopaminergic signaling and sensitivity, increase neurotrophic factors and angiogenesis, and reduce inflammatory pathways, making it an attractive therapeutic target for PD [6].
Combining prefrontal and motor cortex stimulation could reduce the freezing of gait and improve mobility in patients with Parkinson's disease. In summary, the prefrontal cortex can be used to enhance cognitive performance, attention, and executive functions, as well as motor recovery [16].
There are several benefits of exercise for people with Parkinson's disease (PD), including:

1. Improving physiologic, functional, clinical, and molecular outcomes.

2. Enhancing mobility and cognition in PD patients.

3. Preserving and restoring dopaminergic neurons in the midbrain.

4. In Parkinson’s disease patients who completed high-intensity exercise, there was a dose-dependent improvement in mobility as well as a normalization of corticomotor excitability.

5. Improving walking speed, stride, and step length in PD patients with mild-to-moderate disability.

6. Providing maximum benefit to PD patients when exercise is diffuse as opposed to training targeted to specific deficits.

7. Improving both forward and backward walking in PD patients who completed treadmill exercise.

8. Providing some benefit from increased activity in PD patients who completed low-intensity exercise.

Physical exercises' effects on brain plasticity

The positive effects of physical exercise on brain activity, specifically its effects on cognitive functions, spatial learning, and short-term and long-term memory [17].

Physical exercise induces an increase in the synthesis and release of neurotrophins and growth factors, which include brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (EGF). Modulation of

these neuromediators appears to increase neuronal subtype survival and development [9].

Neuroplasticity has been seen in humans by growing white and gray matter in various brain locations following various physical exercise programs. Physical exercise has a positive effect on mental health outcomes. The practice of physical exercise increases the plasticity of the hippocampus, promoting changes in serotonin metabolism and synaptic plasticity [11].
Gross motor performance is increased by resistive training, which increases the maximal voluntary force in specific tasks, an increase in motor performance occurs because of neuroplastic adaptations in the brain [18].

Resistance training (RT) has been shown to induce neuroplasticity, which refers to the ability of the nervous system to adapt and reorganize in response to changes in the environment or behavior. RT can induce favorable changes in the nervous system, which may mediate improvements in physical and cognitive function [18].

The functional relevance of resistance training-induced neuroplasticity in health and disease refers to the potential benefits of resistance training (RT) on improving motor function and physical performance in individuals with various health conditions, such as aging, neurological conditions (e.g., Parkinson's disease, multiple sclerosis, and stroke), and mobility impairments [18].
Fit or aerobically trained older adults have greater functional connectivity between parts of the frontal, posterior, and temporal cortices involved in spatial selection and inhibitory function [19].

Several studies mentioned in the document suggested that resistance training can enhance motor cortical plasticity, increase gray matter density in elderly individuals, and lead to functional and/or structural brain changes that improve cognitive function [18].

Physiotherapy interventions

Physiotherapy interventions can assist patients to enhance their performance and abilities. Both Conventional physiotherapy interventions and a standard protocol called neurorestoration are effective in improving balance and functional ability in acute stroke survivors. The neurorestoration protocol, which combined several established interventions, was found to be more effective. The Physiotherapy interventions, including the neurorestoration protocol, should be considered as a core intervention in treatment alongside medical and pharmaceutical interventions [21].

Physical exercises are described as a non-pharmacological method that has a positive effect on memory, spatial learning, and cognitive function. Also, it helps in treating

neurodegenerative diseases and improving brain health.
The recommendation of the American College of Sports and Exercise is to train most of the week with aerobic and resistance exercises.
The different types of physical exercises are non-forced, such as activity wheels, and forced, such as the treadmill, which causes hippocampal plasticity, cell proliferation, and branching of the dendrites.

A study of the effect of running on the dentate gyrus for long-term potential showed that running decreases the age associated with long-term potential. Another study showed that neuroreceptors can improve the capacity of cells in the long term. A study using radiant as an animal model showed that the radiant subjected to aerobic exercises on treadmills for 12 weeks had better outcomes in hippocampal plasticity, memory, and spatial learning after training than other groups [17].

Based on the randomized control trial that reviewed the relation between balance training exercises in cortical thickness in visual and vestibular cortical regions, Participants had 12 weeks of continuous training; they took 2 sessions/week, and the duration of each session was 50 mins. They were categorized into 2 groups: the balance group and the relaxation group. Each group had from 10-12 participants [22].

1) **Balance training:** This section was directed as a circuit training with 8 stations, the duration of each station lasted 5 mins.
   The participants trained on different surfaces, such as a firm foam surface, and in different conditions such as dynamic or static balance, eyes open or closed, a wide base of support, and a narrow base of support. The exercise station was replaced with a new one after six weeks of training to make it more challenging.22

   2) Relaxation training: This group practiced progressive muscle relaxation and autogenic exercises. The short form of progressive muscle relaxation was instructed in the first 6 weeks. The single muscle group tensed 5-7sec, then 45-sec relaxation, and repeated 2 times per session [22].

The autogenic training was introduced after 6 weeks; this training included breathing exercises, and the participants were trained on how to concentrate on the breathing rhythm as well as on heartbeats. The enhancements in balance performance have a relationship with the change in cortical thickness in both the left and right pre-central gyrus.

The improvement in balance performance is associated with a huge increase in pre-central cortical thickness, there is no significant difference for relaxation groups [22].

Another study showed that Aerobic, resistance, and balance activities may be beneficial in improving physical function and increasing brain activity. The exercise intervention increased step length but decreased cadence in the intervention group. The changes in gait are associated with age-related brain changes, including global brain atrophy, cerebral white matter lesions, and micro-bleeds. In older persons, exercise and gait training can enhance both physical and mental performance [19].

Recent studies of animals and humans showed that acute exercises could make changes in muscle activation after having cerebral ischemia and the early treadmill exercises make neuroplasticity by working on the angiogenesis and vasomotor activity of the brain.
Preischemic exercises like treadmill workouts for 30 mins. for 5 days/week for 3 weeks decrease infarct volume and edema [13].

Virtual reality (VR) can have a positive impact on neural plasticity. VR-based interventions can provide enriched environments for rehabilitation, which can promote experience-dependent plasticity in stroke patients.20
The mirror neuron system is a neural network that is involved in motor observation, imitation, and imagery and can be activated by VR-based interventions, the mirror neuron system can be encompassed in VR interventions, and it reveals the possible specific neural mechanisms of VR. The core mirror neuron system in humans includes the inferior parietal lobule, ventral premotor cortex, and inferior frontal gyrus, and it is more like a functionally distributed network involving the primary and secondary motor areas than specific separate regions [20].

VR systems should be designed to provide a high level of immersion and engagement, as this can enhance the effectiveness of VR-based interventions. Additionally, the development of VR systems that can be used in a variety of settings, including inpatient and outpatient rehabilitation, and that can be adapted to the changing needs of stroke patients over time [20].

VR makes neural plasticity changes in stroke survivors, and there is a positive relationship between neural plasticity changes and functional recovery [20].

The neurophysiological effects are enhancing inter-hemispheric balance; improving cortical connectivity, raising the cortical mapping of the affected muscles, and increasing the activation in the frontal cortex regions, involving the mirror neuron system, and all the improvements of the behavioral outcomes related to the improvement in neural plasticity [20].
Balance performance can be improved by specific exercise programs for blind adults. A blind adult showed an improvement in static, dynamic, and functional balance after 12 weeks of balance exercises [23].

Electrical stimulation

Electrical stimulation is used in neuromuscular electrical stimulation (NMES) to activate muscles that have become weak or paralyzed as a result of stroke. The electrical stimulation is delivered through electrodes placed on the skin over the targeted muscles. The purpose of NMES is to improve muscle strength, reduce muscle atrophy, and promote motor relearning. NMES can be used as a standalone therapy or in combination with other rehabilitation therapies. The peripheral and central effects of NMES include an increase in contractile force and fatigue resistance, as well as changes in cortical excitability and functional cortical reorganization. There are various NMES modalities used for upper and lower limb rehabilitation, such as cyclic, EMG-triggered, and contralaterally controlled NMES, and they have been evaluated for therapeutic effects [24].

The purposes of NMES for upper and lower limb rehabilitation after stroke. One of the most common manifestations of stroke is paresis, which is the inability or decreased ability to volitionally activate motor units. Paresis manifests as muscle weakness and decreased activation speed, as well as the inability to generate functionally effective movement of the afflicted limb. The combination of paresis, loss of fractionated motions, flexor hypertonia, and somatosensory anomalies frequently appear as trouble functionally extending the elbow and opening the hand, significantly limiting the functional workspace. There are several NMES modes available for upper limb rehabilitation. Cyclic NMES is a technique that employs a one- or two-channel stimulator to repeatedly stimulate (cyclically) via surface electrodes implanted on specific areas of the body above the motor sites of those muscles [24].

The peripheral effects of NMES include an increase in contractile force and fatigue resistance, as well as a reduction in muscle atrophy. NMES can also promote motor relearning by offering an artificial way of ensuring synchronized presynaptic and postsynaptic activity. This is especially true if the electrical stimulation is combined with a concurrent voluntary effort that activates the remaining upper motor neurons. Cortical excitability alterations and functional cortical reconfiguration are two of the main impacts of NMES. By causing long-term potentiation in the sensorimotor cortex brought on by proprioceptive and cutaneous afferent input occurring concurrently with attempted movements, NMES may improve cortical excitability [24].

The combination of central and peripheral stimulation, specifically the use of transcranial direct current stimulation (tDCS) and transcutaneous electrical nerve stimulation (TENS) together [16].

Studies have shown positive results on the combination of central and peripheral stimulation, including pain relief in patients with chronic pain and substantial functional improvements in patients with motor deficits. The benefits of peripheral stimulation, specifically the use of (TENS), which is a safe and non-invasive device that

aims to stimulate nerves for therapeutic purposes, have been proven. The gate control theory, which says that physical pain is not a direct outcome of the activation of pain receptor neurons, has been suggested to explain how TENS functions; its perception is influenced by the interaction of distinct neurons [16].

The benefits of central stimulation, specifically the use of (tDCS), which is a non-invasive technique that aims to modulate cortical excitability by applying a weak electrical current to the scalp, have been investigated for different conditions, such as stroke, Parkinson's disease, and depression. tDCS can alter a response and facilitate cortical remodeling when it is applied across a specific motor cortex region. By combining central stimulation with peripheral stimulation, it would be possible to enhance the effects of each intervention individually and achieve faster and long-lasting results. The utilization of prefrontal montage to improve motor, cognitive, and attentional functions. Specifically, the document mentions the use of anodal tDCS over the dorsolateral prefrontal cortex (DLPFC) for enhancing cognitive performance, including attention and executive functions [16]. The use of cerebellar stimulation, specifically transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), for motor and cognitive functions. Cerebellar stimulation has been investigated for different conditions, such as stroke, Parkinson's disease, and balance disorders. The cerebellum is known to play a crucial role in motor coordination, balance, and cognitive functions. Cerebellar stimulation can modulate cortical excitability using cerebello-cortical connectivity, which can lead to improvements in motor learning, cognitive functions, and balance. Furthermore, cerebellar stimulation can be used to augment language treatment post-stroke as well as modulate the acquisition of conditioned eyeblink responses. In conclusion, cerebellar stimulation can help with balance, emotional perception, and motor and cognitive abilities [16].

Conclusion

The findings of this literature review are that physical exercise has a positive effect on brain activity, specifically its effects on cognitive functions, spatial learning, and short-term and long-term memory.
Resistance training exercises affect neuroplasticity in the brain by improving motor function and physical performance in individuals with various health conditions.

A study of Aerobic exercises showed that running decreases the age associated with long-term potential.

Virtual reality (VR) has a positive impact on neural plasticity because it provides enriched environments for rehabilitation, which can promote experience-dependent plasticity.

Studies showed positive effects regarding the combination of central and peripheral stimulation, including pain relief in patients with chronic pain and substantial functional improvements in patients with motor deficits.

References

[1]Neurorehabilitation: applied neuroplasticity, 264 (2016) 603–615. https://doi.org/10.1007/s00415-016-8307-9.
[2]Principles of neuroplasticity-based rehabilitation, 207 (n.d.) 141–171. https://doi.org/10.1016/B978-0-444-63327-9.00009-6.
[3]Role of Lifestyle in Neuroplasticity and Neurogenesis in an Aging Brain, 12 (n.d.) e10639. https://doi.org/10.7759/cureus.10639.
[4]Molecular Mechanisms of Neuroplasticity: An Expanding Universe, 82 (2017) 237–242. https://doi.org/10.1134/S0006297917030014.
[5]Lifestyle Modulators of Neuroplasticity: How Physical Activity, Mental Engagement, and Diet Promote Cognitive Health during Aging., 2017 (2017) 3589271–3589271. https://doi.org/10.1155/2017/3589271.
[6]The protective role of exercise against age-related neurodegeneration, 74 (2021) 101543. https://doi.org/10.1016/j.arr.2021.101543.
[7]Impact of Coffee and Cacao Purine Metabolites on Neuroplasticity and Neurodegenerative Disease, 44 (2018) 214–227. https://doi.org/10.1007/s11064-018-2492-0.
[8]Alzheimer disease and neuroplasticity, 184 (n.d.) 473–479. https://doi.org/10.1016/B978-0-12-819410-2.00027-8.
[9]Physical Exercise and Brain Mitochondrial Fitness: The Possible Role Against Alzheimer's Disease, 26 (n.d.) 648–663. https://doi.org/10.1111/bpa.12403.
[10]Exercise, brain plasticity, and depression., 26 (n.d.) 885–895. https://doi.org/10.1111/cns.13385.
[11]Effects of Physical Exercise on Neuroplasticity and Brain Function: A Systematic Review in Human and Animal Studies, 2020 (2020) 8856621–8856621. https://doi.org/10.1155/2020/8856621.
[12]Neuroplasticity in the context of motor rehabilitation after stroke, 7 (2010) 76–85. https://doi.org/10.1038/nrneurol.2010.200.
[13]Physical Exercise as a Diagnostic, Rehabilitation, and Preventive Tool: Influence on Neuroplasticity and Motor Recovery after Stroke, 2015 (2015) 608581–608581. https://doi.org/10.1155/2015/608581.
[14]Brain Functional Reserve in the Context of Neuroplasticity after Stroke, 2019 (2019) 9708905–9708905. https://doi.org/10.1155/2019/9708905.
[15]Neuroplasticity of spinal cord injury and repair, 184 (n.d.) 317–330. https://doi.org/10.1016/B978-0-12-819410-2.00017-5.
[16]Searching for the optimal tDCS target for motor rehabilitation, 16 (2019) 1–12. https://doi.org/10.1186/s12984-019-0561-5.
[17]Physical exercise, neuroplasticity, spatial learning and memory, 73 (2015) 975–983. https://doi.org/10.1007/s00018-015-2102-0.
[18]Functional relevance of resistance training-induced neuroplasticity in health and disease, 122 (2020) 79–91. https://doi.org/10.1016/j.neubiorev.2020.12.019.
[19]Effects of exercise on brain activity during walking in older adults: a randomized controlled trial., 14 (2017) 50–50. https://doi.org/10.1186/s12984-017-0263-9.
[20]Effects of Virtual Reality Intervention on Neural Plasticity in Stroke Rehabilitation: A Systematic Review, 103 (2021) 523–541. https://doi.org/10.1016/j.apmr.2021.06.024.
[21]Effectiveness of physiotherapy interventions in brain plasticity, balance and functional ability in stroke survivors: A randomized controlled trial., 47 (n.d.) 463–470. https://doi.org/10.3233/NRE-203210.
[22]Exercise-induced neuroplasticity: Balance training increases cortical thickness in visual and vestibular cortical regions., 179 (2018) 471–479. https://doi.org/10.1016/j.neuroimage.2018.06.065.
[23]Improved balance performance accompanied by structural plasticity in blind adults after training., 129 (2019) 318–330. https://doi.org/10.1016/j.neuropsychologia.2019.04.005.
[24]Neuromuscular Electrical Stimulation for Motor Restoration in Hemiplegia, 26 (2015) 729–745. https://doi.org/10.1016/j.pmr.2015.06.002.

Article topic: Blepharospasm.

Authors: Noha el Masri, Rawan Chazbek.

Editor: Lubna AL-Rawabdeh.

Reviewer: Ethar Hazaimeh.

Keywords: Blepharospasm, Dystonia, Botulinum Toxin, Blink reflex.

Overview

Dystonia refers to a movement disorder causing intermittent or sustained muscle contraction, resulting in repetitive movements or postures. Dystonia can affect any body part whether an isolated region (focal dystonia) or multiple regions [1]. The most common types of dystonia are the ones involving one region of the body such as cervical dystonia in the neck, blepharospasm around the eyes, and writer's cramp in the upper limb [2].

Blepharospasm is a form of focal cranial dystonia characterized by sustained, involuntary spasms of the muscles around the eyes (orbicularis oculi, corrugator, and procerus muscles). Symptoms can range from increased blinking to forceful eyelid closure leading to functional blindness (difficulty opening the eyes) [3].

It is sometimes referred to as benign essential blepharospasm when it occurs as an isolated condition. However, blepharospasm usually occurs with other types of focal dystonia such as oromandibular, facial, lingual, or oral dystonia… the co-existence of blepharospasm and oromandibular dystonia (involving oropharyngeal and jaw muscles) is called Miege syndrome [4].

The pathogenesis of blepharospasm is not fully understood yet. The main problem in many types of dystonia is traditionally thought to be dysfunction of the basal ganglia. However, a growing body of evidence suggests the involvement of a network of other cortical and subcortical structures [5].

Treatment is based on symptom severity with botulinum toxin injection being the current first-line therapy, yet there are other medical and surgical options [4].

Introduction

The hallmark of blepharospasm is uncontrolled spasms in the orbicularis Oris. However, it may involve other periocular muscles and even muscles of the face. In

addition, the patients may present with non-motor manifestations including psychiatric and sensory disturbances [6].

Etiology

Studies suggest that blepharospasm has a multifactorial etiology. Multiple genes may be implicated, in addition to epigenetic and environmental factors that combine to induce the condition [6]. 25% of patients with blepharospasm have at least 1 family member having dystonia. The suggested pattern of inheritance is autosomal dominant with reduced penetrance [6].

Hypotheses suggest that phenotypic expression of blepharospasm and penetrance in individuals carrying susceptibility genes depends on the type and duration of environmental exposure, sunlight intensity may be an example [7].

On the contrary, secondary blepharospasm is usually caused by lesions affecting many brain regions including the thalamus, basal ganglia, cerebellum, midbrain, and cortex… which provides clues on the origin of the condition [6].

Neuropathology

Current (theories) argue that blepharospasm results from defects in neural circuitry rather than defective single locus [3]. These abnormalities include loss of inhibition in many levels of the central nervous system, abnormal sensory-motor integration, and maladaptive plasticity. Yet it is still unclear how each abnormality is responsible for specific motor symptoms [6].

Early hypotheses suggest that descending pathways from basal ganglia might be responsible for the hyperexcitability of brainstem interneurons involved in the blink reflex. Subsequent studies doubted this concept by showing thalamic lesions causing blepharospasms that are not in areas receiving striatopallidal input (from basal ganglia) but receiving cerebellar afferents. Other studies propose that cerebellar lesions might lead to blepharospasm by causing loss of inhibition of the primary motor cortex [5].

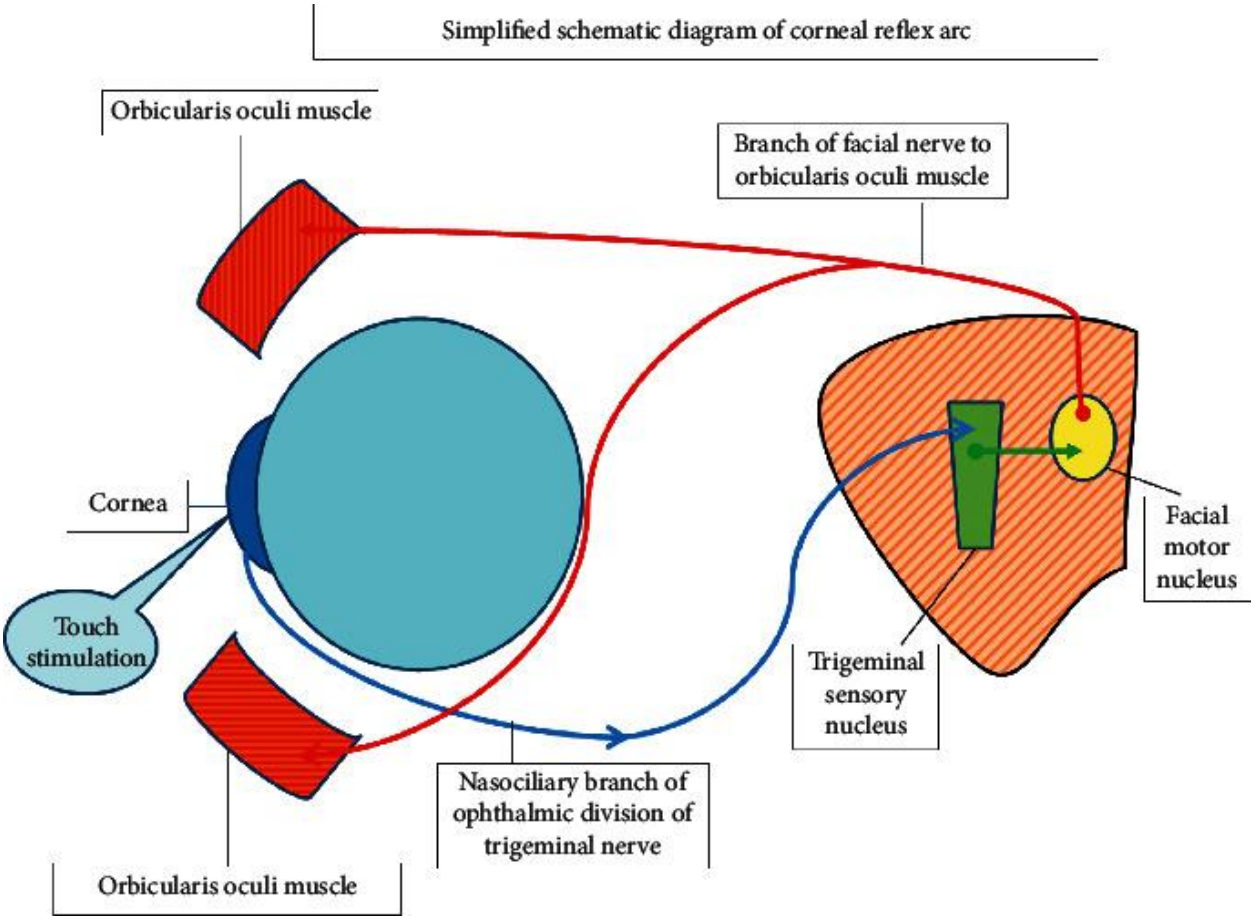


Figure 1 displays a simplified schematic diagram of a corneal reflex arc.[34] Khan Z. A. (2021).

Blepharospasm patients exhibit a more intense R2 phase (efferent phase) of the trigeminal blink reflex as compared to healthy subjects, which causes excessive blinking [1]. This can be explained by evidence correlating blepharospasm with increased plasticity in the trigeminal blink reflex circuit. Experiments have shown increased responsiveness to high-frequency stimulation of the trigeminal nerve in blepharospasm compared to a control, suggesting that LTP-like plasticity is increased in the blink reflex circuit of the patients. Hence, this supports the concept of maladaptive plasticity [8].

Clinical manifestations and Complications

Motor manifestations

The most common symptom of blepharospasm is orbicularis oculi muscle spasms that are synchronous and bilateral [1]. Spasms can be transient or prolonged, and they can cause the eyelids to constrict or close [9].

Another manifestation that happens in some individuals is apraxia of eyelid opening (AEO). This symptom manifests as difficulty in opening the eyes and is caused by spasms of the pretarsal orbicularis oculi muscle [1]. It might also be present due to the failure of contraction of the levator muscle [6].

The contraction of the orbicularis oculi can also spread and extend to the muscles of the lower face and neck causing what is known as Meige Syndrome [1].

Non motor manifestations

Sensory manifestations can occur in blepharospasm, including burning and grittiness in the eyes, discomfort, and sensitivity to light and dry eyes [9].

The frequency of depression, obsessive-compulsive disorders, and mild cognitive disturbances is higher in subjects with blepharospasm, yet it does not correlate with the severity of motor signs [6]. This cognitive impairment has been reported in the fields of working, memory, processing speed, visual-motor ability, and short-term memory reflecting the changes in the cortical and subcortical areas of the brain [10].

Sleep impairment has also been reported in blepharospasm cases. However, it is unclear if the disturbance is due to the depression associated with the blepharospasm or if it is present as an entity by itself [6]. An association has been found between blepharospasm and abnormal sleep-wake patterns [11].

An additional feature in this subtype of cranial dystonia is the presence of abnormal dystonic eye movements during sleep but with lower frequency and duration [6].

Exacerbating and Relieving factors

Blepharospasm tends to be exacerbated with activity such as walking, driving reading, watching television, Enhanced light, Fatigue, stress, feeling sick, and dry eye symptoms also tend to cause an exacerbation of the symptoms [1][12].

On the other side, blepharospasm tends to be alleviated with relaxation, talking, and even when focusing on tasks. It is also relieved after sleeping, at nighttime, by looking down, closing the eyes, and even applying pressure on the temples [12].

Diagnosis

A diagnostic algorithm has been developed to differentiate blepharospasm from other conditions. The first step is to diagnose the presence of bilateral, synchronous, and stereotyped movements of the orbicularis oculi muscle, the presence of a sensory trick,

or increased blinking. The following step is the detection of a sensory trigger or an increased blinking [13].

Multiple scales have been available to assess the severity of the blepharospasm. We have the Jankovic Rating Scale, the Blepharospasm Disability Scale, the Functional Disability Score, the Blepharospasm Disability Index, and a recent one developed and confirmed in 2015 by Defazio G, Hallett M, Jinnah HA, and others [3].

The most used one is the Jankovic Rating Scale which assesses the severity and frequency separately by giving a score from 0 to 4 to each of the items with 0 representing the absence of symptoms and 4 representing the most severe symptoms.

Blepharospasm Severity

0=None

1= Minimal, increased blinking present only with external stimuli (e.g. bright light, wind, reading, driving, etc.)

2= Mild, but spontaneous eyelid fluttering (without actual spasm), noticeable, embarrassing, but not functionally disabling)

3=Moderate, very noticeable spasm of eyelids only, mildly Incapacitating

4=Severe, incapacitating of eyelids and other facial muscles

Blepharospasm Frequency

0= None

1= Slightly increased frequency of blinking

2= Eyelid fluttering lasting less than 1 second in duration

3= Eyelid spasms lasting more than 1 second, but eyes open more than 50% of the waking time

4= Functionally blind" due to persistent eye closure (blepharospasm) more than 50% of the waking time [14].

Management of blepharospasm

Botulinum toxins injection

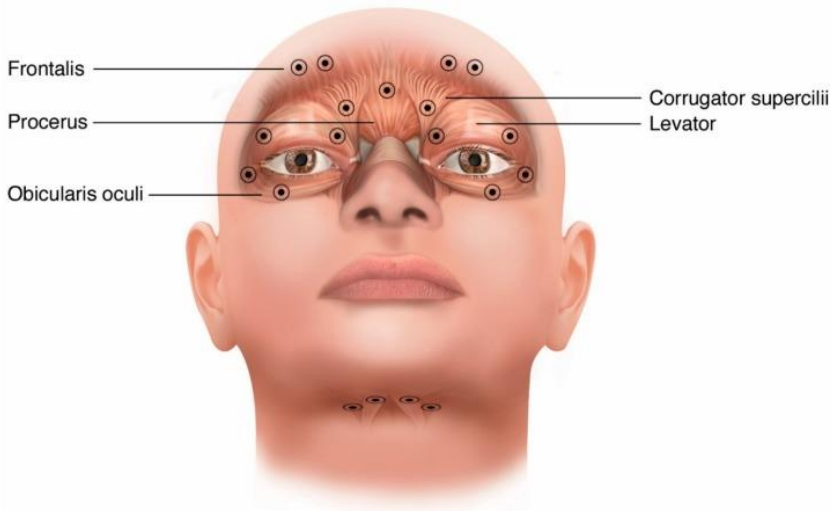


Figure 2 displays botulinum toxin injection site options for blepharospasm [35]. Hassell, T. J. W., & Charles, D. (2020).

The injection of Botulinum neurotoxins (BoNT) has been considered the treatment of choice in multiple dystonic disorders including blepharospasm [15]. The most recommended types of botulinum neurotoxin for blepharospasm are OnabotulinumT (A) and Incobotulinium (A) [4]. Patient satisfaction with botulinum toxin injections is often excellent, although most patients see a significant reduction in therapeutic effects at the end of the treatment and trouble with daily tasks such as driving and reading, requiring more injections than the standard 12 weeks interval, suggesting the need for individualized treatment [16]. Despite the common muscle used, the injection session should be adjusted for each specific patient. There is no direct relation between the dose used and the level of impact and duration [4]. Electromyography (EMG) and ultrasound can be used to guide BoNT injections, but it is not needed for facial muscle injections [4].

The most common side effect of BoNT is focal muscle weakness, including ptosis and lagophthalmos in blepharospasm. Other side effects include dryness of the eyes, diplopia, chewing weakness, dysphagia, dysarthria, mouth dryness, generalized weakness, allergic reactions, and flu-like symptoms [4].

Oral medications

Multiple oral medications varying in efficacy can be used. These drugs include anticholinergics, benzodiazepines, VMAT2 inhibitors, levodopa, and baclofen. Anticholinergic drugs and benzodiazepines are shown to be the most effective [4].

However, the most common use of these drugs is as an addition to Botulinum Toxins injections or before referring the patient for a more invasive method and in case of refraction to Botulinum Toxins injection [1] [3].

And these medications are known to have multiple side effects, the most important one is dependence on benzodiazepines [4].

Deep brain stimulation

Deep brain stimulation of the Globus Pallidus Internus has been used in multiple forms of medication refractory dystonia. While genetic testing can help guide expectations for hereditary variants of dystonia, the choice to proceed with deep brain stimulation should be based on clinical presentation [17].

In the case of blepharospasm, the use of deep brain stimulation is still limited. However, multiple case reports have proven the efficacy of using deep brain stimulation in the management of refractory isolated blepharospasm and Meige syndrome [18] [19] [20] [21].

A case report has shown the success of deep brain stimulation in treating medically resistant focal tardive blepharospasm. In addition, it has been proved that small pulse widths and high-frequency stimulations can regulate eyelid spasms [22].

Another report has suggested that in contrast to more globalized dystonic phenotypes, isolated cranial blepharospasm requires lower voltage needs and longer pulse widths [23].

Surgery

Surgery is used for the management of blepharospasm in case of refractory disease. It is based on recognizing the function of individual orbicularis oculi portions and the facial nerve branches [24]. The surgery of choice is myectomy, which showed a lower likelihood of recurrence and required fewer additional procedures when compared to facial nerve dissection. In addition, facial nerve surgery showed greater side effects from nerve palsy to regeneration [3].

The commonly used technique is the partial myectomy with correction of blepharospasm impacts on the face. Total myectomy can also be performed but increases the risk of postoperative lymphedema, lagophthalmos, and facial anesthesia [1].

Transcranial magnetic stimulation (TMS)

A repetitive TMS with low frequency aiming at reducing cortical excitability has shown positive feedback from both the subjective patient rating and physician rating and an acceleration in the blink reflex recovery curve based on a pilot study, however, more studies should be made [6] [25].

Photochromatic modulation

The wavelength and light intensity both contribute to the photophobia associated with blepharospasm [1]. Yet, photophobia is more triggered by the wavelength than the intensity of the light [26].

Lenses provide an excellent way of symptomatic treatment for this photophobia in blepharospasm patients, especially the FL-41 lens tint [27].

Risk factors

Multiple risk factors have been associated with blepharospasm. The first risk factor is a positive family history since multiple genes have been found to play a role in the development of blepharospasm [28] [29] [1].

The risk of blepharospasm is increased in women and the age group between 40 and 60 [6].

Other important risk factors that are non-inherited such as urbanization and jobs associated with stressful lifestyles [3]. Also, it is associated with increased screen usage and reading, psychiatric conditions, and previous ophthalmic conditions [1][30] [31] [32] [33].

References

[1]Titi-Lartey OA, Patel BC. Benign Essential Blepharospasm. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; August 7, 2023.
[2]Fagan, M., Scorr, L., Bernhardt, D., Hess, E. J., Perlmutter, J. S., Pardo, C. A., & Jinnah, H. A. (2021). Neuropathology of blepharospasm. *Experimental neurology*, *346*, 113855.
[3]Hwang, C. & Eftekhari, K. (2018). Benign Essential Blepharospasm: What We Know and What We Don't. *International Ophthalmology Clinics, 58* (1), 11-24. DOI: 10.1097/IIO.0000000000000207.
[4]Hassell, T. J. W., & Charles, D. (2020). Treatment of Blepharospasm and Oromandibular Dystonia with Botulinum Toxins. *Toxins*, *12*(4), 269. https://doi.org/10.3390/toxins12040269
[5]Khooshnoodi, M. A., Factor, S. A., & Jinnah, H. A. (2013). Secondary blepharospasm associated with structural lesions of the brain. *Journal of the neurological sciences*, *331*(1-2), 98–101.
[6]Defazio, G., Hallett, M., Jinnah, H. A., Conte, A., & Berardelli, A. (2017). Blepharospasm 40 years later. *Movement disorders : official journal of the Movement Disorder Society*, *32*(4), 498–509.
[7]Molloy A, Williams L, Kimmich O, et al. Sun exposure is an environmental factor for the development of blepharospasm. *J Neurol Neurosurg Psychiatry*. 2016;87(4):420-424. doi:10.1136/jnnp-2014-310266
[8]Quartarone A, Sant'Angelo A, Battaglia F, Bagnato S, Rizzo V, Morgante F, Rothwell JC, Siebner HR, Girlanda P. Enhanced long-term potentiation-like plasticity of the trigeminal blink reflex circuit in blepharospasm. J Neurosci. 2006 Jan 11;26(2):716-21. doi: 10.1523/JNEUROSCI.3948-05.2006. PMID: 16407569; PMCID: PMC6674398.

[9]Valls-Sole, J., & Defazio, G. (2016). Blepharospasm: Update on Epidemiology, Clinical Aspects, and Pathophysiology. *Frontiers in neurology*, *7*, 45. https://doi.org/10.3389/fneur.2016.00045
[10]Romano, R., Bertolino, A., Gigante, A., Martino, D., Livrea, P., & Defazio, G. (2014). Impaired cognitive functions in adult-onset primary cranial cervical dystonia. *Parkinsonism & related disorders*, *20*(2), 162–165. https://doi.org/10.1016/j.parkreldis.2013.10.008
[11]Yang, J., Zhang, L., Hou, Y., Wei, Q., Ou, R., Lin, J., Song, W., Cao, B., & Shang, H. (2021). Excessive daytime sleepiness in idiopathic blepharospasm. *Parkinsonism & related disorders*, *89*, 134–138. https://doi.org/10.1016/j.parkreldis.2021.07.005
[12] Lee, J. M., Baek, J. S., Choi, H. S., Kim, S. J., & Jang, J. W. (2018). Clinical Features of Benign Essential Blepharospasm in Korean Patients. *Korean journal of ophthalmology : KJO*, *32*(5), 339–343. https://doi.org/10.3341/kjo.2018.0038
[13]Defazio, G., Hallett, M., Jinnah, H. A., & Berardelli, A. (2013). Development and validation of a clinical guideline for diagnosing blepharospasm. *Neurology*, *81*(3), 236–240. https://doi.org/10.1212/WNL.0b013e31829bfdf6
[14]Wabbels, B., Jost, W. H., & Roggenkämper, P. (2011). Difficulties with differentiating botulinum toxin treatment effects in essential blepharospasm. *Journal of neural transmission (Vienna, Austria : 1996)*, *118*(6), 925–943. https://doi.org/10.1007/s00702-010-0546-9
[15]Simpson, D. M., Hallett, M., Ashman, E. J., Comella, C. L., Green, M. W., Gronseth, G. S., Armstrong, M. J., Gloss, D., Potrebic, S., Jankovic, J., Karp, B. P., Naumann, M., So, Y. T., & Yablon, S. A. (2016). Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*, *86*(19), 1818–1826. https://doi.org/10.1212/WNL.0000000000002560
[16]Fezza, J., Burns, J., Woodward, J., Truong, D., Hedges, T., & Verma, A. (2016). A cross-sectional structured survey of patients receiving botulinum toxin type A treatment for blepharospasm. *Journal of the neurological sciences*, *367*, 56–62. https://doi.org/10.1016/j.jns.2016.05.033
[17]Tisch, S., & Kumar, K. R. (2021). Pallidal Deep Brain Stimulation for Monogenic Dystonia: The Effect of Gene on Outcome. *Frontiers in neurology*, *11*, 630391. https://doi.org/10.3389/fneur.2020.630391
[18]Luthra, N. S., Mitchell, K. T., Volz, M. M., Tamir, I., Starr, P. A., & Ostrem, J. L. (2017). Intractable Blepharospasm Treated with Bilateral Pallidal Deep Brain Stimulation. *Tremor and other hyperkinetic movements (New York, N.Y.)*, *7*, 472. https://doi.org/10.7916/D8SJ1V9F
[19]Santos, A. F., Veiga, A., Augusto, L., Vaz, R., Rosas, M. J., & Volkmann, J. (2016). Successful Treatment of Blepharospasm by Pallidal Neurostimulation. *Movement disorders clinical practice*, *3*(4), 409–411. https://doi.org/10.1002/mdc3.12297
[20]Ostrem, J. L., Marks, W. J., Jr, Volz, M. M., Heath, S. L., & Starr, P. A. (2007). Pallidal deep brain stimulation in patients with cranial-cervical dystonia (Meige syndrome). *Movement disorders : official journal of the Movement Disorder Society*, *22*(13), 1885–1891. https://doi.org/10.1002/mds.21580
[21]Yamada, K., Shinojima, N., Hamasaki, T., & Kuratsu, J. (2016). Pallidal stimulation for medically intractable blepharospasm. *BMJ case reports*, *2016*, bcr2015214241. https://doi.org/10.1136/bcr-2015-214241
[22]Tardive Blepharospasm May Respond to Bilateral Pallidal Deep Brain Stimulation, Tremor and Other Hyperkinetic Movements. (n.d.). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7977745/.
[23]Bilateral pallidal DBS for blepharospasm: A case report and review of the literature, Surgical Neurology International. (n.d.).
[24]Surgical aspect of blepharospasm treatment: a case report., Acta Clinica Croatica. (2023). https://hrcak.srce.hr/clanak/354214 (accessed September 30, 2023).
[25]Blepharospasm and the modulation of cortical excitability in primary and secondary motor areas, Neurology. (n.d.).
[26]Modulation of Sensory Photophobia in Essential Blepharospasm with Chromatic Lenses, Ophthalmology. (n.d.).
[27]FL-41 Tint Improves Blink Frequency, Light Sensitivity, and Functional Limitations in Patients with Benign Essential Blepharospasm, Ophthalmology. (n.d.).
[28]Screening Gene Mutations in Chinese Patients With Benign Essential Blepharospasm, Frontiers in Neurology. (2019). https://www.frontiersin.org/articles/10.3389/fneur.2019.01387 (accessed September 30, 2023).
[29]Blepharospasm: A genetic screening study in 132 patients, Parkinsonism & Related Disorders. (2019). https://www.sciencedirect.com/science/article/pii/S135380201930197X.
[30]Computer vision syndrome: a study of the knowledge, attitudes and practices in Indian ophthalmologists, 55 (n.d.) 289–294. https://doi.org/10.4103/0301-4738.33042.
[31]Nonmotor manifestations of dystonia: a systematic review, 26 (n.d.) 1206–1217. https://doi.org/10.1002/mds.23709.
[32]Non-motor symptoms in patients with adult-onset focal dystonia: Sensory and psychiatric disturbances, 22 (2015) S111–114. https://doi.org/10.1016/j.parkreldis.2015.09.001.
[33]Italian Movement Disorders Study Group, Possible risk factors for primary adult onset dystonia: a case-control investigation by the Italian Movement Disorders Study Group, 64 (n.d.) 25–32. https://doi.org/10.1136/jnnp.64.1.25.
[34]Revisiting the Corneal and Blink Reflexes for Primary and Secondary Trigeminal Facial Pain Differentiation., 2021 (2021) 6664736. https://doi.org/10.1155/2021/6664736.
[35]Treatment of Blepharospasm and Oromandibular Dystonia with Botulinum Toxins, 12 (n.d.) 269. https://doi.org/10.3390/toxins12040269.

Article Topic: Medication Overuse Headache (MOH).

Author: Nurhan Al-Hroub.

Editors: Ainaa A.Alzamari, Hamid Ghanem.

Reviewer: Ethar Hazaimeh.

Keywords: headache, drugs, chronic headache syndrome, secondary headache, medication overuse.

Abstract

Introduction: Medication overuse headache (MOH) is a headache caused by abuse of acute headache medications for more than 15 days per month in patients who have preexisting primary headaches. There are no significant laboratory tests, images, or specific features to diagnose it. So, it will be preventable by education and awareness.

Methods: A systematic review search was done which studied primarily medication overuse headache (MOH) through the research database.

Conclusion: MOH is a result of excessive use of acute headache treatments with a history of primary headache. Numerous people increase their analgesic consumption without being aware of the long-term consequences. Education is therefore the most essential technique to avoid MOH.

Overview

The International Headache Society defines MOH as a headache that occurs for at least 15 days each month for more than three months in a patient with a pre-existing primary headache disorder and develops because of repeated overuse of symptomatic headache medications or when the symptoms are not better described by other diagnoses [1]. MOH is treated and preventive; hence, it merits more attention [2].

Pathogenesis

MOH is classified as a chronic headache or secondary headache in (ICHD-3) [3]. The most important risk factor for the development of MOH is chronic medication usage, with varying risk profiles for different classes of analgesics [4]. The lowest-risk analgesics include combination analgesics forming opiates or barbiturates,

triptans/ergotamine, and single analgesic drugs (NSAIDs, acetaminophen) [4]. However, it has been discovered that using combination analgesics, especially those that contain opioids and/or barbiturates, results in markedly increased relative risk for developing MOH [4].

Although the pathophysiology of MOH is still poorly understood [5], it has been discovered that MOH is intimately linked to alterations in various brain networks and areas [6]. Thus, it is associated with abnormal gray matter in a number of areas, including subcortical nuclei, the brain stem, and the cerebellum [6]. Therefore, MOH reversibly affects the reward system, the prefrontal cortex, and the pain network, as shown in Figure (1) [6].

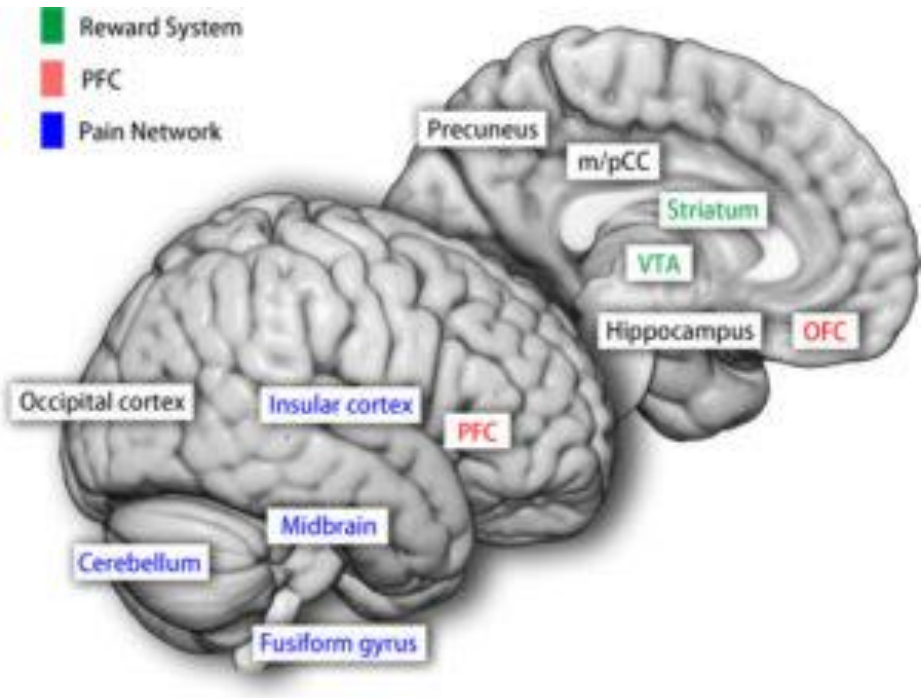


Figure (1): An example of altered networks discovered by meta-analytical activation likelihood estimation on gray matter alteration in medication-overuse headache patients VTA, ventral tegmental area; m/pCC, middle/posterior cingulate cortex; PFC, prefrontal cortex; OFC, orbitofrontal cortex.

MOH also demonstrates the interaction between brain networks involved in the response to socioeconomic stressors and specific psychosocial disorders [7]. This may be due to neuronal hyper-excitability in the trigeminal nervous system and the cerebral cortex [8]. The trigeminal nerve system's hyper-excitability promotes central and peripheral sensitization, which is key in the development of chronic pain. While cortical neuron hyper-excitability resulted from increased inhibition across the neuronal cell, this is comparable to the aura of a migraine [7].

So, chronic acute care medication use compromises the function of diffuse noxious inhibitory control and the central 5-HT-dependent modulating system [9], leading to an

increase in neuronal excitability in brain areas, which facilitates the development of cortical spreading depression more easily [9]. Increased activity of trigeminal neurons promotes the process of nociception, causing hyperalgesia and allodynia [9]. Derangement of the 5-HT-dependent modulating system additionally upregulates the calcitonin gene-related peptide (CGRP) system, resulting in trigeminal nociceptive facilitation, as Figure (2) illustrates [9].

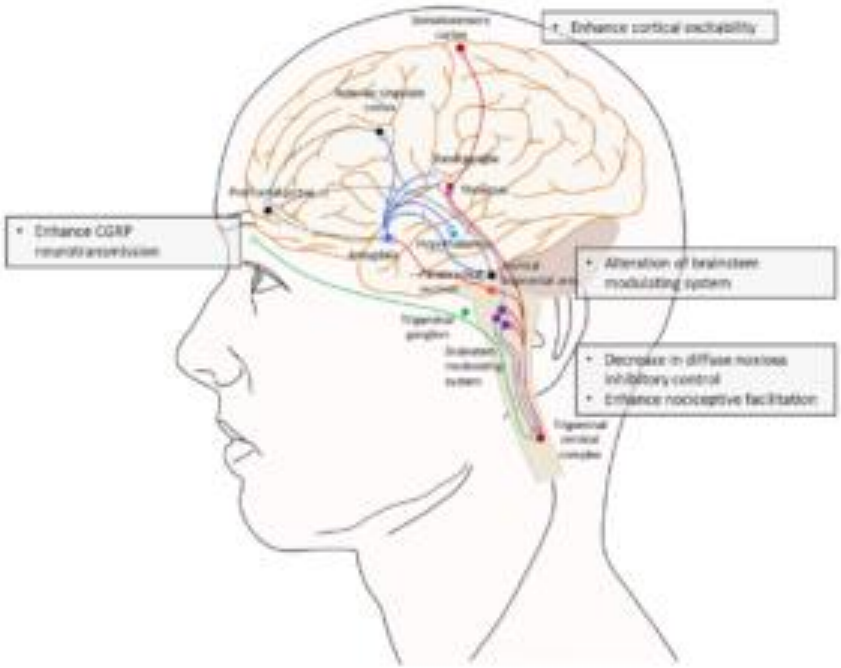


Figure (2): Possible MOH pathogenesis.

The clinical success of anti-CGRP in the treatment of MOH raises the possibility that acute migraine treatments may promote MOH in susceptible individuals, Figure (3). [10].

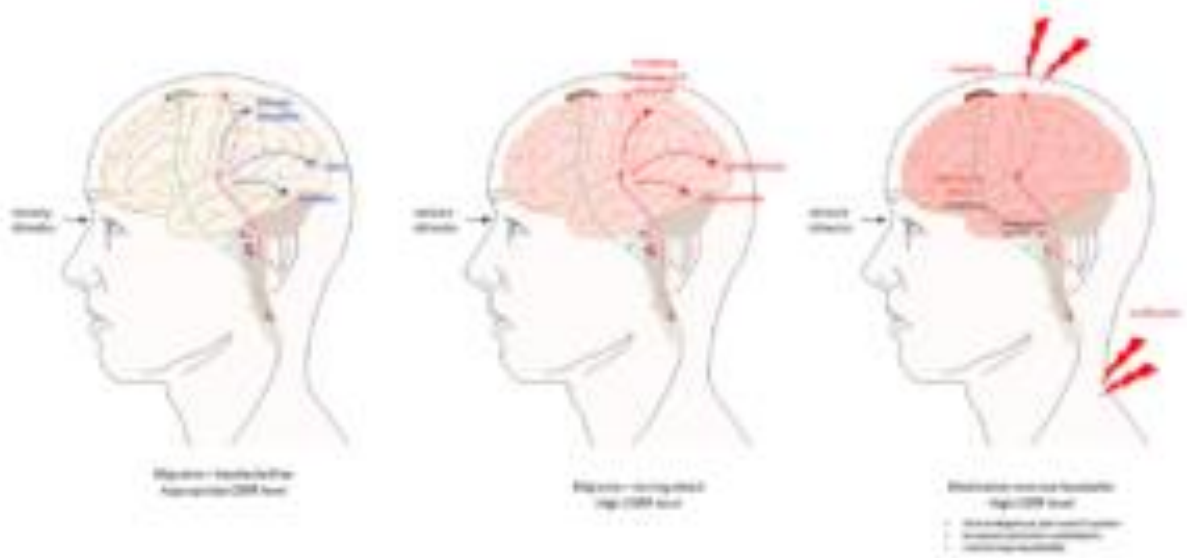


Figure (3): Patients with primary headaches, particularly migraines, have changes in the functioning of the brain-modulating system resulting in the fluctuation of the migraine threshold. During the headache-free period, the threshold is normal, and low-intensity stimuli are perceived as non-noxious. During the attack, the threshold is more sensitive when there is a high calcitonin gene-related peptide (CGRP) level. As a result, the sensory system is more sensitive. Low-intensity stimuli such as head motion, vascular pulsation, light, or sound can be perceived as unpleasant sensations like headaches, photophobia, or phonophobia. whereas, the brainstem modulating system is further suppressed in MOH. This causes chronically increased cortical excitability as well as nociceptive sensitivity.

It has recently been approved that acute-care migraine therapies may also shed some light on MOH and its treatment, as the discovery of the small molecule CGRP receptor antagonists, the 'Gepants', for both acute and preventive migraine therapy is particularly patient. It seems unlikely that the Gepants will relate to MOH given their preventive effect when used frequently [9]. Preclinical data indicate that Ubrogepant is not likely to cause early or latent trigeminal sensory sensitization when used repeatedly [11]. A migraine prevention strategy is being developed for Rimegepant, which the FDA approved in February 2020 for the acute treatment of migraines [9]. Preclinical animal models indicate that the recently FDA-approved Ditan, lasmiditan, a selective 5-HT1F receptor agonist with a mechanism of action more similar to triptans than CGRP inhibition, has the ability to produce MOH through persistent latent peripheral and central sensitization processes [12]. We excitedly anticipate new clinical trials examining these drugs in relation to MOH or its progression [9].

Genetic variation has been implicated in playing a role in the pathogenesis of such susceptibility [13]. According to one study, the clinical signs of MOH are related to Val66Met gene polymorphism, which is a brain-derived neurotrophic factor [14]. Another study found that additional polymorphisms, including the dopamine D2 receptor (DRD2) C939T (rs6275) and the methylenetetrahydrofolate reductase (MTHFR) C677T (rs1801133), influence the onset of MOH in patients with migraine [15].

There are many similarities between MOH and drug addiction [16]. New research in neuroimaging shows that changes in the orbitofrontal cortex and the mesocorticolimbic dopamine circuit are associated with the pathophysiological mechanisms of MOH and substance-related disorders [17]. As a result, it has been hypothesized that MOH is a kind of dependency behavior [18]. Codeine, opioids, and caffeine are psychotropic drugs, that are widely available as over-the-counter medications in several countries, so abuse and dependence may occur if they are used with some headache medications, which may accentuate the presence of MOH [19,20].

So, histone deacetylase 3 (HDAC3) seems to be involved in the memory processes that lead to the disappearance of drug-seeking behavior in animal models. Sodium valproate, a medication that has been demonstrated to work in MOH, inhibits HDAC3 [21].

Contrary to drug abusers, MOH patients were more concerned about the drug's effects than its type [22]. Even after a successful medication withdrawal and an improvement in the headache situation, a high rate of drug usage has been identified as a "drive" for medication [23].

Given what is known at this time, it is impossible to tell whether the dependency-like behavior seen in MOH patients constitutes a true dependence or if it is only a "pseudoaddiction" brought on by recurrent headaches [24]. However, further research will be required in the future.

Risk Factors

The actual prevalence of MOH is unknown, however, estimates for the general population range from 0.5 to 2.6% [25], and for those who experience persistent daily headaches, up to 11-70% [26].

The primary cause of MOH is migraine, followed by tension-type headaches, and rarely cluster headaches. The effects will worsen for those who abuse medication while suffering from headaches [27, 28].

MOH most frequently affects those aged thirty to fifty years, with a peak incidence in the fourth decade [25, 29]. This disorder has a high prevalence among females, as it affects them three to four times more than males [29]. Also, MOH patients have a high prevalence of smoking, sleeping problems, and an elevated BMI [37].

Although the name of MOH seems to reflect the role of overuse in developing it, on the other hand, it is challenging to confirm it because not everyone who suffers from daily headaches and takes painkillers frequently develops this type of chronic headache [30].

Any analgesic has the potential to cause MOH from medication overuse, but opioids and triptans seem to have the greatest risk of developing it in a very short period [31]. Other medications that can cause MOH are NSAIDs, acetaminophen-aspirin-caffeine combinations, butalbital-containing combination analgesics, and calcitonin gene-related peptide antagonists [32, 25].

Many socioeconomic and psychosocial factors influence MOH [29]. There is a relationship between MOH, mood, and subclinical obsessive-compulsive disorders [34]. Moreover, people who have psychiatric comorbidities, such as depression and anxiety, appear most susceptible to developing this headache [33]. In addition, more than half of patients with MOH exhibit dependence-type behaviors, such as tolerance [26]. Also, patients who have low education, low income, and low socioeconomic status develop MOH more than other people, although it is not obvious if this contributes to or worsens the headache [38].

Family history suggests a possible underlying genetic predisposition and hereditary susceptibility to develop this disorder [35]. This theory is supported by the fact that people with primary headaches are more likely to develop MOH than people who take medications for other conditions [36].

Other risk factors include chronic gastrointestinal or musculoskeletal disorders, tranquilizer use, high caffeine intake, and physical inactivity [39].

Clinical picture

An episodic headache disease that has been treated with frequent use of acute medicines, frequently in excess doses, is typically present before the onset of medication-overuse headache. Medication-overuse headache commonly appears as a morning headache when you first wake up, and symptomatic headache treatments typically only offer temporary relief [40].

The patient will notice a change in his typical headache, including an increase in intensity and frequency, greater sensitivity to triggers of these episodes, and resistance to conventional treatment [41].

Table (1) summarizes the main clinical characteristics of MOH [41].

Episodic periodic migraine/Episodic tension-type headache
Increasing usage of acute medications, including triptans, simple analgesics (except plain aspirin), ergotamine tartrate derivatives, mixed analgesics (particularly containing barbiturate), possibly NSAIDs
Regular, reliable, and predictable use of medication along with regular reliable and predictable development of a headache when medication is delayed, withheld, or in between doses
Escalation in frequency of headaches and medication usage
Increasing refractoriness to otherwise appropriate medications until, at times, long after detoxification occurs
Possible spontaneous improvement in headache with detoxification alone
Accompaniments, including depression, anxiety, and sleep disturbance, among others

Table (1) summarizes the main clinical characteristics of MOH.

Diagnosis

The diagnosis is not based on physical examination findings or certain laboratory tests [42]. The criteria for diagnosis according to (ICHD-3) are an alteration in the baseline headache in people with a pre-existing headache disorder who routinely take acute symptomatic drugs for more than ten to fifteen days per month for longer than three months [43], as shown in Figure (4) [44]. As mentioned before, opioids, triptans, and ergotamine have the greatest and fastest effect on developing MOH, as they can develop it by taking them for more than 10 days per month, unlike other medications, which may develop it after taking them for more than 15 days per month [42].

Medication-overuse headache

A. Headache present on ≥15 days per month

B. Regular overuse for more than 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache

C. Headache has developed or markedly worsened during medication-overuse
(For simple analgesics and for combination of acute medications, the intake must be 15 days or more per month; for triptans, ergotamines, opioids, and combination analgesics, 10 days per month is enough for a diagnosis of medication-overuse headache)

Figure (4): International Classification of Headache Disorders, 3rd beta edition criteria for medication-overuse headache.

The patient is most likely to have a primary headache and present with a change in his underlying headache after abusing the offending medications, as mentioned earlier [42].

Before the diagnosis, it is important to exclude other causes of chronic daily headaches, such as hypertension, obstructive sleep apnea, pituitary disease, depression vasculitis, medications, increased intracranial hypertension, or malignancy. So, further investigations are required to exclude other causes [45].

Treatment

It is challenging to treat medication overuse headaches and requires individualized care [42]. Prevention, patient counseling, and detoxification are the backbone of treatment. Patients who are suspected of abusing medications, such as those with a history of substance abuse, as well as psychiatric patients who overlap with MOH, may need to be referred to a specialized headache center as part of treatment [46].

Educate patients

MOH management is a long-term process that may take weeks or months [47]. So, it is important to manage expectations and adequately prepare the patient before attempting drug withdrawal or adding a migraine preventative [42].

The patient should understand that the frequent use of analgesics can cause MOH, and the headache is likely to improve when the overused medication is removed [47]. Furthermore, using migraine preventatives and treating psychiatric comorbidities may reduce MOH. In addition, re-exposure to medication overuse will result in MOH recurrence [47].

Withdrawal from the drug

Patients are instructed to withdraw their analgesics to an acceptable level [48]. The speed of drug withdrawal is determined by the class of drug being overused [48]; this takes no more than fifteen days for simple analgesics and, no more than ten days for opioid/triptans.

Abrupt withdrawal is preferable for triptans and analgesics, which can induce some unfavorable symptoms, such as nausea, vomiting, sleep disturbance, and anxiety [42]. Patients who overuse triptans typically improve over seven–ten days, while those overusing simple analgesics improve over two–three weeks [49]. As a result, simple analgesic and triptan overuse can often be treated as an outpatient [42].

Opioid medication overuse, on the other hand, is more disturbing and may require inpatient supervision. Withdrawal tends to be more gradual and takes longer time [42]. Individuals with substantial opiate overuse may benefit from inpatient detoxification and intravenous lidocaine infusions [50].

Prevention of migraine

Adding migraine preventatives to the management of MOH; once proven, may make it easier to withdraw from the acute headache medications in the future [42]. Topiramate and botulinum toxin is beneficial in some patients to treat MOH [51].

Moreover, transitional approaches can be employed to aid in discontinuing the overused medicine and reducing MOH [25]. One of them is to replace the overused drug with an alternative symptomatic therapy for less than or equal to two days per week with preventive therapy [52]. This approach may be beneficial for patients who are more likely to experience drug toxicity from overuse than withdrawal symptoms [52].

Continuing overused medication during initial treatment is beneficial for patients who are hesitant to discontinue the medication but are not at risk of toxicity [25].

Transitional therapy (bridge therapy) is advised for individuals with severe or regular headaches who are more prone to have headaches while quitting the overused medication with the commencement of symptomatic and preventative therapy [25]. Many NSAIDs, including naproxen, indomethacin, and ketorolac, have been studied and proven to be beneficial [25]. Tizanidine is sometimes utilized as a supplement to NSAID therapy [53]. Several antiemetics and neuroleptics, such as prochlorperazine, diphenhydramine, promethazine, metoclopramide, and chlorpromazine have been beneficial during this phase [41].

Consequently, multiple general aspects should be considered in the treatment of MOH. The correct diagnosis, stopping the offending drug(s), preventive treatment, using medications during the withdrawal period, aside with education to the patient, the partner, and the family, psychological treatment, and physician support for the patient all play a vital role in the management [41].

Follow-up and relapse rate

Most follow-up studies are conducted in tertiary care centers [29]. However, few studies support that follow-up can be done by the general practitioner [54].

According to studies, the relapse rate is 20%-40% within the first year of withdrawal [29], with some claiming that most patients relapse within the first six months and others between six and twelve months [55]. However, the results on relapse should be

evaluated with some care given that the studies varied in their use of headache classification systems, withdrawal, and prophylaxis, as well as follow-up periods and the criteria employed to determine improvement [29].

Prevention

Education is the most crucial factor in preventing MOH [42]. It is important to counsel patients who experience episodic attacks of primary headaches to stay away from some medications, especially simple over-the-counter painkillers [42].

Prognosis

A poor prognosis for persistent headaches and a worse quality of life can result from using acute treatment excessively [56].

Numerous studies show that MOH patients who stop using acute drug overdose successfully recover, with a success rate of more than 50% compared to baseline headache frequency [25]. Relapse rates after six years vary from 40 to 50% [57]. Even in patients with little to no improvement in headache frequency, a successful withdrawal phase improves response to prophylactic treatment [58].

Patient motivation is essential in MOH treatment [41]. Although the quality of the treatment has a significant impact on the outcome, patient motivation has a greater impact [41]. Even the most successful treatment programs will fail if patient motivation and discipline are absent [41].

Conclusion

MOH is a secondary headache disorder that is caused by the overuse of acute headache medications by a person with an underlying headache disorder. The underlying mechanisms of the MOH are poorly understood, but they are thought to be closely related to chronic migraine.

A standard neurological examination and the patient's medical history help to determine the diagnosis. Treating this disorder is complex and must be individualized to the person, and the single most important strategy to prevent medication-overuse headaches is education.

References

1. Diener, H. C., Dodick, D., Evers, S., Holle, D., Jensen, R. H., Lipton, R. B., Porreca, F., Silberstein, S., & Schwedt, T. (2019). Pathophysiology, prevention, and treatment of medication overuse headache. In *The Lancet Neurology* (Vol. 18, Issue 9,
2. pp. 891–902). Lancet Publishing Group. https://doi.org/10.1016/S1474-4422(19)30146-2
3. Ashina, S., Terwindt, G. M., Steiner, T. J., Lee, M. J., Porreca, F., Tassorelli, C., Schwedt, T. J., Jensen, R. H., Diener, H.-C., & Lipton, R. B. (2023). Medication overuse headache. *Nature Reviews. Disease Primers*, *9*(1), 5. https://doi.org/10.1038/s41572-022-00415-0
4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. (2018). *Cephalalgia : An International Journal of Headache*, *38*(1), 1–211. https://doi.org/10.1177/0333102417738202
5. Fischer, M. A., & Jan, A. (2023). *Medication-overuse Headache*.
6. Wakerley, B. R. (2019). Medication-overuse headache. *Practical Neurology*, *19*(5), 399–403. https://doi.org/10.1136/practneurol-2018-002048
7. Chen, W., Li, H., Hou, X., & Jia, X. (2022). Gray matter alteration in medication overuse headache: a coordinates-based activation likelihood estimation meta-analysis. *Brain Imaging and Behavior*, *16*(5), 2307–2319. https://doi.org/10.1007/s11682-022-00634-9
8. Wakerley, B. R. (2019). Medication-overuse headache. *Practical Neurology*, *19*(5), 399–403. https://doi.org/10.1136/practneurol-2018-002048
9. Srikiatkhachorn, A., le Grand, S. M., Supornsilpchai, W., & Storer, R. J. (2014). Pathophysiology of medication overuse headache - An update. In *Headache* (Vol. 54, Issue 1, pp. 204–210). https://doi.org/10.1111/head.12224
10. Sun-Edelstein, C., Rapoport, A. M., Rattanawong, W., & Srikiatkhachorn, A. (2021). The Evolution of Medication Overuse Headache: History, Pathophysiology and Clinical Update. *CNS Drugs*, *35*(5), 545–565. https://doi.org/10.1007/s40263-021-00818-9
11. Kopruszinski, C. M., Xie, J. Y., Eyde, N. M., Remeniuk, B., Walter, S., Stratton, J., Bigal, M., Chichorro, J. G., Dodick, D., & Porreca, F. (2017). Prevention of stress- or nitric oxide donor-induced medication overuse headache by a calcitonin gene-related peptide antibody in rodents. *Cephalalgia : An International Journal of Headache*, *37*(6), 560–570. https://doi.org/10.1177/0333102416650702
12. Navratilova, E., Behravesh, S., Oyarzo, J., Dodick, D. W., Banerjee, P., & Porreca, F. (2020). Ubrogepant does not induce latent sensitization in a preclinical model of medication overuse headache. *Cephalalgia*, *40*(9), 892–902. https://doi.org/10.1177/0333102420938652
13. Rau, J. C., Navratilova, E., Oyarzo, J., Johnson, K. W., Aurora, S. K., Schwedt, T. J., Dodick, D. W., & Porreca, F. (2020). Evaluation of LY573144 (lasmiditan) in a preclinical model of medication overuse headache. *Cephalalgia : An International Journal of Headache*, *40*(9), 903–912. https://doi.org/10.1177/0333102420920006
14. Chen, Y.-Y. (2013). Medication Overuse Headache-A Complex Neurologic Disorder: Genetic Susceptibility Deserves to be Studied. In *Acta Neurologica Taiwanica* (Vol. 22).
15. di Lorenzo, C., di Lorenzo, G., Sances, G., Ghiotto, N., Guaschino, E., Grieco, G. S., Santorelli, F. M., Casali, C., Troisi, A., Siracusano, A., & Pierelli, F. (2009). Drug consumption in medication overuse headache is influenced by brain-derived neurotrophic factor Val66Met polymorphism. *The Journal of Headache and Pain*, *10*(5), 349–355. https://doi.org/10.1007/s10194-009-0136-0
16. Abbott, F. v, & Fraser, M. I. (1998). Use and abuse of over-the-counter analgesic agents. *Journal of Psychiatry & Neuroscience : JPN*, *23*(1), 13–34.
17. Calabresi, P., & Cupini, L. M. (2005). Medication-overuse headache: similarities with drug addiction. *Trends in Pharmacological Sciences*, *26*(2), 62–68. https://doi.org/10.1016/j.tips.2004.12.008
18. Pisanu, C., Caproni, S., Congiu, D., Cupini, L. M., Squassina, A., Patrinos, G. P., Corbelli, I., Calabresi, P., del Zompo, M., & Sarchielli, P. (2015). HDAC3 role in medication consumption in medication overuse headache patients: a pilot study. *Human Genomics*, *9*, 30. https://doi.org/10.1186/s40246-015-0051-1
19. Saper, J. R., & Lake, A. E. (2006). Medication overuse headache: type I and type II. *Cephalalgia : An International Journal of Headache*, *26*(10), 1262. https://doi.org/10.1111/j.1468-2982.2006.01198.x
20. Bendtsen, L., Evers, S., Linde, M., Mitsikostas, D. D., Sandrini, G., Schoenen, J., & EFNS. (2010). EFNS guideline on the treatment of tension-type headache - report of an EFNS task force. *European Journal of Neurology*, *17*(11), 1318–1325. https://doi.org/10.1111/j.1468-1331.2010.03070.x
21. Onaya, T., Ishii, M., Katoh, H., Shimizu, S., Kasai, H., Kawamura, M., & Kiuchi, Y. (2013). Predictive index for the onset of medication overuse headache in migraine patients. *Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *34*(1), 85–92. https://doi.org/10.1007/s10072-012-0955-7
22. Chanraud, S., di Scala, G., Dilharreguy, B., Schoenen, J., Allard, M., & Radat, F. (2014). Brain functional connectivity and morphology changes in medication-overuse headache: Clue for dependence-related processes? *Cephalalgia : An International Journal of Headache*, *34*(8), 605–615. https://doi.org/10.1177/0333102413519514
23. Ferrari, A., Cicero, A. F. G., Bertolini, A., Leone, S., Pasciullo, G., & Sternieri, E. (2006). Need for analgesics/drugs of abuse: a comparison between headache patients and addicts by the Leeds Dependence Questionnaire (LDQ). *Cephalalgia : An International Journal of Headache*, *26*(2), 187–193. https://doi.org/10.1111/j.1468-2982.2005.01020.x
24. Kristoffersen, E. S., & Lundqvist, C. (2014). Medication-overuse headache: a review. *Journal of Pain Research*, *7*, 367–378. https://doi.org/10.2147/JPR.S46071
25. Saper, J. R., Hamel, R. L., & Lake, A. E. (2005). Medication overuse headache (MOH) is a biobehavioural disorder. *Cephalalgia : An International Journal of Headache*, *25*(7), 545–546. https://doi.org/10.1111/j.1468-2982.2005.00879.x

26. Fischer, M. A., & Jan, A. (2023). *Medication-overuse Headache*.
27. Diener, H.-C., Holle, D., Solbach, K., & Gaul, C. (2016). Medication-overuse headache: risk factors, pathophysiology and management. *Nature Reviews. Neurology*, *12*(10), 575–583. https://doi.org/10.1038/nrneurol.2016.124
28. Aaseth, K., Grande, R. B., Kvaerner, K. J., Gulbrandsen, P., Lundqvist, C., & Russell, M. B. (2008). Prevalence of secondary chronic headaches in a population-based sample of 30-44-year-old persons. The Akershus study of chronic headache. *Cephalalgia : An International Journal of Headache*, *28*(7), 705–713. https://doi.org/10.1111/j.1468-2982.2008.01577.x
29. Paemeleire, K., Bahra, A., Evers, S., Matharu, M., & Goadsby, P. (2006). Medication-overuse headache in patients with cluster headache. In *NEUROLOGY* (Vol. 67). www.neurology.org
30. Kristoffersen, E. S., & Lundqvist, C. (2014). Medication-overuse headache: A review. In *Journal of Pain Research* (Vol. 7, pp. 359–366). Dove Medical Press Ltd. https://doi.org/10.2147/JPR.S46071
31. Katsarava, Z., & Obermann, M. (2013). Medication-overuse headache. *Current Opinion in Neurology*, *26*(3), 276–281. https://doi.org/10.1097/WCO.0b013e328360d596
32. Limmroth, V., Katsarava, Z., Fritsche, G., Przywara, S., Diener, H., & Peters, by. (2002). *Features of medication overuse headache following overuse of different acute headache drugs*.
33. Johnson, J. L., Hutchinson, M. R., Williams, D. B., & Rolan, P. (2013). Medication-overuse headache and opioid-induced hyperalgesia: A review of mechanisms, a neuroimmune hypothesis and a novel approach to treatment. *Cephalalgia : An International Journal of Headache*, *33*(1), 52–64. https://doi.org/10.1177/0333102412467512
34. Hagen, K., Linde, M., Steiner, T. J., Stovner, L. J., & Zwart, J. A. (2012). Risk factors for medication-overuse headache: An 11-year follow-up study. the Nord-Trøndelag Health Studies. *Pain*, *153*(1), 56–61. https://doi.org/10.1016/j.pain.2011.08.018
35. Cupini, L. M., de Murtas, M., Costa, C., Mancini, M., Eusebi, P., Sarchielli, P., & Calabresi, P. (2009). Obsessive-compulsive disorder and migraine with medication-overuse headache. *Headache*, *49*(7), 1005–1013. https://doi.org/10.1111/j.1526-4610.2009.01457.x
36. Cevoli, S., Sancisi, E., Grimaldi, D., Pierangeli, G., Zanigni, S., Nicodemo, M., Cortelli, P., & Montagna, P. (2009). Family history for chronic headache and drug overuse as a risk factor for headache chronification. *Headache*, *49*(3), 412–418. https://doi.org/10.1111/j.1526-4610.2008.01257.x
37. Bahra, A., Walsh, M., Menon, S., & Goadsby, P. J. (2003). Does chronic daily headache arise de novo in association with regular use of analgesics? *Headache*, *43*(3), 179–190. https://doi.org/10.1046/j.1526-4610.2003.03041.x
38. Wiendels, N. J., Knuistingh Neven, A., Rosendaal, F. R., Spinhoven, P., Zitman, F. G., Assendelft, W. J. J., & Ferrari, M. D. (2006). Chronic frequent headache in the general population: prevalence and associated factors. *Cephalalgia : An International Journal of Headache*, *26*(12), 1434–1442. https://doi.org/10.1111/j.1468-2982.2006.01210.x
39. Jonsson, P., Hedenrud, T., & Linde, M. (2011). Epidemiology of medication overuse headache in the general Swedish population. *Cephalalgia : An International Journal of Headache*, *31*(9), 1015–1022. https://doi.org/10.1177/0333102411410082
40. Diener, H. C., Holle, D., Solbach, K., & Gaul, C. (2016). Medication-overuse headache: Risk factors, pathophysiology and management. In *Nature Reviews Neurology* (Vol. 12, Issue 10, pp. 575–583). Nature Publishing Group. https://doi.org/10.1038/nrneurol.2016.124
41. Dodick, D., & Freitag, F. (2006). Evidence-based understanding of medication-overuse headache: Clinical implications. In *Headache* (Vol. 46, Issue SUPPL. 4). https://doi.org/10.1111/j.1526-4610.2006.00604.x
42. Saper, J. R., & da Silva, A. N. (2013). Medication overuse headache: History, features, prevention and management strategies. *CNS Drugs*, *27*(11), 867–877. https://doi.org/10.1007/s40263-013-0081-y
43. Wakerley, B. R. (2019). Medication-overuse headache. *Practical Neurology*, *19*(5), 399–403. https://doi.org/10.1136/practneurol-2018-002048
44. Olesen, J. (2018). Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. In *Cephalalgia* (Vol. 38, Issue 1, pp. 1–211). SAGE Publications Ltd. https://doi.org/10.1177/0333102417738202
45. Headache Classification Committee of the International Headache Society (IHS). (2013). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia : An International Journal of Headache*, *33*(9), 629–808. https://doi.org/10.1177/0333102413485658
46. Martin, V. T. (2011). *CURRENT LITERATURE: CLINICAL SCIENCE*.
47. Diener, H.-C., Holle, D., Solbach, K., & Gaul, C. (2016). Medication-overuse headache: risk factors, pathophysiology and management. *Nature Reviews. Neurology*, *12*(10), 575–583. https://doi.org/10.1038/nrneurol.2016.124
48. Couch, J. R. (2006). Can medication overuse headache be treated by abrupt withdrawal of the overused agent? Commentary. In *Nature Clinical Practice Neurology* (Vol. 2, Issue 12, pp. 654–655). https://doi.org/10.1038/ncpneuro0350
49. MacGregor EA, Steiner TJ, Davies PTG. Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type,Cluster and Medication-Overuse Headache. 3rd edition, 2010
50. Katsarava, Z., Limmroth, V., Finke, M., Diener, H. C., & Fritsche, G. (2003). Rates and predictors for relapse in medication overuse headache: A 1-year prospective study. *Neurology*, *60*(10), 1682–1683. https://doi.org/10.1212/01.WNL.0000063322.14078.90
51. Williams, D. R., & Stark, R. J. (n.d.). *Intravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse*.

52. Diener, H. C., Bussone, G., van Oene, J. C., Lahaye, M., Schwalen, S., & Goadsby, P. J. (2007). Topiramate reduces headache days in chronic migraine: A randomized, double-blind, placebo-controlled study. *Cephalalgia*, *27*(7), 814–823. https://doi.org/10.1111/j.1468-2982.2007.01326.x
53. Schwedt, T. J., Hentz, J. G., Sahai-Srivastava, S., Murinova, N., Spare, N. M., Treppendahl, C., Martin, V. T., Birlea, M., Digre, K., Watson, D., Leonard, M., Robert, T., Dodick, D. W., & MOTS Investigators. (2022). Patient-Centered Treatment of Chronic Migraine With Medication Overuse: A Prospective, Randomized, Pragmatic Clinical Trial. *Neurology*, *98*(14), e1409–e1421. https://doi.org/10.1212/WNL.0000000000200117
54. Smith, T. R. (2002). Low-dose tizanidine with nonsteroidal anti-inflammatory drugs for detoxification from analgesic rebound headache. *Headache*, *42*(3), 175–177. https://doi.org/10.1046/j.1526-4610.2002.02048.x
55. Bøe, M. G., Salvesen, R., & Mygland, A. (2009). Chronic daily headache with medication overuse: a randomized follow-up by neurologist or PCP. *Cephalalgia : An International Journal of Headache*, *29*(8), 855–863. https://doi.org/10.1111/j.1468-2982.2008.01810.x
56. Grazzi, L., Andrasik, F., D'Amico, D., Usai, S., Kass, S., & Bussone, G. (2004). Disability in chronic migraine patients with medication overuse: treatment effects at 1-year follow-up. *Headache*, *44*(7), 678–683. https://doi.org/10.1111/j.1526-4610.2004.04127.x
57. Probyn, K., Bowers, H., Caldwell, F., Mistry, D., Underwood, M., Matharu, M., Pincus, T., & CHESS Team. (2017). Prognostic factors for chronic headache: A systematic review. *Neurology*, *89*(3), 291–301. https://doi.org/10.1212/WNL.0000000000004112
58. Katsarava, Z., Muessig, M., Dzagnidze, A., Fritsche, G., Diener, H. C., & Limmroth, V. (2005). Medication overuse headache: rates and predictors for relapse in a 4-year prospective study. *Cephalalgia : An International Journal of Headache*, *25*(1), 12–15. https://doi.org/10.1111/j.1468-2982.2004.00789.x

Article Topic: Highly Aggressive Multiple Sclerosis.

Author: Abdeljaber Tayyem.

Editor: Haneen Al-Abdallat, Haneen A. Banihani.

Reviewer: Lobana Mahdawi, Ethar Hazaimeh.

Keywords: Aggressive Multiple Sclerosis, Expanded Disability Status Scale, Humanized Monoclonal Antibodies, Immunosuppressants, Induction therapy, Escalation therapy.

Overview

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease that affects the central nervous system (CNS). It has various clinical presentations according to the site of the central nervous system involved and is categorized according to clinical course into clinically isolated syndrome, relapsing-remitting, secondary progressive, and primary progressive according to 2013 disease course definitions (1). A subset of MS patients experiences an aggressive form of the disease where they progress rapidly to a disability or have a higher number of relapses. They need special attention to define this form of the disease to facilitate early identification and intervention to prevent rapid progression to disability (2)(3).

Etiology and pathogenesis

Generally speaking, MS is thought to be caused by the accumulation of genetic and environmental risk factors, which lead to the activation of autoreactive lymphocytes in the CNS, including B lymphocytes which release proinflammatory cytokines, chemokines, and autoantibodies, as well as T lymphocytes which include CD8+ T cells that release perforins and granzymes which will damage the axons and found in vast areas of brain parenchyma as well as CD4+ T cells which are more concentrated in the perivascular cuffs. In addition to glutamatergic excitotoxicity, this inflammatory cascade, hypoxia, and reactive oxygen species lead to calcium influx, thus causing mitochondrial dysfunction, oxidative stress, and cell death, which will cause demyelination and axonal damage. However, aging-related neurodegeneration, meningeal lymphoid-like follicles, and innate immunity involving microglial activation, which is not targeted by current MS therapies, are thought to be the cause of late progression of the disease where there is increased neurodegeneration, axonal damage, and a more indolent form of inflammation are involved. (4)(5)(6)

The development of permanent disability in MS is related to axonal loss, i.e., a higher rate of axonal loss would relate to a more aggressive disease. Macrophage infiltration

contributes to inflammation, and decreased myelin trophic factors increase axons' vulnerability to inflammation, leading to axonal transection and cortical involvement and causing neuronal death. This leads to a more aggressive and less treatment-responsive form of MS. There is also an association between dysregulated subgroups of T cells and NK cells and decreased diversity of T cell receptors on CD4+ T cells with aggressive MS (2).

Risk factors

Multiple risk factors were associated with aggressive MS, such as Male sex, older age at onset (more than 35), smoking, and non-white ethnicities. Multiple genetic markers are also related to aggressive MS including HLA-DRB1, APOE4, PD-1, MGAT-5, and BDNF. (2)(3)(6)

Clinical presentation

Optic neuritis

Patients present with eye pain and visual blurring or vision loss for hours to days. In a fundoscopic examination, the optic disc appears normal (retrobulbar optic neuritis) in two-thirds of cases or swollen (papillitis) in one-third of patients. Relative afferent pupillary defect (Marcus Gunn pupil) can also be present. (7)

Myelitis

This could be either transverse myelitis, in which sensory, motor, and bladder or bowel spinal cord tracts are involved, or partial myelitis, where one or more spinal cord tracts are involved but not all. However, MS typically presents with partial myelitis. (7)

Brainstem syndromes

Brainstem could be affected in MS by the involvement of cranial nerves (III, IV, and VI), causing diplopia, medial longitudinal fasciculus damage leading to ophthalmoplegia, cranial nerve VII leading to facial palsy, cranial nerve VIII leading to vertigo, cranial nerves (IX, X or XII) causing bulbar symptoms including dysphagia or dysarthria or cranial nerve V leading to sensory impairment in the face. However, facial sensory impairment can also be related to cervical spinal cord lesions. In addition, there might be cerebellar involvement leading to unilateral ataxia, dysdiadochokinesia, dysmetria, or cerebellopontine involvement, causing pendular nystagmus. (7)

Motor symptoms

Since the corticospinal tracts are usually involved, the upper motor neuron syndrome usually presents with hyperreflexia, spasticity, weakness, and positive Babinski sign. (7)

Sensory symptoms

Sensory symptoms include numbness, paresthesia, pain, and Lhermitte sign in which neck flexion causes an electric shock-like sensation running through the spine, indicating cervical or upper thoracic dorsal column involvement. (7)

Imbalance

It is caused by cerebellar involvement, vestibular dysfunction, or sensory impairment (sensory ataxia). (7)

Cognitive, psychological, and functional symptoms

The most common cognitive symptoms of MS are mental slowing, executive function impairment, or long-term verbal and visual memory. Less commonly, MS patients can have dementia. However, cognitive impairment indicates white matter, cortical involvement, and brain atrophy. Depression is present in some patients of MS as well as fatigue which is a highly prevalent presentation of MS and is related to depression or even diseases other than MS, warranting further investigations. (7)

Uthoff's phenomenon

Patients experience heat sensitivity in which symptoms are worsened by heat due to higher temperatures causing less efficient conduction in demyelinated fibers (7).

Bladder and bowel dysfunction

Bladder involvement is manifested in a neurogenic bladder, leading to patients experiencing urinary retention, urinary frequency, difficulty initiating urine stream, or urinary incontinence. MS can also lead to bowel involvement, which is less common than bladder involvement, and usually presents as constipation and less commonly as incontinence, where a severe spinal cord injury could be related (7).

Sexual dysfunction

Erectile dysfunction is the most common symptom in men, and fatigue or loss of libido is common in women (7).

Headaches

Migraine is the most common type of headache. However, MS is not related to an increased risk of migraines, but migraines are linked to an increased risk of MS. (7)

MS exhibits multiple disease courses. These include clinically isolated syndrome, where patients have an initial attack of MS but need more attacks to prove the diagnosis of MS, and relapsing-remitting form, in which patients suffer from multiple attacks with periods of recovery that could be partial or complete without progression of the disease during recovery periods. Such disease courses also include a secondary progressive form in which relapsing-remitting disease becomes progressive with worsening disability and is associated with relapses, as well as a primary advanced form in which the disability progresses at disease onset without early relapses or remissions. (1)

The expanded disability status scale (EDSS) can be used to define aggressive MS and predict the risk of progression to aggressive MS. (2) The EDSS scale was established in 1983 and is still used to describe the degree of disability and response to therapy in MS using multiple functional systems (Table 1). (8) Initially, EDSS was named the Disability status scale (DSS), which included the same functional systems but differed in the number of steps on the scale, which were ten steps on DSS and became 20 in EDSS (Table 2). (9)

1) Pyramidal Functions 0. Normal. 1. Abnormal signs without disability. 2. Minimal disability. 3. Mild or moderate paraparesis or hemiparesis. 4. Marked paraparesis or hemiparesis, moderate quadriparesis; or monoplegia. 5. Paraplegia, hemiplegia, or marked tetraparesis. 6. Quadriplegia. V. Unknown.
2) Cerebellar Functions. 0. Normal. 1. Abnormal signs without disability. 2. Mild ataxia. 3. Moderate truncal or limb ataxia. 4. Severe ataxia, in all limbs. 5. Unable to perform coordinated movements due to ataxia. V. Unknown. X. Used throughout after each number when weakness (grade 3 or more on pyramidal) interferes with testing.
3) Brain Stem Functions.

0. Normal.
1. Signs only.
2. Moderate nystagmus or other disability.
3. **Severe nystagmus** marked extraocular weakness, or moderate disability of other cranial nerves.
4. Marked dysarthria or other marked disability.
5. Inability to swallow or speak.
V. Unknown.

4) Sensory Function (revised in 1982).
0. Normal.
1. Vibration or figure-writing decreases only in one or two limbs.
2. Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory (c/s figure-writing decrease alone in three or four limbs.
3. Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs.
4. Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs.
5. Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioceptive for most of the body below the head.
6. Sensation **lost** below the head.
V. Unknown.

5) Bladder-Bowel Functions (revised in 1982).
0. Normal.
1. Mild urinary hesitancy, **urgency,** or retention.
2. Moderate hesitancy, urgency, retention of bladder or bowel, or rare urinary incontinence.
3. Frequent urinary incontinence.
4. In need of almost complete constant catheterization.
5. Loss of bladder and bowel function.
V. Unknown.

6) Visual (Optical) Functions.
0. Normal.
1. Scotoma with visual acuity (corrected) better than 20/30.
2. Worse eye with scotoma with maximal visual acuity (corrected) of 20/30 to 20/59.
3. Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20-60 to 20-99
4. Worse eye with a marked decrease in fields and maximal visual acuity (corrected) of 20/100-20/200; grade 3 plus maximal acuity of the better eye
20/60 or less.
5. Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of the better eye of 20/60 or less.
6. Grade 5 plus maximal acuity of better eye of 20/60 or less.
V. Unknown.
X. Added to grades 0 to 6 for the presence of temporal pallor.

7) Cerebral (Cognitive) Functions.
0. Normal.

1. Mood alteration only (does not affect D5S score). 2. Mild decrease in mentation. 3. Moderate decrease in mentation. 4. Marked decrease in mentation (chronic brain syndrome- moderate). 5. Dementia or chronic brain syndrome-severe or incompetent. V. Unknown.
8) Other Functions. 0. None. 1. Any other neurologic findings attributed to MS (specify). V. Unknown

Table 1: functional systems, reprinted from Piri Çınar B, Güven Yorgun Y (9)

1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but is self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500 m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300 m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200 m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100 m
6.0	Requires a walking aid-cane, crutch, etc. -to walk about 100 m with or without resting
6.5	Requires two walking aids-pair of canes, crutches, etc. -to walk about 20 m without resting
7.0	Unable to walk beyond approximately 5 m even with aid. Essentially restricted to wheelchair, though wheels self in a standard wheelchair and transfers alone. Up and about in a wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to a wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorized wheelchair
8.0	Essentially restricted to a bed or chair or pushed in a wheelchair. May be out of bed much of the day. Retains many self-care functions. Generally, has effective use of arms
8.5	Essentially restricted to bed much of the day. Has some effective use of arms and retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and dependent. Unable to communicate effectively or eat/swallow

10.0	Death due to MS

Table 2: EDSS, reprinted from Piri Çınar B, Güven Yorgun Y (9)

Diagnosis

In general, the primary investigations used to diagnose multiple sclerosis include Magnetic Resonance Imaging (MRI), cerebrospinal fluid (CSF) analysis, visual evoked potential (VEP), and blood tests including hemogram, renal and liver function tests, lipid profile, vitamins and electrolytes levels, viral serology and autoantibodies present in other autoimmune diseases such as lupus.(10)Investigations and clinical findings are integrated within the 2017 McDonald criteria (Table 3), which should be used with caution, especially in patients with an atypical presentation, such as initial presentation of progressive form, in children and elderly, or other patients with high suspicion of other differential diagnoses. (11)

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥ 2 clinical attacks	≥ 2	None
≥ 2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	None
≥ 2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 clinical attack	≥ 2	Dissemination in time demonstrated by an additional clinical attack or by MRIS OR demonstration of CSF-specific oligoclonal bands
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different NS site or by MRI AND Dissemination in time demonstrated by an additional clinical attack or by MRIS OR demonstration of CSF-specific oligoclonal bands

Table 3: McDonald 2017 criteria, reprinted from Alan J Thompson et al. (11).

Aggressive MS

Aggressive MS can show any of the clinical features and courses of MS (2)(3)(6), some clinical characteristics are related to aggressive MS including:

Frequent attacks and shorter inter-attack intervals

Shorter inter-attack intervals correlate with faster progression to disability, walking difficulty, and need for a cane. Unresponsiveness to treatment and frequent attacks, especially within the first year of therapy, correlate with poor prognosis. Each episode in the early few years increases the risk of reaching disability milestones, including limited walking distance, need for a cane, and single neurological system moderate disability. (3)

Incomplete recovery after attacks

Incomplete recovery after MS exacerbations were associated with reaching disability milestones more quickly. A ten-fold increase in reaching the milestones was shown in patients with incomplete recovery. The strongest predictor of walking disability after ten years was a higher EDSS score after exacerbations. (3)

Motor, sphincter, cognitive or multifocal nature of symptoms

An increased proportion of patients reaching disability milestones in patients with pyramidal, sphincter, cerebellar, or brain stem dysfunction. However, patients with sensory or visual symptoms had a better prognosis, but the effect of visual symptoms on prognosis was modest after controlling for male gender, age, and progressive disease onset. In addition, the relation between motor symptoms and age, gender, and progressive onset are confounding factors in the relationship between motor symptoms and disability progression. Cognitive symptoms also predicted a higher EDSS. Although not found in all studies, an onset of multifocal symptoms was associated with a higher risk of disability in many studies. (3)

Progressive disease onset

Progressive disease onset is strongly related to a more aggressive course of MS in which patients' risk of disability is two times higher than those with a relapsing-remitting disease course. Patients reach disability milestones one-third to half of the time that patients with relapsing-remitting disease need. (3)

Increased disease severity

Patients with aggressive MS exhibit more severe relapses that can increase EDSS by one or more points, increase any functional system score by two or more points, or increase two or more functional system scores by one or more points. Patients with aggressive

disease acquire disability more rapidly and are more prone to reach an EDSS of 3 or more within the first year. (2)

findings associated with aggressive multiple sclerosis, include the following:

MRI findings

A high number of T2-enhanced lesions (⩾20) or gadolinium-enhanced lesions (⩾2), and T1 black holes indicating tissue loss and lesions in the spinal cord can predict increased severity of multiple sclerosis. Furthermore, spinal cord lesions, atrophy, and decreased upper cervical surface area are highly related to higher EDSS scores. The development of more than one gadolinium-enhanced lesion or new T2 lesions at follow-up is associated with a worse disease course. Also, early atrophy in the brain, including the cortex, deep grey matter, thalamus, basal ganglia, or infratentorial regions, is associated with aggressive MS and faster progression to disability. In addition, smoldering lesions indicating delayed recovery, persistent inflammation, and neurodegeneration are used as markers for aggressive MS (2)(3)(5). Figure (1) Figure (2)

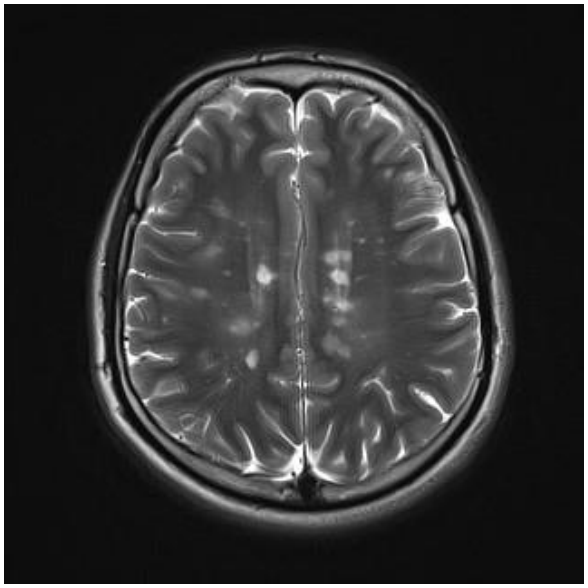


Figure 1: T2 MRI enhanced lesions, Case courtesy of Associate Professor Frank Gaillard, (12)

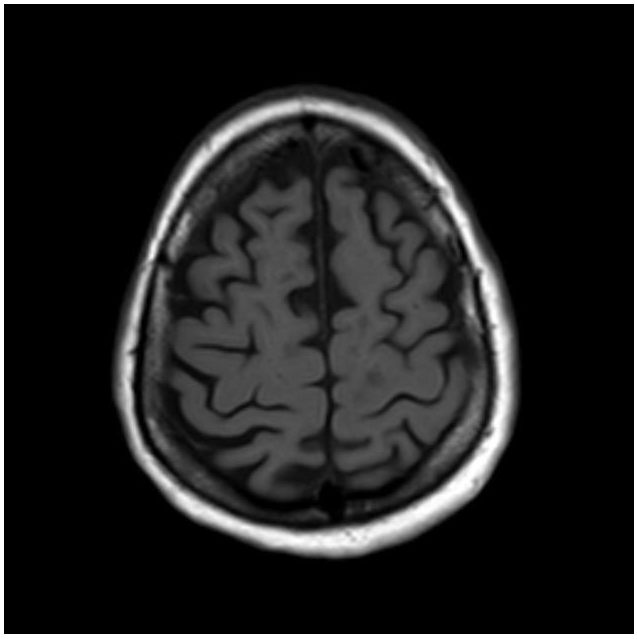


Figure 2: T1 black holes, Case courtesy of Dr Ahmed Abdrabou,(13)

Biochemical markers

Presence of IgM oligoclonal bands, B lymphocyte chemoattractant (CXCL13), neurofilament light chain (NFL), or Chitinase-3-like protein 1 (CHI3L1) in CSF, elevated IgG index and Elevated NFL in serum. (2)(3)(5)

There are many names and definitions used to describe aggressive multiple sclerosis for research or clinical purposes, and still no specific diagnostic criteria are agreed upon (2)(6), definitions include:

- **Malignant MS:** describes a very rapid progression of the disease, but the term is ambiguous because it is more commonly used to describe an unstoppable form of MS that can result in death within months to a few years, such as the Marburg variant of MS. Some researchers define malignant MS as rapid progression to death or disability. Another definition is the progression of EDSS to a score of 6 points in 5 years which is sometimes called ever malignant MS. Based on whether relapses or sustained progression is present, some research groups classify malignant MS into transient or sustained. (2)(6)

- ***Aggressive MS:*** has various definitions, including reaching an EDSS of 6 within five years, reaching an EDSS of 6 at 40, or transforming to secondary progressive MS within three years since relapsing-remitting MS onset. Other researchers use the definition of reaching an EDSS of 6 within ten years since disease onset. Aggressive MS is also defined as relapsing-remitting MS with one or more of an EDSS score of 4 within the first five years, two or more relapses in the last year with incomplete recovery, presence of more than two new or enlarging T2 or gadolinium-enhanced MRI lesions

despite treatment or use of 1 or more disease-modifying therapies (DMTs) for one year with no response.(2)(6)

- ***Aggressive relapsing-remitting MS:*** where the baseline EDSS is 2.5-5, one or more gadolinium-enhancing lesions are present on MRI, and two or more relapses or an increase in EDSS of 2 or more points in the last 12 months. (2)(6)

- *Aggressive onset MS* is also used to describe patients having two or more relapses and two or more gadolinium-enhancing MRI lesions or having one relapse in the last year that results in a sustained increase of EDSS of 3 with two or more gadolinium-enhancing MRI lesions. (2)(6)

-Highly active MS is used to identify patients eligible for immunoablative therapy with homologous stem cell transplant and indicates a poor prognosis. It is defined as conventional treatment failure with one or more relapsed and incomplete recovery, MRI with one or more gadolinium-enhancing lesions of 3mm diameter or more, or an increase in T2 lesion of 0.3 or more per month in two consecutive MRI 6-12 months apart. (2)(6)

Multiple criteria are used to identify aggressive MS (3), as shown in Table 4, Table 5, and Table 6 below:

Table 4: Canadian working group assessment, reprinted from Dr James D. Bowen (3)

Criteria	**Low Level of concern**	**Moderate Level of concern**	**High Level of concern**
Relapses			
Rate	One in the second year of treatment	One in the first year of treatment	More than one in the first year of treatment
Severity	Mild: Steroids not required Minimal effect on activities of daily living One functional domain affected No or mid motor/cerebella Involvement	Moderate: Steroids required Moderate effect on activities of daily living More than one functional domain affected Moderate motor/ cerebellar involvement	Severe: Steroids/hospitalization required Severe effect on activities of daily living More than one functional domain affected Severe motor/ cerebellar involvement

Recovery	Prompt recovery; no functional deficit	Incomplete recovery at 3 months; some functional impairment	Incomplete recovery at 6 months: functional impairment
Disability Progression			
EDSS less than or equal 3.5	Less than or equal 1 point	2 points at 6 months	>2 points at 6 months 2 points at 12 months
EDSS 4.0-5.0	<1 point	1 point at 6 months	>1 point at 6 months 1 point at 12 months
EDSS more than or equal 5.5	NA	0.5 points at 6 months	>0.5 points at 6 months
Clinically documented progression	No motor symptoms; minor sensory symptoms	Some motor, cerebellar, or cognitive symptoms; multiple EDSS domains affected	Pronounced motor, cerebellar, or cognitive symptoms; multiple EDSS domains affected
Timed 25-foot walk	Less than or equal 20% confirmed at 6 months	>20% and <100% increase confirmed at 6 months	≥ 100% increase confirmed at 6 months
MRI activity			
New gadolinium-enhancing lesions OR	1 lesion	2 lesions	≥ 3 lesions
Accumulation of new T2 lesions per year			

Table 5: modified Rio score, reprinted from Dr James D. Bowen (3)

Criteria	Points assigned

MRI done at 6 months	
≤ 5 new T2 lesions	0
>5 new T2 lesions	1
MRI done at 1 year	
≤ 4 new T2 lesions	0
>4 new T2 lesions	1
Relapse over 1 year	
0 relapses	0
1 relapse	1
≥ 2 relapses	2

Table 6: MS decision model, reprinted from Dr James D. Bowen (3). HADS: hospital anxiety and depression scale. If green was found on interpretation in all domains no change in therapy is needed, while patients with one yellow domain should be reassessed in three months and patients with two yellow domains or one red domain should have their therapies changed.

Criteria	Points Assigned	Interpretation
Relapse		0 points = green 1-4 points = yellow ≥ 5 points = red
Each relapse	3	
Characteristics of relapses		
Functionally relevant	1	
Residual symptoms after 3-6 months	2	
Interval since the start or change of therapy		

More than or equal to 12 months	0	
6-12 months	1	
3-6 months	2	
Disability		**0 points = green** **1 point = yellow** **≥ 2 points = red**
MS Functional Composite		
Each test with worsening by 20%	1	
Each test worsened by 40%	2	
Symbol Digit Modality Test		
Worsening by more than or equal 4 points	1	
Worsening by more than or equal 8 points	2	

Neuropsychology		**0 points = green** **1 point =yellow** **≥ 2 points = red**
Fatigue Scale for Motor and Cognitive Functions		
Worsening by 1 category	1	
Worsening by 2 categories	2	
Worsening by 3 categories	3	
Depression (HADS]	-1	
Anxiety (HADS)	-1	
Quality of life (MSIS-29)	No points	
MRI		**0-2 points = green**

Each gadolinium-enhancing lesion	1	**≥ 3 points = yellow**
Each new/enlarging T2 lesion	1	

An EDSS of 6 or more was associated with a secondary progressive disease which is of unfavorable response to aggressive treatment and hence can be used as a good criterion to identify aggressive MS. (6)

Differential diagnoses of MS that could also have aggressive presentation

Other inflammatory demyelinating diseases, some of which can be considered atypical forms of MS, such as Acute disseminated encephalomyelitis (ADEM) or acute hemorrhagic leukoencephalitis, Shidler disease, Balo concentric sclerosis, Marburg variant of MS, Tumefactive demyelination, Solitary sclerosis and Cavitary MS. (10)(14)

-Balo concentric sclerosis: Is a monophasic acute demyelinating disease most frequently affecting Asian women. Patients usually present with encephalopathy, headache, cognitive impairment, or seizures which are atypical of classical MS and might help differentiate the disease (10). Antibodies are usually negative, and patients are negative for oligoclonal bands. T2 enhanced MRI shows hyperintense alternating with a hypointense lamella, which is related to regions of preserved myelin alternating with legions of severe demyelination. The disease is treated with corticosteroids and other immunosuppressants. The disease can be identified in patients with previous MS diagnoses, other atypical forms of MS, or previously healthy patients. On pathology oligodendrocytes, loss and MS immune pattern III are seen (14). Figure (3)

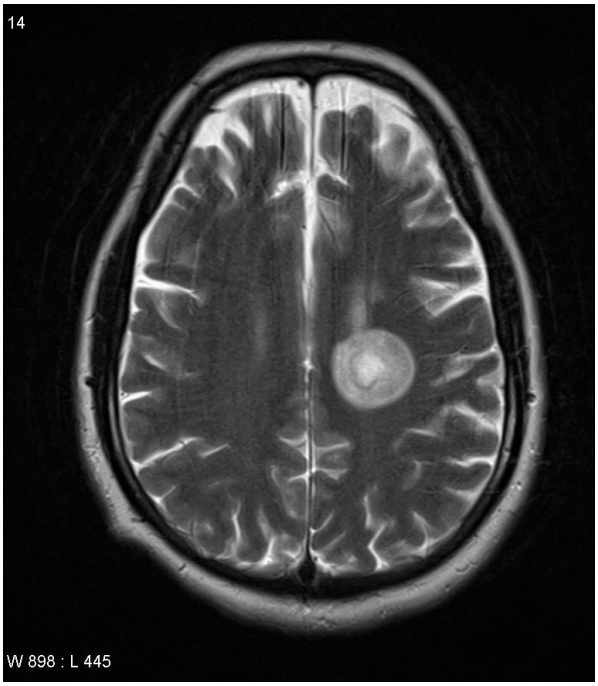


Figure 3: Balo concentric sclerosis on axial T2 enhanced MRI, Case courtesy of Austin Neuropathology (15).

- Tumefactive demyelination: patients usually present with atypical MS symptoms such as lethargy, headaches, and seizures. On MRI patients who have>2 cm well-defined demyelinating lesions (Figure 4) that can be isolated, multiple, or associated with other MS lesions. The lesions are ring-like or of infiltrative pattern and are in supratentorial areas. The oligoclonal band is an inconsistent finding in CSF analysis, but patients usually have higher CSF interleukin (IL)-6 and similar CSF IL-10 compared to MS. On histopathology, patients exhibit more Creutzfeldt Peter cells and dystrophic astrocytes, displayed in fewer numbers in typical MS (14). However, patients with tumefactive lesions have a favorable prognosis compared to other MS patients and are usually treated with corticosteroids or DMTS (16).

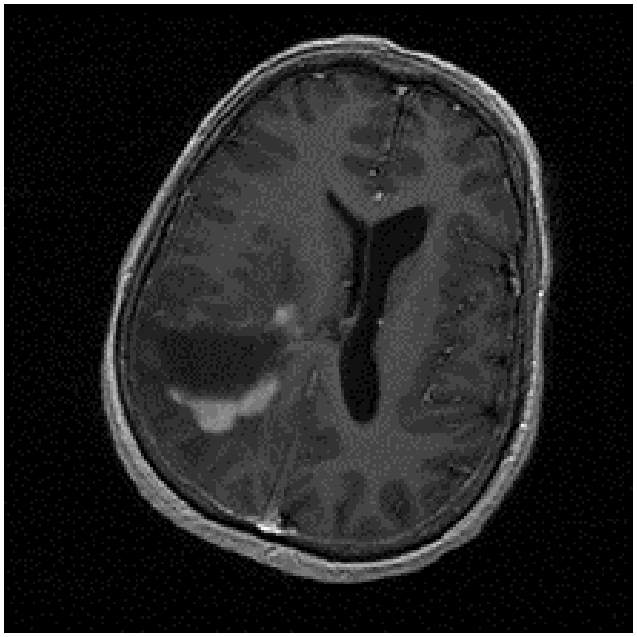


Figure 4: Tumefactive demyelinating lesion on MRI, Case courtesy of Dr Hani Makky Al Salam, (17)

-Schiller's disease: Is another severe atypical MS variant that can be misdiagnosed as MS in the early stages because of the presence of white matter lesions. However, the disease progresses more rapidly and presents with impaired consciousness. On MRI, Schilder's disease lesions are similar to tumefactive lesions. The disease affects children more frequently than adults. (10)

-Marburg variant of MS: This is a deadly atypical variant presenting with loss of consciousness, coma, and death within weeks. On MRI, supratentorial, infratentorial, and spinal cord lesions are present and progress rapidly. (Figure 5)
Marburg variant and Shidler's disease have poor prognoses as corticosteroids or other immunosuppressants are ineffective in stopping disease progression. (14)

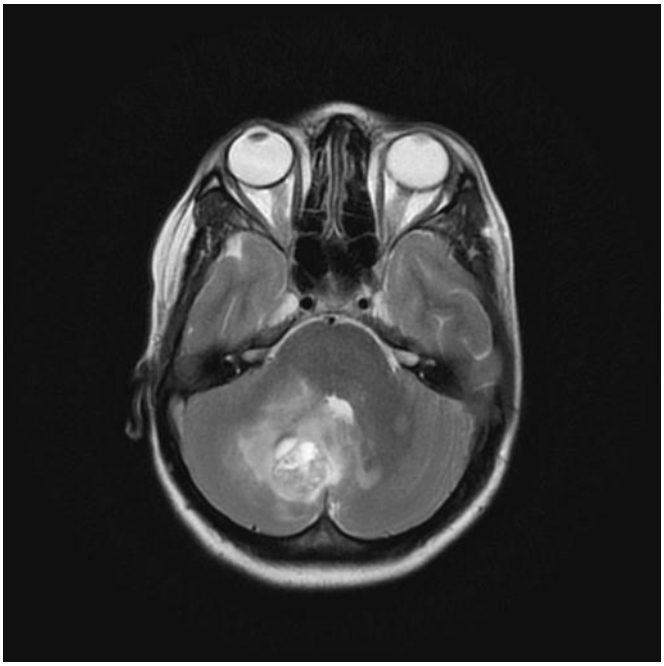


Figure 5: Marburg variant MS on MRI, Case courtesy of Dr Mohammad A. ElBeial.

Acute disseminated encephalomyelitis (ADEM): Is usually present in pediatric patients but rarely in adults. Patients typically present with acute or subacute encephalopathy and can progress to coma, in addition to fever, headache, fatigue, and nausea related to encephalitis. Furthermore, patients can have focal or multifocal symptoms according to sights affected by demyelination. The disease's cause is idiopathic but related to a recent infection or vaccination. On MRI, multiple T2 hyperintense lesions are present bilaterally and asymmetrically (Figure 6). CSF analysis can show increased lymphocytes, an elevation in CSF pressure, mild protein elevation, normal glucose levels, elevated IgG index, and oligoclonal bands. The disease has a favorable prognosis and is usually monophasic, although some patients can have a non-monophasic presentation mainly related to MS. However, Acute hemorrhagic leukoencephalitis is a rare, severe variant with similar symptoms and a less favorable prognosis. The disease is distinguished by having hemorrhagic lesions. (10)(14)

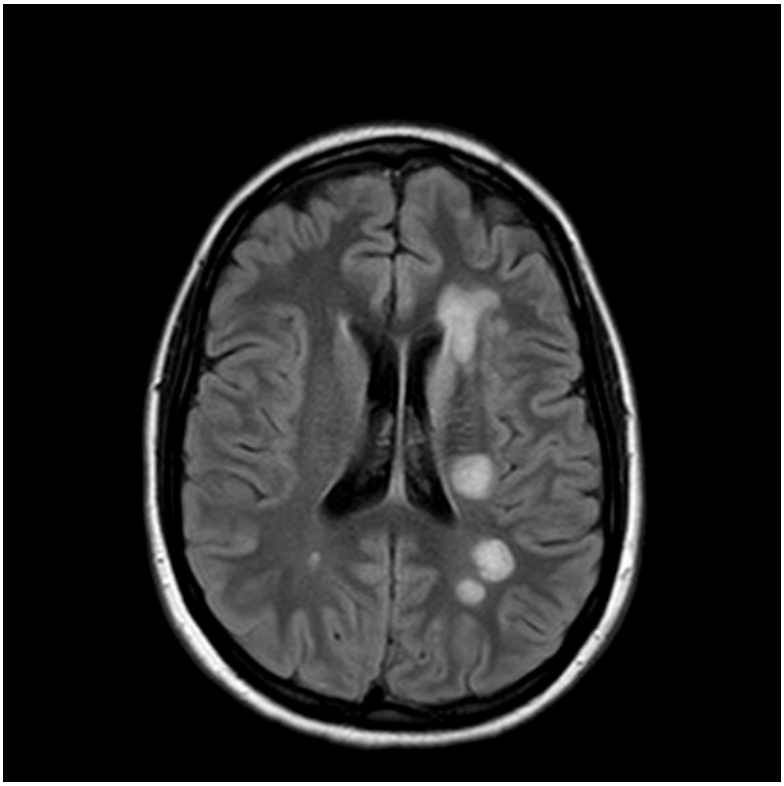


Figure 6: Axial FLAIR MRI Acute Disseminated Encephalomyelitis, Case courtesy of Assoc. Prof Frank Gaillard, (19)

Solitary sclerosis: Is a progressive disease causing spastic paraparesis or hemiparesis. It is caused by an isolated demyelinating lesion in the corticomedullary junction which is found on MRI (Figure 7), through the involvement of other sites of the corticospinal tract. CSF analysis also shows oligoclonal bands. The disease is related to MS and can progress to MS. However, this is yet to be more thoroughly evaluated (14).

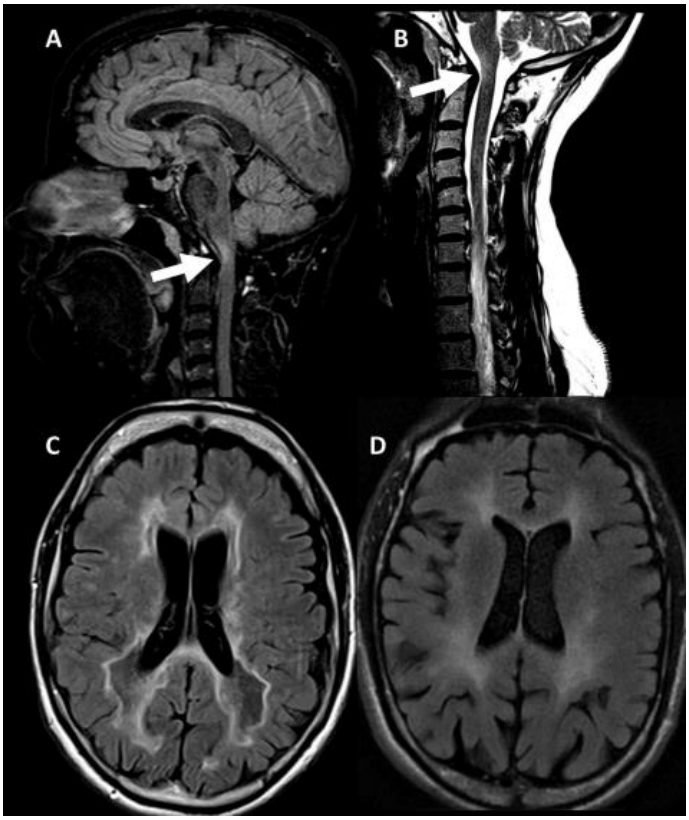


Figure 7: Solitary sclerosis on MRI, (A,B) showing lesions on cervicomedullary junction, C and D showing FLAIR hypointensities and hyperintensities respectively, reprinted from X. Ayrignac, C. Carra-Dallie`re and P. Labauge, (14).

Neuromyelitis Optica (Devic's disease): This is a demyelinating disease that is no longer considered an atypical variant of MS (13). This disease is related to channelopathy due to antibodies against aquaporin-4 in the astrocyte foot processes. It presents with transverse myelitis and optic neuritis that occur simultaneously or separately. The disease is distinguished from MS by aquaporin-4 antibodies or anti-myelin oligodendrocyte glycoproteins. Also, the disease differs from MS by lack of remissions, rapid progression, and unresponsiveness to corticosteroids or other MS therapies; thus, the disease requires different treatments that can be more aggressive such as plasma exchange. (14)

Other non-demyelinating diseases to be considered as differential diagnoses to MS include inflammatory diseases such as systemic lupus erythematosus, Bechet disease, Sjogren syndrome, paraneoplastic syndromes, sarcoidosis and Wegener granulomatosis, infectious disease such Lyme disease, Human T-lymphotropic Virus-1 Associated Myelitis, CNS involvement in Human immunodeficiency virus, progressive multifocal leukoencephalopathy and neurosyphilis, in addition to metabolic disorders such as Adrenoleukodystrophies, Leber's Hereditary Optic Neuropathy and Subacute Combined Degeneration. Physical examination and investigations are required to differentiate them from aggressive MS. (10)

Treatment

FDA-approved aggressive treatments for MS are shown in Table 7.

Drug	Mechanism of action	Uses	Adverse effects	Monitoring
Alemtuzumab	Humanized monoclonal antibody against CD-52. It targets CD-52 on lymphocytes, leading to cell death and lyses. The different recovery rate of lymphocytes leads to a change in the lymphocyte profile, where TH1 and TH17 lymphocytes are depleted, and memory and regulatory T cells are increased (3)(6).	Approved for relapsing-remitting MS unresponsive to two or more treatments (3)(6).	Infusion reactions Anaphylaxis Infections include herpes virus, human papillomavirus, fungal infections, tuberculosis, and bacterial infections. Autoimmune diseases include Graves' disease, immune thrombocytopenia, autoimmune glomerulopathy, and Guillain-Barre syndrome. Malignancies are the most common thyroid cancer and Melanoma. Acute acalculous cholecystitis Hypersensitivity pneumonitis and pneumonitis leading to lung fibrosis (3)(6)	A complete blood count (CBC), kidney function tests (KFT), Liver function tests (LFT), urinalysis, purified protein derivative (PPD) or QuantiFERON Gold test for tuberculosis and varicella-zoster titer should be done before drug administration. Also, baseline skin examination for skin cancers and vaccination is done before treatment. During treatment, monthly CBC, KFT and urinalysis, quarterly thyroid function tests and thyroid examination for nodules, and annual human papillomavirus screening in women (6).
Cladribine	A purine analog has antineoplastic and immunosuppressive effects and works	Used in aggressive, relapsing-remitting MS and active secondary	Increased risk of malignancies	Screening for malignancies.

	selectively in lymphocytes, especially CD4+ and CD8+ lymphocytes leading to inhibition of DNA repair in these cells and cell death (3)(6).	progressive MS unresponsive to other treatments (3)(6).	Rash Alopecia Lymphopenia and neutropenia Infections include varicella-zoster, hepatitis B, hepatitis C, tuberculosis reactivation, and progressive multifocal leukoencephalopathy. Liver injury Teratogenicity warrants the use of contraceptives until six months after the last dose. There are case reports of myocarditis and acute heart failure (3)(6).	CBC and liver function tests before each dose and 2-6 months after each dose. Varicella-zoster antibodies. Hepatitis B and C, tuberculosis, and HIV screening. Pregnancy tests and use of contraception (6)(22).
Fingolimod	Binds all subtypes f sphingosine-1-phosphate receptor except type 2, causing these receptors to be internalized and degraded in the cells. This causes the inactivation of these receptors on naive lymphocytes, leading to the inability of these lymphocytes to exit lymph nodes and go into the	Approved for relapsing-remitting MS (3).	Cardiac side effects include bradycardia or atrioventricular block after the first dose. However, drugs that prolong QT interval should be stopped. Herpes infections include herpes simplex encephalitis, varicella-zoster (shingles), and Kaposi sarcoma caused by the human herpesvirus 8. Other	An ECG should be done before and after the first dose, and hourly monitoring of pulse and blood pressure for 6 hours after the first dose. Liver function tests every 3-6 months. Ophthalmological evaluation every 3-4 months and when the patient reports visual problems.

	circulation and to the CNS (3).		infections include cryptococcal meningitis, atypical mycobacteria, and progressive multifocal leukoencephalopathy. Cutaneous malignancies include basal cell carcinoma, melanoma, and Merkel cell carcinoma. Liver and respiratory side effects. Macular edema. Headaches Back pain Bloody diarrhea. Elevated blood pressure Posterior reversible encephalopathy syndrome (3).	Regular skin examination. Varicella-zoster antibodies before treatment initiation. Baseline respiratory function tests. Use of contraception during therapy (22).
Siponimod	Binds sphingosine-1-phosphate receptors, subtypes 1 and 5(3).	Approved for the clinically isolated syndrome, relapsing-remitting, and active secondary progressive MS(3)	Like fingolimod(3)	Same monitoring as fingolimod in addition to genetic testing before treatment initiation. Some variants of CYP450 metabolize Siponimod more slowly; thus, genotypic testing

				must be done before treatment. CYP2C9*1/*3 or *2/*3 genotypes should receive half of the dose, and CYP2C9*3/*3 homozygous patients should not receive the drug (3)(22).
Natalizumab	A humanized monoclonal antibody against alpha-4 integrin subunit of adhesion molecules. Works by preventing endothelial adhesion of leukocytes, leading to impaired entry to target tissues, including the CNS (3).	Used for relapsing-remitting MS (3).	Hypersensitivity reactions and anaphylaxis. Liver injury. Malignancies include melanoma and primary central nervous system lymphoma. Increased risk of infections, including primary multifocal leukoencephalopathy. Rebound disease after stopping (3).	Brain MRI CBC and LFT JC virus antibodies (22)(23)
Ocrelizumab	A humanized monoclonal antibody against CD-20. Works by fixing complement to target cells and causing cell lysis. Target B cells but not plasma cells, thus, don't affect levels of antibodies but prevent B cells from	Approved for primary progressive and relapsing-remitting MS (3).	Infusion reactions. Hypogammaglobinemia Infections include upper and lower respiratory infections, herpes viruses, hepatitis B reactivation, and progressive multifocal	Baseline CBC and LFT and every six months during treatment. Vaccination. Hepatitis B, hepatitis C, and tuberculosis screening. Pregnancy tests and contraception.

	presenting antigens to T cells (3).		leukoencephalopathy. Increased risk of malignancies including breast cancer (3).	Breast cancer screening In patients with recurrent or severe infection, test for immunoglobulin levels (22).
Mitoxantrone	An anthracenedione antineoplastic agent blocks type II topoisomerase, leading to disruption in DNA replication and repair. This causes inhibition of the proliferation of B and T cells and TH1-mediated release of cytokines (3)(6).	Higher benefit in young patients with more frequent relapses and lower EDSS, aggressive relapsing-remitting MS, and early secondary progressive MS (3)(6).	Gonadal dysfunction and amenorrhea in women. Leukaemia and Cardiotoxicity, which lead to its use being less favorable recently. Liver toxicity (3)(6)	Monitoring fertility and trying to preserve it. Annual echocardiogram or mitigated acquisition scan for five years after treatment. Doing blood counts every six months for five years. Liver function tests Monitoring of lifetime dose, which should not exceed 140mg/ m2 (6)

Table 7: FDA-approved aggressive MS drugs

Patients with aggressive MS are unresponsive to conventional first- or second-line treatments of MS; thus, these patients mostly will have tried drugs that either block inflammatory cells' access to the CNS, such as Natalizumab or that sequester these inflammatory cells in lymph nodes such as fingolimod. Second-line agents such as Natalizumab and fingolimod exert their effect if patients use these drugs. Natalizumab discontinuation is associated with severe, dangerous rebound disease, and prolonged use is associated with progressive multifocal leukoencephalopathy, although used anecdotally in some aggressive MS patients. On the other hand, fingolimod with a less severe rebound effect after discontinuation is not completely effective for aggressive MS. Therefore, therapies that eliminate immunoreactive cells, including alemtuzumab, rituximab, cladribine, mitoxantrone, cyclophosphamide or the use of immunoablative therapy and homologous stem cell transplant are more effective in aggressive MS. (3)(6)(21)

Non-FDA-approved drugs for aggressive MS are shown in Table 8:

Drug	Mechanism of action	Uses	Adverse effects	Monitoring
Cyclophosphamide	An alkylating agent used in cancer and autoimmune diseases has cytotoxic effects on a broad spectrum of B and T and works by cross-linking DNA leading to cell death independent of the cell cycle(3)(6).	Used in early secondary progressive MS, especially in young patients and aggressive MS (3)(6).	Hemorrhagic cystitis. Gonadal toxicity. Bladder cancer Brain atrophy Syndrome of the inappropriate release of ADH Cardiotoxicity Ototoxicity Immunosuppression and myelosuppression Nausea Alopecia Malignancies including hematological malignancies (3)(6)	Hemorrhagic cystitis can be prevented by adequate hydration, Mensa administration, and frequent voiding or bladder catheterization if needed Every six months, do cytology and urinalysis, if cytology is abnormal, do annual cystoscopy. Neurocognitive examination Fertility monitoring and preservation (6).
Rituximab	A partially humanized monoclonal antibody against CD-20	Used in relapsing-remitting MS. However, further studies	Like side effects of ocrelizumab (3).	Like ocrelizumab (3).

	on B cells leads to B cell depletion with a mechanism similar to ocrelizumab(3)(6).	are needed to confirm its efficacy in aggressive MS (3)(6).		

Table 8: Non-FDA approved aggressive MS drugs

Immunoablative therapy with stem cell transplantation

It is a non-FDA-approved approach used in autoimmune diseases, including MS, and is the most aggressive treatment of MS with high efficacy as there is no evidence of disease activity at 50 years approached 70%, which is twice as effective as other aggressive MS therapies. However, this increased efficacy is at the cost of increased risk of severe side effects, including allergic reactions and anaphylaxis, transplant reactions, myelosuppression, liver toxicity, and gastrointestinal toxicity, all of which depend on the type of therapy used. The more effective the therapy is, the more myelosuppression it will involve. (3)(6)(24)

This therapy involves multiple steps starting with stem cell mobilization using granulocyte colony-stimulating factor or immunosuppressants, leukapheresis to collect stem cells, and a conditioning regimen involving high-dose chemotherapy. Examples are:

Highly myeloablative busulfan plus anti-thymocyte globulin in which the risks of myelosuppression and veno-occlusive liver disease are high.

intermediate myeloablative therapy involving Carmustine, etoposide, cytarabine, and melphalan plus anti-thymocyte globulin (BEAM/ATG), which has an intermediate risk of myelosuppression.

Nonmyeloablative therapy involves cyclophosphamide and anti-thymocyte globulin, whose side effects are mainly caused by cyclophosphamide. Finally, stem cell infusion leads to bone marrow reconstitution. This will lead to the elimination of autoreactive cells and a reset of the immune system. Immunoablative therapy with stem cell transplant was primarily effective in relapsing-remitting MS patients younger than 32 who did not use more than two other therapies. (3)(6)

Treatment approaches

The escalation approach is the first approach to treating aggressive MS (Figure 8). Treatment starts with less aggressive and effective drugs and escalates to higher efficacy drugs according to disease activity and responsiveness, thus, reducing the risk of unnecessary immunosuppression. The escalation approach is more effective in relapsing-remitting MS, but in aggressive MS, the narrow time window to progress to disability will make this approach less effective. However, replacing monotherapy of low-efficacy drugs with monotherapy of high-efficacy medications is found to be preferable to adding high-efficacy drugs to low-efficacy drugs as no increase in effectiveness was found, in addition to the fact that there is a risk of more side effects. The drug to be used next depends on the patient profile and which drugs were used before (6)(23).

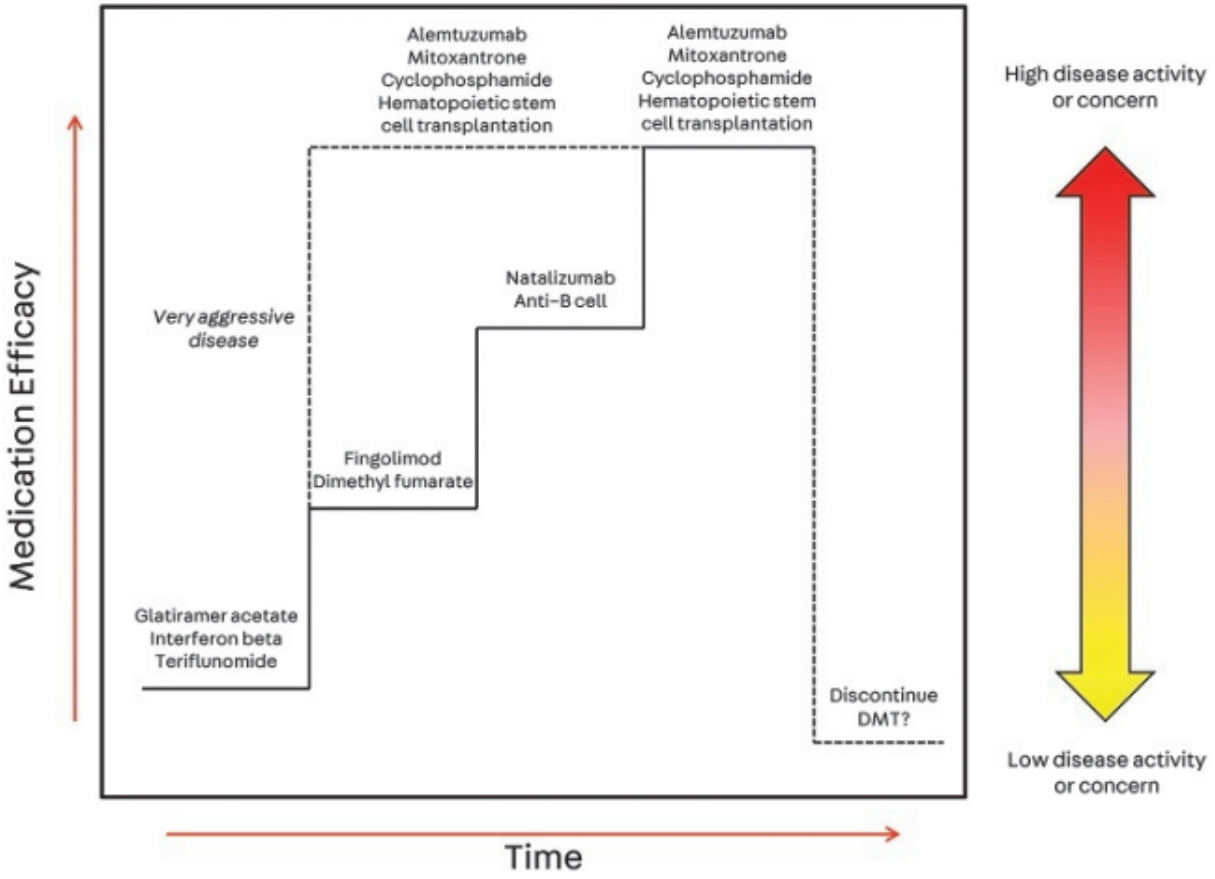


Figure 8: Escalation approach for aggressive MS, reprinted from Robert H. Gross, MD; John R. Corboy, MD, FAAN, (23).

The other approach is the induction approach, in which patients with high-risk features of aggressive MS start directly with high-efficacy treatments. This approach comes at the cost of increased toxicity of high-efficacy treatments. The induction approach can be done either by using an induction treatment for a specific period, such as potent

lymphocyte-depleting agents including cyclophosphamide and mitoxantrone, alemtuzumab or hematopoietic stem cell transplant, then using a less aggressive maintenance DMT (Figure 9), or by using long term use of high efficacy treatments such as Natalizumab, or anti-CD-20 drugs without de-escalation(Figure 10). (6)(23)

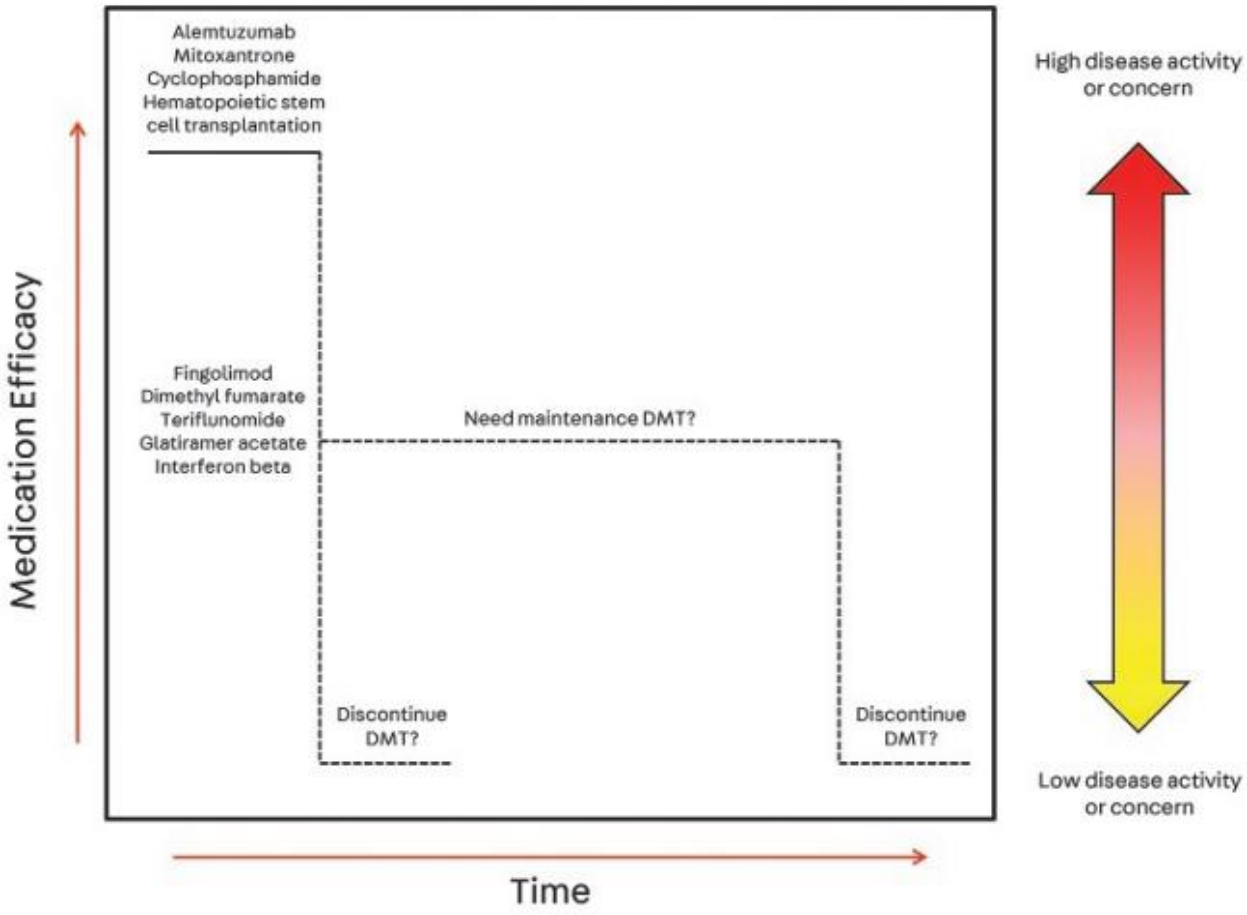


Figure 9: induction approach followed by maintenance, reprinted from Robert H. Gross, MD; John R. Corboy, MD, FAAN, (23).

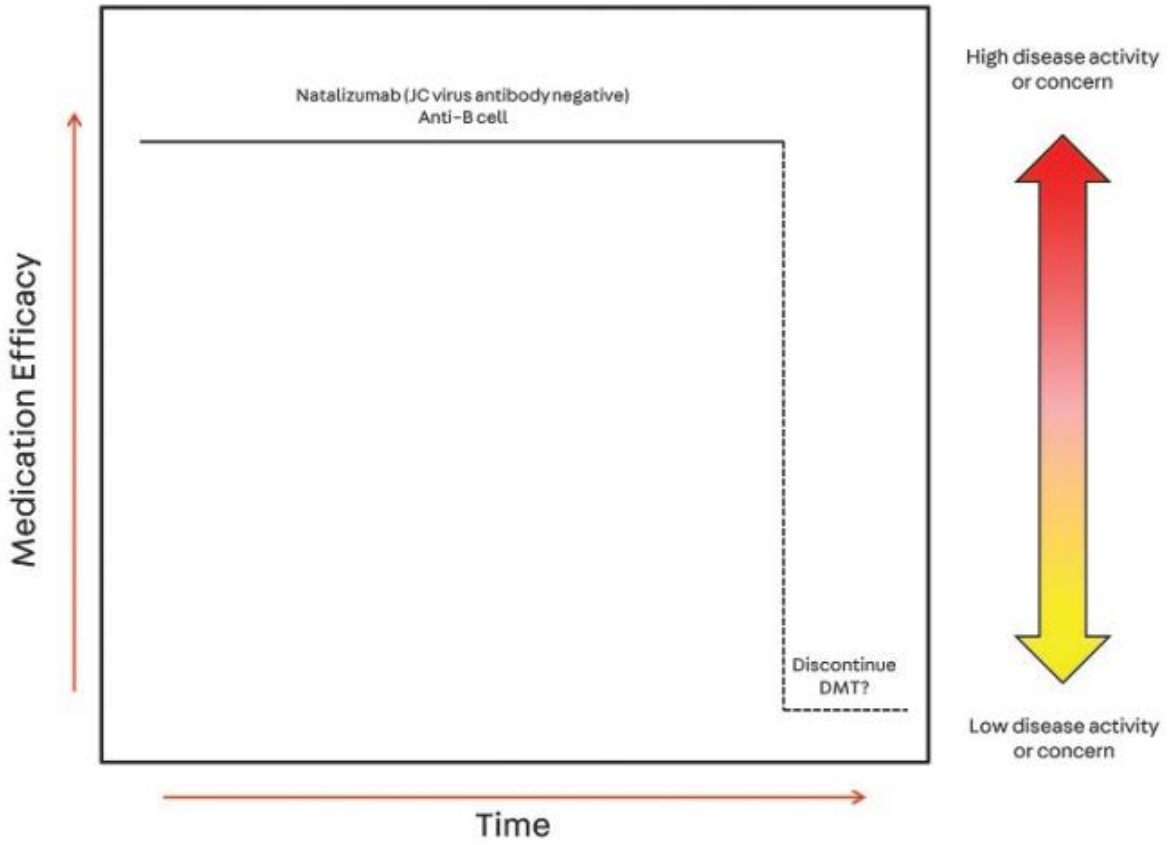


Figure 10: maintenance doses of second-line agents, reprinted from Robert H. Gross, MD; John R. Corboy, MD, FAAN, (23).

Recommendations

Future retrospective studies or prospective studies that evaluate patients until fulfilling aggressive MS criteria should focus on arriving at a consensus on aggressive MS definition by confirming the best criteria to define patients early and use more aggressive treatments if needed. Risk factors for aggressive MS must be studied to predict patients requiring aggressive treatment. (2) More randomized controlled trials should be done to compare the effectiveness of different approaches in treating aggressive MS, drugs used within these approaches, and treatment algorithms. (6)(23) Also, an excellent endpoint to monitor patients' response to aggressive MS treatment must be established. One proposed endpoint is NEDA (no evidence of disease activity), with no disease progression, new MRI lesions or new relapses, or a point close to NEDA. (6)

References

1. Klineova S, Lublin FD. Clinical Course of Multiple Sclerosis. Cold Spring Harb Perspect Med. 2018 Sep;8(9).
2. Iacobaeus E, Arrambide G, Amato MP, Derfuss T, Vukusic S, Hemmer B, et al. Aggressive multiple sclerosis (1): Towards a definition of the phenotype. Mult Scler. 2020 Jun;26(9):1352458520925369.

3. Bowen JD. Highly Aggressive Multiple Sclerosis. Continuum (Minneap Minn). 2019 Jun;25(3):689–714.
4. Nourbakhsh B, Mowry EM. Multiple Sclerosis Risk Factors and Pathogenesis. Continuum (Minneap Minn). 2019 Jun;25(3):596–610.
5. Díaz C, Zarco LA, Rivera DM. Highly active multiple sclerosis: An update. Mult Scler Relat Disord. 2019 May;30:215–24.
6. Rush CA, MacLean HJ, Freedman MS. Aggressive multiple sclerosis: proposed definition and treatment algorithm. Nat Rev Neurol. 2015 Jul;11(7):379–89.
7. Gelfand JM. Multiple sclerosis: diagnosis, differential diagnosis, and clinical presentation. Handb Clin Neurol. 2014;122:269–90.
8. Meyer-Moock S, Feng Y-S, Maeurer M, Dippel F-W, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC Neurol. 2014 Mar;14:58.
9. Çinar BP, Yorgun YG. What We Learned from The History of Multiple Sclerosis Measurement: Expanded Disability Status Scale. Noro Psikiyatr Ars. 2018;55(Suppl 1):S69–75.
10. Ömerhoca S, Akkaş SY, İçen NK. Multiple Sclerosis: Diagnosis and Differential Diagnosis. Noro Psikiyatr Ars. 2018;55(Suppl 1):S1–9.
11. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018 Feb;17(2):162–73.
12. Gaillard PF. t2 lesions. In: radiopedia.
13. Abdrabou DA. t1 black holes. In: radiopedia.
14. Ayrignac X, Carra-Dallière C, Labauge P. Atypical inflammatory demyelinating lesions and atypical multiple sclerosis. Rev Neurol (Paris). 2018 Jun;174(6):408–18.
15. Neuropathology A. balo concentric sclerosis. In: radiopedia.
16. Brod SA, Lindsey JW, Nelson F. Tumefactive demyelination: Clinical outcomes, lesion evolution and treatments. Mult Scler J - Exp Transl Clin. 2019;5(2):2055217319855755.
17. Salam DHM Al. tumefactive demeyilnation. In: radiopedia.
18. ElBeialy DMA. marburg variant ms. In: radiopedia.
19. Gaillard PF. acute dissiminated encephalomyelitis. In: radiopedia.
20. Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. Curr Opin Neurol [Internet]. 2019;32(3). Available from: https://journals.lww.com/co-neurology/Fulltext/2019/06000/Neuromyelitis_optica_spectrum_disorders__still.11.aspx
21. Freedman MS, Rush CA. Severe, Highly Active, or Aggressive Multiple Sclerosis. Continuum (Minneap Minn). 2016 Jun;22(3):761–84.
22. Jalkh G, Abi Nahed R, Macaron G, Rensel M. Safety of Newer Disease Modifying Therapies in Multiple Sclerosis. Vaccines. 2020 Dec;9(1).
23. Gross RH, Corboy JR. Monitoring, Switching, and Stopping Multiple Sclerosis Disease-Modifying Therapies. Continuum (Minneap Minn). 2019 Jun;25(3):715–35.
24. Kuan TLT, Amini F, Seghayat MS. Feasibility and toxicity of hematopoietic stem cell transplant in multiple sclerosis. Iran J Basic Med Sci. 2017 Jul;20(7):729–38.

Psychiatry

Article Title: Somatic Symptom Disorder.

Author: Abdullah Jabeiti.

Editor: Hala Qaryouti.

Reviewer: Ahda Jbarah.

Keywords: Somatic, Psychiatry, Somatization.

Introduction

Somatic Symptom Disorder (SSD), previously called Somatoform Disorder, is a condition characterized by the presence of one or more somatic symptoms (e.g. fatigue, abdominal pain, headache, etc.) that are unexplained by an organic disease process. Somatic Symptom Disorder Symptoms are accompanied by excessive thoughts, feelings, and/or behaviors related to the symptom(s), causing the patient significant distress alongside social, individual, and/or occupational impairment. This diagnosis falls under the wider category of "Somatic Symptom Disorder and Related Disorders" in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).

Brief History of Diagnosis

Somatic Symptom Disorder Originally referred to as **Briquet's syndrome**, which was first described by the physician Paul Briquet in 1859. He described these patients as having a constant feeling and worry of being sick, along with a multitude of symptoms attributable to several different organ systems. Even after countless consultations, investigations, and procedures that showed no proof of illness, the idea of illness and worry about the symptoms persists (1).

Epidemiology

SSD can occur in childhood, adolescence, or adulthood (2)(3). Prevalence is estimated to be around 5-7% of the general population, with a higher predominance among females evidenced by a female-to-male ratio of 10:1 (2)(3). Along with females, younger children tend to have a higher risk for somatization (4)(5). Furthermore, in recent light of the COVID-19 pandemic, it has been found that individuals affected by the pandemic may have a high epidemiological burden of SSD, among many other mental health problems (6). Prevalence is also higher among patient groups with functional somatic syndromes, including fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome (7).

Etiology

Somatization can be a normative part of coping and development. It only becomes a disorder when it impairs several aspects of the patient's daily life and meets specific criteria described in the DSM-5 (8). In terms of symptoms, there is no well-defined structural organic pathology that is explanatory for the symptoms experienced by the patient. And even if an organic pathology is present, the extent of symptoms and suffering they cause is still not explained, and treatment or remission of the underlying pathology does not alleviate the symptoms. This is partly the reason why the symptoms are referred to be functional in nature (9)(10).

Although the disorder is suggested to stem from a heightened awareness of multiple bodily sensations mixed with the inclination to interpret these sensations as attributable to medical illness, the exact etiology still remains unclear (2). A study demonstrating the increased prevalence of both SSD and antisocial personality disorder among family members led to the belief that there might be genetic components influencing the development of both diseases (11). Another study with monozygotic and dizygotic twins showed evidence that genetic factors contributed to somatic symptoms by 7-21%, whereas the remaining was attributable to environmental factors (12).

Pathophysiology

SSD's pathophysiology remains enigmatic. However, autonomic arousal from endogenous noradrenergic compounds has been implicated in causing gastric hypermotility, tachycardia, increased arousal, muscle tension, and pain associated with muscular hyperactivity in SSD patients (12).

Risk Factors

As far as risk factors are involved, studies have proved childhood neglect, sexual abuse, a chaotic lifestyle, and history of alcohol and substance abuse as risk factors (2). Psychosocial stressors have also been implicated and include, but are not limited to, unemployment and impaired occupational functioning (3). Patients suffering from SSD also have higher rates of having a concurrent personality disorder, including histrionic, narcissistic, paranoid, borderline, antisocial, and avoidant personality disorders (13–16).

Clinical Presentation

Patients with SSD more commonly present to medical and primary care settings, rather than a psychiatric healthcare setting (8), with one or more somatic symptoms (most commonly pain) that cause them distress or impaired functioning. Patients also often have a rich history of futile medical visits, investigations and interventions with multiple physicians. They also demonstrate significant worry over the symptom(s) as excessive thoughts, feelings and/or behaviors revolving around their symptom(s) despite enough reassurance of not having any organic disease (8). In Children, the most common presenting symptoms are abdominal pain and headache, followed by back pain, limb pain, other neurologic symptoms and fatigue (4)(5)(8)(17)(18).

Diagnosis

Patients should undergo a thorough history with a full review of systems and a comprehensive physical exam to evaluate for physical causes of somatic complaints before considering the diagnosis of SSD. Since SSD is often comorbid with other psychiatric diseases, a mental status examination should be performed (19). Diagnostic criteria set by the DSM-5 are as follows (8):

1. One or more somatic symptoms inducing distress, disturbance, and impairment of daily life.
2. Excessive thinking, feelings, and/or behaviors related to the symptoms or the associated health concerns which manifest as one or more of the following:
    - persistent thoughts disproportionate to the seriousness of symptoms
    - persistent anxiety about health or symptoms
    - excessive time and energy allocated to these symptoms
3. Symptoms typically lasting for more than 6 months, even if a somatic symptom is not continuously present.

SSD specifiers include (8):

- If the SSD presents with pain (previously known as pain disorder)
- If it is persistent. To be considered persistent, the SSD course must have severe symptoms with significant impairment and a duration of more than 6 months
- If SSD is mild, moderate, or severe:
    - Mild: only one of the criterion B symptoms is met
    - Moderate: two or more of criterion B symptoms are met
    - Severe: two or more of criterion B symptoms are met, as well as multiple somatic complaints (or one very severe somatic symptom)

Treatment

The main aim of treatment should be focused on building trust between the physician and the patient. Symptoms seem to improve when patients feel understood by their physicians or when they are satisfied with the explanation provided for their symptoms (20). For this reason, good physician-patient communication and relationship are often more important for the health of the patient than finding a somatic explanation (21). Thus, the primary care provider for such patients should schedule regular visits to reinforce the idea that the experienced symptoms are not indicative of a life-threatening or disabling medical condition and to avoid further unnecessary interventions (22).

Conversely, SSD can be managed through psychotherapy by cognitive-behavioral therapy (CBT) or through pharmacologic approaches. Studies have shown that CBT is associated with significant improvement in functioning reported by patients and somatic symptoms, as well as a decrease in healthcare costs (23), and a reduction in depressive symptoms (24).

Any pharmacologic approach should be limited. However, antidepressants (SSRIs and SNRIs) can be initiated to treat relevant psychiatric comorbidities such as anxiety, depressive symptoms, and OCD since SSRIs and SNRIs have shown efficacy in SSD improvement compared to a placebo (25).

Prognosis

Longitudinal studies show that almost 90% of SSD cases last longer than 5 years (26)(27). Around 50-75% of patients show improvement, whereas 10-30% deteriorate (28).

References

1. Biondi M, Pasquini M, Picardi A. Dimensional Psychopathology. 2018. 82–125 p.
2. Kurlansik SL, Maffei MS. Somatic Symptom Disorder. Am Fam Physician. 2016 Jan;93(1):49–54.
3. Harris AM, Orav EJ, Bates DW, Barsky AJ. Somatization increases disability independent of comorbidity. J Gen Intern Med. 2009 Feb;24(2):155–61.
4. Ibeziako P, Bujoreanu S. Approach to psychosomatic illness in adolescents. Curr Opin Pediatr. 2011 Aug;23(4):384–9.
5. Bujoreanu S, Randall E, Thomson K, Ibeziako P. Characteristics of medically hospitalized pediatric patients with somatoform diagnoses. Hosp Pediatr. 2014 Sep;4(5):283–90.
6. Hossain MM, Tasnim S, Sultana A, Faizah F, Mazumder H, Zou L, et al. Epidemiology of mental health problems in COVID-19: a review. F1000Research. 2020;9:636.
7. Häuser W, Bialas P, Welsch K, Wolfe F. Construct validity and clinical utility of current research criteria of DSM-5 somatic symptom disorder diagnosis in patients with fibromyalgia syndrome. J Psychosom Res. 2015 Jun;78(6):546–52.
8. American Psychiatric Association (2013). Somatic Symptom and Related Disorders. In: Diagnostic and Statistical Manual of Mental Disorders DSM. (5th ed.).
9. Eikelboom EM, Tak LM, Roest AM, Rosmalen JGM. A systematic review and meta-analysis of the percentage of revised diagnoses in functional somatic symptoms. J Psychosom Res. 2016 Sep;88:60–7.
10. Stone J, Carson A, Duncan R, Coleman R, Roberts R, Warlow C, et al. Symptoms “unexplained by organic disease” in 1144 new neurology out-patients: how often does the diagnosis change at follow-up? Brain. 2009 Oct;132(Pt 10):2878–88.
11. Lilienfeld SO. The association between Antisocial Personality and Somatization Disorders: A review and integration of theoretical models. Clin Psychol Rev [Internet]. 1992;12(6):641–62. Available from: http://www.sciencedirect.com/science/article/pii/027273589290136V

12. Kato K, Sullivan PF, Pedersen NL. Latent class analysis of functional somatic symptoms in a population-based sample of twins. J Psychosom Res. 2010 May;68(5):447–53.
13. Stern J, Murphy M, Bass C. Personality disorders in patients with somatisation disorder. A controlled study. Br J Psychiatry. 1993 Dec;163:785–9.
14. Noyes RJ, Langbehn DR, Happel RL, Stout LR, Muller BA, Longley SL. Personality dysfunction among somatizing patients. Psychosomatics. 2001;42(4):320–9.
15. Bornstein RF, Gold SH. Comorbidity of Personality Disorders and Somatization Disorder: A Meta-analytic Review. J Psychopathol Behav Assess [Internet]. 2007;30(2):154. Available from: https://doi.org/10.1007/s10862-007-9052-2
16. Garcia-Campayo J, Alda M, Sobradiel N, Olivan B, Pascual A. Personality disorders in somatization disorder patients: a controlled study in Spain. J Psychosom Res. 2007 Jun;62(6):675–80.
17. Kozlowska K. Good Children with Conversion Disorder: Breaking the Silence. Clin Child Psychol Psychiatry [Internet]. 2003 Jan 1;8(1):73–90. Available from: https://doi.org/10.1177/1359104503008001008
18. Campo J V, Fritsch SL. Somatization in children and adolescents. J Am Acad Child Adolesc Psychiatry. 1994;33(9):1223–35.
19. Tylee A, Gandhi P. The importance of somatic symptoms in depression in primary care. Prim Care Companion J Clin Psychiatry. 2005;7(4):167–76.
20. Downes-Grainger E, Morriss R, Gask L, Faragher B. Clinical factors associated with short-term changes in outcome of patients with somatized mental disorder in primary care. Psychol Med. 1998 May;28(3):703–11.
21. Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician-patient interaction. Ann Intern Med. 1995 Jan;122(2):107–12.
22. den Boeft M, Claassen-van Dessel N, van der Wouden JC. How should we manage adults with persistent unexplained physical symptoms? BMJ. 2017 Feb;356:j268.
23. Allen LA, Woolfolk RL, Escobar JI, Gara MA, Hamer RM. Cognitive-behavioral therapy for somatization disorder: a randomized controlled trial. Arch Intern Med. 2006 Jul;166(14):1512–8.
24. Beltman MW, Voshaar RCO, Speckens AE. Cognitive-behavioural therapy for depression in people with a somatic disease: meta-analysis of randomised controlled trials. Br J Psychiatry. 2010 Jul;197(1):11–9.
25. Kleinstäuber M, Witthöft M, Steffanowski A, van Marwijk H, Hiller W, Lambert MJ. Pharmacological interventions for somatoform disorders in adults. Cochrane database Syst Rev. 2014 Nov;(11):CD010628.
26. Rief W, Rojas G. Stability of somatoform symptoms--implications for classification. Psychosom Med. 2007 Dec;69(9):864–9.
27. Jackson JL, Kroenke K. Prevalence, impact, and prognosis of multisomatoform disorder in primary care: a 5-year follow-up study. Psychosom Med. 2008 May;70(4):430–4.
28. olde Hartman TC, Borghuis MS, Lucassen PLBJ, van de Laar FA, Speckens AE, van Weel C. Medically unexplained symptoms, somatisation disorder and hypochondriasis: course and prognosis. A systematic review. J Psychosom Res. 2009 May;66(5):363–77.

Article topic: Specific Phobia.

Author: Norah Nawaf Elenizi.

Editor: Aroob Awwad.

Reviewers: Hala Qaryouti, Ahda Jbarah, Hassan Abushukair

Keywords: Specific Phobia, Anxiety disorder, Psychiatry, Mental disorder.

Introduction

A specific phobia is an excessive, constant fear of a certain object, situation, activity, or person. Although individuals with specific phobias know that there is no real threat or danger to them, they try hard to avoid triggers of their phobia and cannot stop their irrational fear (1). An example of the characteristic exaggerated fear in specific phobias is the terror of falling that occurs in about 50% of the elderly who have recently fallen (2). In 10–30% of cases, phobias can persist for many years and lead to the onset of other mental disorders such as anxiety, mood, and substance use disorders (3).

Specific phobias can be divided according to the stimulus causing fear into the following subcategories: (4)

- Animals such as spiders, insects and dogs.
- Natural environment such as heights, storms and water.
- Blood injection injury such as with needles and invasive medical procedures.
- Situational fear in airplanes, elevators and enclosed spaces.
- Other types of phobias with characteristics that are not well-suited into any of the previous four categories.

Epidemiology

About 5% to 10% of the US population is affected with specific phobia (4). Previous studies showed that the lifetime prevalence of specific phobias worldwide ranges from 3% to 15%, with animal phobia and fear of heights being the most common (5).

Etiology

A specific cause of specific phobias is not identified. Some theories suggest that it may develop as a result of an event linked with an emotional stressor such as a car accident where the event of driving is paired with an emotion which is fear. As a result, a person may develop an emotional connection that links driving with fear which can grow to become a driving phobia. The person may not meet the criteria for a panic attack, but

their specific phobia can manifest as generalized fear. Another method of linking events is through modeling where a person notes a reaction to a stimulus in another person and internalizes other people's fears or warnings about the dangers of a specific object or situation so that they become his fears as well (2)(6).

Signs and symptoms

Common signs and symptoms seen in specific phobia as a result of exaggerated fear or anxiety may include (4):

- Feeling nauseous, dizzy, or fainting when facing the stimulus.
- Difficulty breathing and chest tightness.
- Tachycardia and palpitations.

Risk Factors

Risk factors for specific phobias are not well-studied yet (3). However, female sex is the most important demographic risk factor for specific phobias as shown by a study investigating the lifetime prevalence of specific mental disorders across New Haven, Conn, Baltimore, and St Louis, where the lifetime prevalence of specific phobias was higher in female participants than in male participants in all the previously mentioned locations (7). The association between the prevalence of specific fears and each of education, marital status, and residence was calculated in another study sample. Results showed lower educational status as a risk factor, with an association of 40% in people who have less than high school education versus 29% in college graduates. Regarding marital status, divorced or separated people scored 38%, while widowed scored an association of 42% and married people 35% (3). Both family and twin studies showed good evidence of hereditary contribution to social phobia combined with genetic and environmental factors (8).

DSM-5 Diagnostic Criteria

1. Specific fear or anxiety from a specific object or situation.
2. The specific object or situation always stimulates fear or anxiety.
3. The specific object or situation is deliberately avoided.
4. Fear or anxiety exceeds the actual danger faced by the specific object or situation.
5. Fear, anxiety, or avoidance is continuous and lasts for 6 months or more.
6. Fear, anxiety, or avoidance causes remarkable distress in social and occupational functioning in general.
7. The upset is not better explained by symptoms of another mental disorder.

Diagnostic Features and Specifiers

A key feature of specific phobias disorder, according to the DSM-5 criteria, is that fear or anxiety is restricted to the presence of a particular situation or object called the phobic stimulus. A person can fear more than one phobic stimulus. An average patient has three specific phobias, according to DSM-5, and 75% of patients fear more than one situation or object. In such situations, a diagnosis of multiple specific phobias would be given, each with its own code to show the phobic stimulus.

However, to diagnose a specific phobia, the physician must ensure that patient's reaction differs from normal transient fears commonly seen in the population. To achieve the criteria for a diagnosis, the fear or anxiety have to be intense or severe. Another feature is that fear or anxiety is triggered nearly every time the individual faces the phobic stimulus, so occasional anxiety upon being faced with a certain situation or object would not be sufficient to diagnose a subject with specific phobia.

This fear or anxiety must last for at least 6 months to permit a correct diagnosis, which aids in differentiating the disorder from transient fears common in the population, especially in children. However, the duration standard should be used with some degree of flexibility among patients.

Treatment

According to current treatment guidelines both psychotherapy and pharmacotherapy can be utilized. The treatment of choice in psychotherapy is cognitive behavioral therapy (CBT), while for pharmacological treatment antidepressants and pregabalin are the drugs of choice (9).

Behavioral therapy is first line treatment in most cases and has a positive outcome. However, the period of desensitization of the patient's fears can take a long time. To achieve the benefits, patients must adhere to a behavioral therapy schedule to deal with the specific problems and objectives.

Alternatives for dealing with the patient's feelings can include virtual therapy in which the patient is exposed to or interacts with the phobic object or situation on the computer screen (4). In a study conducted by Watson et al., a group of ten adult patients with known long-standing specific phobias were exposed to their phobic stimuli continuously in fantasy and reality as a method of treatment. After two to three sessions, all patients have shown significant improvement (10).

References

1. Garcia R. Neurobiology of fear and specific phobias. Learn Mem. 2017 Sep;24(9):462–71.
2. Pary R, Sarai SK, Micchelli A, Lippmann S. Anxiety Disorders in Older Patients. Prim care companion CNS Disord. 2019 Jan;21(1).

3. Stinson FS, Dawson DA, Patricia Chou S, Smith S, Goldstein RB, June Ruan W, et al. The epidemiology of DSM-IV specific phobia in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med. 2007 Jul;37(7):1047–59.
4. Samra CK, Abdijadid S. Specific Phobia. In Treasure Island (FL); 2020.
5. Eaton WW, Bienvenu OJ MB. Specific Phobias. Lancet psychiatry. 2018;
6. Oing T, Prescott J. Implementations of Virtual Reality for Anxiety-Related Disorders: Systematic Review. JMIR serious games. 2018 Nov;6(4):e10965.
7. Robins LN, Helzer JE, Weissman MM, Orvaschel H, Gruenberg E, Burke JDJ, et al. Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry. 1984 Oct;41(10):949–58.
8. Tillfors M. Why do some individuals develop social phobia? A review with emphasis on the neurobiological influences. Nord J Psychiatry. 2004;58(4):267–76.
9. Zwanzger P. [Pharmacotherapy of Anxiety Disorders]. Fortschr Neurol Psychiatr. 2016 May;84(5):306–14.
10. Watson JP, Gaind R, Marks IM. Prolonged exposure: a rapid treatment for phobias. Br Med J. 1971 Jan;1(5739):13–5.

Article topic: Personality Disorders Cluster A.

Author: Hala Qaryouti.

Editor: Aroob Awwad.

Reviewer: Ahda Jbarah, Hassan Abushukair.

Keywords: Personality Disorders, Cluster A, Psychiatry, Mental disorder.

Overview

Personality is a term derived from Greek word persona, originally used to describe the mask worn by theater players. With time, the term evolved to describe the person's hidden inner psychological qualities. Today, personality is seen as a complex, not easily altered pattern of fixed, nonconscious psychological characteristics expressed automatically in all aspects of daily life to account for the individual's behavior, pattern of perception, feeling, thinking and coping (1).

Although there is no unclouded differentiator between normal and pathological personality traits, the DSM-5 criteria summarize a personality disorder (PD) as a pervasive, inflexible and enduring behavioral pattern that deviates markedly from expectations of the individual's culture. This pattern manifests in at least two of the individual's cognition, affect, interpersonal functioning and impulse control. All personality disorders have an onset in adolescence or early adulthood, and although stable over time, they lead to distress in several aspects of daily functioning. The effect of any other mental disorders (i.e. psychotic spectrum of disease, depressive and anxiety disorders, and PTSD) as well as medical disorders and substance abuse should be excluded before making the diagnosis of a PD (2).

DSM-5 Personality disorders are grouped into three clusters (A, B, C). Paranoid, schizoid and schizotypal personality disorders are included in cluster A, while cluster B includes antisocial, borderline, histrionic, and narcissistic personality disorders. Finally, avoidant, dependent, and obsessive-compulsive personality disorders fall under the umbrella of Cluster C.

Epidemiology

A study has shown that around 12% of people in a general population have a personality disorder (PD) (3). Data from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions estimated that approximately 14.8% of US adults have at least one personality disorder (4), while the WHO has estimated the prevalence of having any

personality disorder to be 6.1% in total, divided among the 3 clusters (A, B, and C) as 3.6%, 1.5%, and 2.7%, respectively (5).

Risk factors

They can differ depending on the personality disorder, but in general, all PDs share the following risk factors:

1. Young age (adolescence to early adulthood).
2. Male sex.
3. Being unmarried.
4. Lower socioeconomic and education levels (6).

Etiology

The precise etiology of personality disorders is not clearly understood and can differ depending on the disorder. Nevertheless, several hypotheses have been suggested. For example, some psychoanalysts attribute these disturbances to failure of proper psychosexual development while others suggest that childhood trauma is a cause. This becomes especially apparent in patients with borderline and antisocial disorders who have intimacy and trust deficits co-related with childhood abuse and trauma. Cultural factors may also play a pivotal role in the development of personality disorders (7).

More recently, researchers have found genetic correlations in schizotypal, borderline and antisocial PD. Genes of interest under investigation are serotonin (5-HT), dopamine (DA), and norepinephrine (5).

Cluster A Personality Disorders

Patients are described as odd, peculiar and withdrawn. They usually utilize defense mechanisms such as projection, magical thinking and intellectualization. All cluster A disorders have a familial association with psychotic disorders.

1. Paranoid Personality Disorder (PPD)

Prevalence

PPD is a disorder characterized by constant suspicion of others. It is a personality disorder which hasn't had its fair share of research mainly due to the paranoia trait in patients, creating obstacles in recruiting and keeping them in a study (8). However, several studies show calculated prevalence, such as the US Epidemiological Survey on

Alcohol and Related Conditions, which showed PPD as the second most prevalent PD with 4.4% out of the total of 14.8% of US adults with personality disorders (9). Another study, conducted by Zimmerman and colleagues, has shown that 4.2% of general psychiatric outpatients meet criteria for PPD, 0.7% of whom have PPD as the only personality disorder (10).

Risk Factors

In addition to the risk factors in common to all PDs mentioned above, negative childhood experiences whether physical, sexual, or emotional abuse correlate to adult-onset PPD more than any other PD (11). However, PPD in late adolescence has only been associated with previous physical abuse (12). Demographic risk factors include a Black, Native-American or Hispanic ethnicity as evidenced by Connolly et. al in a sample of clients at a homeless drop-in center where PPD was the most common personality disorder (13).

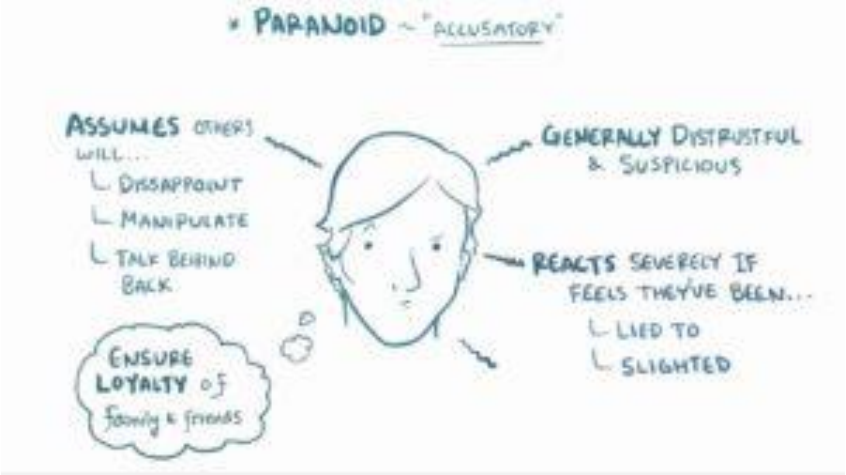
DSM-5 Diagnostic Criteria (2)

To diagnose a patient with PPD, like all personality disorders, the change must start by early adulthood where the following criteria are met:

A. The patient is described as someone constantly suspicious of others and will display four (or more) of the following:

1. Unjustified suspicion of others.
2. Preoccupation with unjustified doubts about whether surrounding people are trustworthy.
3. Reluctance to confide in others due to unnecessary fear of information being used for blackmail.
4. Interpretation of benign remarks as threats with hidden messages.
5. Unforgiving and bears grudges.
6. Angrily counterattacks a perceived attack on character or reputation, not clear to others.
7. Unjustified suspicions of spousal/partner infidelity.

B. All criteria mentioned must be present in the patient's baseline character and not only during the course of schizophrenia, bipolar disorder or depressive disorder with psychotic features.(46)



Although the diagnostic criteria may seem clear-cut, PPD does not clinically present as an isolated PD as almost 75% of cases are accompanied by a comorbid personality disorder, (14) of which avoidant and borderline PD are the most common followed by narcissistic PD (15). Other frequent comorbidities are substance abuse (16) and panic disorder (17).

Treatment

There are no FDA-approved medications for PPD, and systematic data is lacking regarding CBT, although some case studies support its potential effectiveness (18). However, psychiatrists must tread with caution regarding these positive results because PPD still remains one of the strongest predictors of aggressive behavior (19), treatment failure and dropout (20)(21).

Prognosis

Generally, cluster A patients, PPD patients in specific, have a worse prognosis than PD patients of clusters B and C (20). In addition, the long-term prognosis of PPD is not very positive because although its traits can decline by 46% from adolescence to early adulthood (22), it remains one of the three personality disorders most strongly associated with reduction in quality of life (23)(9) and decreased functioning, as measured by the GAF Scale (24), making patients more prone to depression despite intensive psychiatric treatment (20).

2. Schizoid Personality Disorder (ScPD)

Prevalence

ScPD is characterized by asociality and preference of being alone. Although it has been discovered long enough to be listed in all editions of DSM, ScPD is the least common of the cluster A disorders, with studies suggesting that this disorder has a prevalence of less than 1% (8), and no significant difference in frequency between males and females (9). Other studies estimated the prevalence of ScPD as a sole PD among psychiatric patients to be 0.3% (25), while population-based estimates found a 1.7% prevalence of ScPD in Oslo, Norway (26) and a 0.8% prevalence in the United Kingdom (27).

Risk Factors

Major depressive disorder among children and adolescents is the strongest predictor of adult ScPD, and relates to it more than any other adult personality disorder (16).

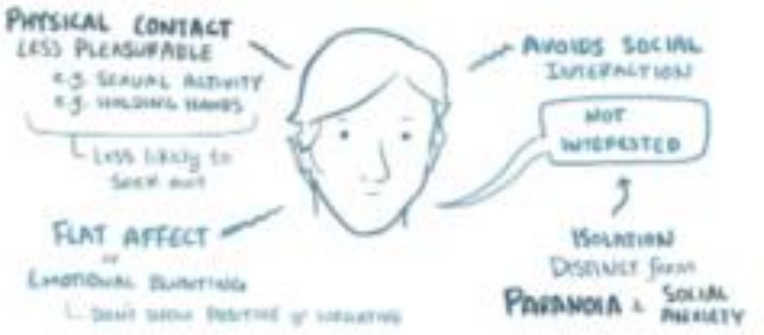
On the other end, ScPD itself is a risk factor for developing other diseases. ScPD, as well as PPD, were found to be associated with dysthymia, mania, panic disorder with agoraphobia, social phobia and generalized anxiety disorder in a population-based study done by Grant et al. (28). ScPD has also been correlated with violent behavior (29), and even organic causes such as arthritis (30), obesity (31) and coronary artery disease, in two separate cohorts (32), (33). Finally, ScPD was found to be the second most common PD in patients with kleptomania. (9).

DSM-5 Diagnostic Criteria (2)

A. An omnipresent pattern of asociality and anhedonia in interpersonal settings, cognitive or perceptual distortions, and eccentric attitude starting early adulthood, manifested by four (or more) of the following:

1. Patient neither desires nor enjoys close relationships, including being part of a family.
2. Prefers solitary activities.
3. Has little, if any, interest in having sexual experiences.
4. Detached, emotionally cold with flat affect.
5. Indifferent to praise and criticism.
6. Has no close friends.
7. Takes pleasure in few (if any) activities.

B. As with PPD, to diagnose a patient with ScPD, their behavioral traits should not occur exclusively during the course of other mental disorders such as schizophrenia, bipolar disorder, depressive disorder with psychotic features, or autism spectrum disorder, and is not caused by any medication side effects.



(46)

It is uncommon for a schizoid personality disorder patient to present willingly on their own unless prompted by family members or presenting for a co-occurring disorder. This is attributed to the egosyntonic nature of personality disorders in general, which makes patients view other people as the problem instead acknowledging their own behavioral flaws (4).

Treatment

There is no approved modality for the management and treatment of schizoid personality disorder. However, some studies suggest that psychotherapy can help improve the secluded nature of patients with the clinician's help to considerately direct the patients to their behavioral abnormalities and encourage them to implement a new healthier behavioral pattern. Pharmacotherapy can be of use for co-morbid disease states, such as SSRIs for depression (34).

Prognosis

In a 2-year follow-up study of personality disorder symptoms in older adolescent psychiatric outpatients, ScPD was the most stable over time (35). Nonetheless, it has been found to cause considerable reduction in quality of life (23), as well as emotional disability (9).

3. Schizotypal Personality Disorder (SPD)

Prevalence

SPD is characterized by patients' eccentric beliefs and is the closest PD to schizophrenia. Community studies report rates from 0.6% in Norwegian samples to 4.6% in U.S. samples. The prevalence of schizotypal personality disorder in clinical populations is

0%-1.9%, with a higher estimated prevalence of 3.9% in the general population as found in the National Epidemiologic Survey on Alcohol and Related Conditions (4). A twin study also found that positive or psychotic-like symptoms in SPD were independently heritable from the negative or deficit symptoms (3).

Risk Factors

Genetic and physiological risk factors are considered since schizotypal personality disorder shows a familial pattern, especially that they are more prevalent among the first-degree relatives of individuals with schizophrenia than among the general population (2).

DSM-5 Diagnostic Criteria (2)

A. SPD patients will have a sustained pattern of social and interpersonal deficits exhibited as discomfort and inability to form intimate relationships, cognitive or perceptual distortions, and an eccentric behavior indicated by five (or more) of the following:

1. Ideas of reference: misinterpretation of normal quotidian incidents done by the patient (should be differentiated from delusions of reference, where the whole incident is imagined by the patient and is not real.)
2. Odd beliefs or magical thinking inconsistent with subcultural norms and affecting behavior. They can include superstition, belief in clairvoyance (having supernatural powers), telepathy, or “sixth sense” in adults. In children and adolescents, bizarre fantasies or preoccupations may be seen.
3. Unusual perceptual experiences such as bodily illusions.
4. Odd thinking and speech. Speech can be unusually phrased and is often vague, but without actual derailment or incoherence.
5. Suspicion or paranoid ideation.
6. Inappropriate or constricted affect.
7. Odd or peculiar behavior or appearance.
8. Lacking close friends and confidants other than first-degree relatives.
9. Excess social anxiety that does not become better with familiarity.

B. As with other personality disorders, the odd behavior must be present as the patient’s baseline and not only during the course of schizophrenia, a bipolar disorder or depressive disorder with psychotic features, another psychotic disorder, or autism spectrum disorder to diagnose SPD.

(46)

Imaging Abnormalities

Despite the fact that patients with SPD are spared the chronic psychosis of schizophrenia, both disorders are closely related. This is shown by similar neuroimaging and neurochemical evidence, treatment and outcome characteristics (36). Like schizophrenic patients, SPD patients show focal cognitive impairment involving working memory, verbal learning, as well as sustained attention deficits and reductions in temporal lobe volume, but without the frontal volume reductions found in some studies of schizophrenic patients (36).

On neuroimaging, ventricular enlargement has been observed in samples of clinically identified SPD patients (37), relatives of schizophrenic patients (38) and schizotypal volunteers. Furthermore, abnormalities such as reduced volume in temporal lobe and hippocampus have been found in schizotypal patients, as have been in schizophrenic patients (39). SPD patients also perform poorly in tests of executive function sensitive to frontal lobe damage, such as the Wisconsin Card Sort Test (WCST) (40).

Treatment

Several studies suggest that treatment with neuroleptic medications can reduce some of the symptoms of schizotypal personality disorder, particularly the psychotic-like symptoms and social anxiety associated with the disorder (41). Studies with agents such as thiothixene (41), haloperidol (42), and risperidone (43) may be helpful in alleviating the symptomatic distress of schizotypal personality disorder.

Prognosis

A study conducted by Henriques-Calado and Duarte-Silva in 2020 showed that a future diagnosis of Alzheimer's disease can be predicted by, but is not limited to, SPD in females (44). Also, OCD comorbid with SPD is associated with poorer treatment outcome (45).

References

1. Millon T. Invited Essay What Is a Personality Disorder? J Pers Disord. 2016;30(3):289–306.
2. American Psychiatric Association 2013. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS FIFTH EDITION DSM-5. In.
3. Skjernov M, Bach B, Fink P, Fallon B, Soegaard U, Simonsen E. DSM-5 Personality Disorders and Traits in Patients with Severe Health Anxiety. J Nerv Ment Dis [Internet]. 2020 Feb 1 [cited 2021 Jan 6];208(2):108–17. Available from: https://pubmed.ncbi.nlm.nih.gov/31821216/
4. Maniacci MP, Sperry L. Neurocognitive disorders. Psychopathology and Psychotherapy: DSM-5 Diagnosis, Case Conceptualization, and Treatment. 2014. 335–355 p.
5. Ma G, Fan H, Shen C, Wang W. Genetic and Neuroimaging Features of Personality Disorders: State of the Art [Internet]. Vol. 32, Neuroscience Bulletin. Science Press; 2016 [cited 2021 Jan 4]. p. 286–306. Available from: /pmc/articles/PMC5563771/?report=abstract
6. Zhang TT, Huang YQ, Liu ZR, Chen HG. Distribution and risk factors of disability attributed to personality disorders: A national cross-sectional survey in China. Chin Med J (Engl) [Internet]. 2016 Aug 5 [cited 2021 Jan 4];129(15):1765–71. Available from: /pmc/articles/PMC4976561/?report=abstract
7. Fariba K, Gupta V, Kass E. Personality Disorder. 2020 Nov 20 [cited 2021 Jan 4]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK556058/
8. Esterberg ML, Goulding SM, Walker EF. Cluster A Personality Disorders: Schizotypal, Schizoid and Paranoid Personality Disorders in Childhood and Adolescence. J Psychopathol Behav Assess. 2010 Dec;32(4):515–28.
9. Grant BF, Hasin DS, Stinson FS, Dawson DA, Chou SP, Ruan WJ, et al. Prevalence, correlates, and disability of personality disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry. 2004 Jul;65(7):948–58.
10. Zimmerman M, Chelminski I, Young D. The frequency of personality disorders in psychiatric patients. Psychiatr Clin North Am. 2008 Sep;31(3):405–20, vi.
11. Bierer LM, Yehuda R, Schmeidler J, Mitropoulou V, New AS, Silverman JM, et al. Abuse and neglect in childhood: relationship to personality disorder diagnoses. CNS Spectr. 2003 Oct;8(10):737–54.
12. Golier JA, Yehuda R, Bierer LM, Mitropoulou V, New AS, Schmeidler J, et al. The relationship of borderline personality disorder to posttraumatic stress disorder and traumatic events. Am J Psychiatry. 2003 Nov;160(11):2018–24.
13. Connolly AJ, Cobb-Richardson P, Ball SA. Personality disorders in homeless drop-in center clients. J Pers Disord. 2008 Dec;22(6):573–88.
14. Gore WL, Widiger TA. The DSM-5 dimensional trait model and five-factor models of general personality. J Abnorm Psychol. 2013 Aug;122(3):816–21.
15. Morey LC. Personality disorders in DSM-III and DSM-III-R: convergence, coverage, and internal consistency. Am J Psychiatry. 1988 May;145(5):573–7.
16. Ramklint M, von Knorring A-L, von Knorring L, Ekselius L. Child and adolescent psychiatric disorders predicting adult personality disorder: a follow-up study. Nord J Psychiatry. 2003;57(1):23–8.
17. Reich J, Braginsky Y. Paranoid personality traits in a panic disorder population: a pilot study. Compr Psychiatry. 1994;35(4):260–4.
18. Kellett S, Hardy G. Treatment of paranoid personality disorder with cognitive analytic therapy: a mixed methods single case experimental design. Clin Psychol Psychother. 2014;21(5):452–64.
19. Berman ME, Fallon AE, Coccaro EF. The relationship between personality psychopathology and aggressive behavior in research volunteers. J Abnorm Psychol. 1998 Nov;107(4):651–8.
20. Karterud S, Pedersen G, Bjordal E, Brabrand J, Friis S, Haaseth O, et al. Day treatment of patients with personality disorders: experiences from a Norwegian treatment research network. J Pers Disord. 2003 Jun;17(3):243–62.
21. Kvarstein EH, Karterud S. Large variations of global functioning over five years in treated patients with personality traits and disorders. J Pers Disord. 2012 Apr;26(2):141–61.
22. Johnson JG, Cohen P, Kasen S, Skodol AE, Hamagami F, Brook JS. Age-related change in personality disorder trait levels between early adolescence and adulthood: a community-based longitudinal investigation. Acta Psychiatr Scand. 2000 Oct;102(4):265–75.
23. Cramer V, Torgersen S, Kringlen E. Personality disorders and quality of life. A population study. Compr Psychiatry. 2006;47(3):178–84.
24. Crawford TN, Cohen P, Johnson JG, Kasen S, First MB, Gordon K, et al. Self-reported personality disorder in the children in the community sample: convergent and prospective validity in late adolescence and adulthood. J Pers Disord. 2005 Feb;19(1):30–52.

25. Zimmerman M, Rothschild L, Chelminski I. The prevalence of DSM-IV personality disorders in psychiatric outpatients. Am J Psychiatry. 2005 Oct;162(10):1911–8.
26. Torgersen S, Kringlen E, Cramer V. The prevalence of personality disorders in a community sample. Arch Gen Psychiatry. 2001 Jun;58(6):590–6.
27. Coid J, Yang M, Tyrer P, Roberts A, Ullrich S. Prevalence and correlates of personality disorder in Great Britain. Br J Psychiatry. 2006 May;188:423–31.
28. Grant BF, Hasin DS, Stinson FS, Dawson DA, Patricia Chou S, June Ruan W, et al. Co-occurrence of 12-month mood and anxiety disorders and personality disorders in the US: results from the national epidemiologic survey on alcohol and related conditions. J Psychiatr Res. 2005 Jan;39(1):1–9.
29. Pulay AJ, Dawson DA, Hasin DS, Goldstein RB, Ruan WJ, Pickering RP, et al. Violent behavior and DSM-IV psychiatric disorders: results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry. 2008 Jan;69(1):12–22.
30. McWilliams LA, Clara IP, Murphy PDJ, Cox BJ, Sareen J. Associations between arthritis and a broad range of psychiatric disorders: findings from a nationally representative sample. J pain. 2008 Jan;9(1):37–44.
31. Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosom Med. 2008 Apr;70(3):288–97.
32. Moran P, Stewart R, Brugha T, Bebbington P, Bhugra D, Jenkins R, et al. Personality disorder and cardiovascular disease: results from a national household survey. J Clin Psychiatry. 2007 Jan;68(1):69–74.
33. Pietrzak RH, Wagner JA, Petry NM. DSM-IV personality disorders and coronary heart disease in older adults: results from The National Epidemiologic Survey on Alcohol And Related Conditions. J Gerontol B Psychol Sci Soc Sci. 2007 Sep;62(5):P295-9.
34. Ward RK. Assessment and management of personality disorders. Am Fam Physician. 2004 Oct;70(8):1505–12.
35. Chanen AM, Jackson HJ, McGorry PD, Allot KA, Clarkson V, Yuen HP. Two-year stability of personality disorder in older adolescent outpatients. J Pers Disord. 2004 Dec;18(6):526–41.
36. Kirrane RM, Siever LJ. New perspectives on schizotypal personality disorder. Curr Psychiatry Rep. 2000;2(1):62–6.
37. Siever LJ, Rotter M, Losonczy M, Guo SL, Mitropoulou V, Trestman R, et al. Lateral ventricular enlargement in schizotypal personality disorder. Psychiatry Res. 1995 Jul;57(2):109–18.
38. Silverman JM, Smith CJ, Guo SL, Mohs RC, Siever LJ, Davis KL. Lateral ventricular enlargement in schizophrenic probands and their siblings with schizophrenia-related disorders. Biol Psychiatry. 1998 Jan;43(2):97–106.
39. Downhill JEJ, Buchsbaum MS, Hazlett EA, Barth S, Lees Roitman S, Nunn M, et al. Temporal lobe volume determined by magnetic resonance imaging in schizotypal personality disorder and schizophrenia. Schizophr Res. 2001 Mar;48(2–3):187–99.
40. Lenzenweger MF, Korfine L. Perceptual aberrations, schizotypy, and the Wisconsin Card Sorting Test. Schizophr Bull. 1994;20(2):345–57.
41. Goldberg SC, Schulz SC, Schulz PM, Resnick RJ, Hamer RM, Friedel RO. Borderline and schizotypal personality disorders treated with low dose thiothixene vs placebo. Arch Gen Psychiatry. 1986 Jul;43(7):680–6.
42. Hymowitz P, Frances A, Jacobsberg LB, Sickles M, Hoyt R. Neuroleptic treatment of schizotypal personality disorders. Compr Psychiatry. 1986;27(4):267–71.
43. Szigethy EM, Schulz SC. Risperidone in comorbid borderline personality disorder and dysthymia. Vol. 17, Journal of clinical psychopharmacology. United States; 1997. p. 326–7.
44. Henriques-Calado J, Duarte-Silva ME. Personality disorders characterized by anxiety predict Alzheimer's disease in women: A case-control studies. J Gen Psychol. 2020;147(4):414–31.
45. Thiel N, Hertenstein E, Nissen C, Herbst N, Külz AK, Voderholzer U. The effect of personality disorders on treatment outcomes in patients with obsessive-compulsive disorders. J Pers Disord. 2013 Dec;27(6):697–715.
46. Cluster A personality disorders. Osmosis. Available at Osmosis

Article Topic: Social Anxiety Disorder.

Author: Ala' Moh'd Al Barbarawi

Editor: Aroob Awwad Awwad.

Reviwer: Ahda jbarah, Hassan Abushukair.

Keywords: Psychiatry, Social Anxiety, Mental Illness, SAD.

Introduction

Social Anxiety Disorder (SAD), also referred to as social phobia, can be defined briefly as the intense fear of social situations in which the person worries excessively about being scrutinized or inspected closely by others, and fears or has anxiety about one or more social situations where they can be looked over by others. In children, this disorder may be overlooked by parents and mistaken for shyness.

Epidemiology

SAD is considered a common disorder with a current prevalence of 5-10%, and a lifetime prevalence between 8.4 and 15% (1). SAD symptoms usually begin in early adolescence, and typically persist unless treated effectively (1).

Etiology

Different factors that may lead to SAD:

1. Genetic/familial factors: There is considerable evidence that SAD has strong familial links. Children of parents with SAD have significantly increased risk of experiencing the disorder, and parents of children with SAD are also more likely to experience it (2). First degree relatives have 2-6 times greater chance of developing SAD (3).
2. Biological factors: there are still no firm associations between SAD and brain structures, neural pathways, neurotransmitters, biochemistry, or psychophysiological processes (2). However, neurobiological research suggests possible dysfunction in distributed circuits involving the amygdala, insula, hippocampus, and orbital frontal regions of the brain (4), and in serotonin regulation (5). However, these proposals require further research.
3. Temperamental – underlying traits that can be associated with SAD are behavioral inhibition and fear of being negatively evaluated (2). Behavioral

inhibition is the tendency to experience distress or discomfort and to withdraw from unfamiliar situations, people or environments (6).

Risk factors

1. First degree relative with SAD. (3)
2. Temperament (3), defined by the Oxford dictionary as getting easily aggravated, upset, excited or angry.
3. Behavioral inhibition. (6)
4. Negative experiences (7), such as being bullied, rejected by parents or friends, and humiliated publicly. They can also include trauma, family problems and abuse (emotional/physical/mental)
5. Mental health conditions – individuals with SAD are most likely to have these disorders (3):
    - Generalized anxiety disorder
    - Panic disorder
    - Bipolar disorder
    - Major Depressive disorder
    - Body dysmorphic disorder

DSM-5 Diagnostic Criteria

Several criteria must be met to diagnose the presenting patient with SAD. These criteria include (3):

1. Notable fear or anxiety related to one or more social situations where the patient worries about being scrutinized or judged negatively by others. These situations can include social interactions (e.g., having a conversation with a stranger, participating in school activities, meeting unfamiliar people), public performances (singing, acting, giving a speech), being observed (e.g., when eating or drinking)
2. Fear of behaving in a way that can be judged negatively by others; the patient worries about showing symptoms of anxiety, believing that it can cause embarrassment, humility, or rejection.
3. Social situations almost always provoke anxiety.
4. Social situations are either avoided or endured with intense fear or anxiety.
5. Fear or anxiety is out of proportion in comparison to the actual threat created by the social situation.
6. Persistent fear, anxiety, or avoidance, lasting for 6 or more months.
7. The fear or anxiety causes significant distress in different aspects of functioning.
8. Fear, anxiety, or avoidance is not caused by or related to the physiological effects of substance use (e.g., drug abuse or medication) or another medical condition.

9. Fear, anxiety, or avoidance is not better explained or diagnosed by symptoms of another mental disorder (e.g., panic disorder, body dysmorphic disorder, or autism spectrum disorder).
10. The presence of a comorbid medical condition such as obesity, Parkinson's disease, or disfigurement due to burns or injury, is not related to the fear, anxiety, or avoidance or is excessive compared to it.

In children, these observations must be noted in peer settings as well as with adult interactions. Children can express their fear by crying, throwing tantrums, clinging, failing to speak or to interact. Some individuals may not raise their hands or participate in class discussions either.

Treatment

Assessment is the first step of treatment. Individuals with social anxiety disorder tend to have less frequent visits to their primary care physician compared to patients with other mental disorders (8). Moreover, they tend to avoid consulting a physician for psychological problems (9).

To screen for the disorder, clinicians usually ask patients two important questions. The first one is whether they frequently avoid social situations or activities, and the second is whether they feel afraid or embarrassed in social situations. Clinical experience suggests that these questions are useful in screening for SAD, but their sensitivity and specificity are unknown (10).

There are different approaches to treat SAD including psychotherapy, pharmacotherapy, or both (11), (12). The treatment of choice depends on the patient's choice and the clinical judgement (11). A positive or negative response to a previous treatment choice can guide future treatment decisions (13). Pharmacotherapy may be preferred initially for patients who view psychotherapy as a feared situation, at least until anxiety has been reduced and psychotherapy becomes a more acceptable option.

Psychotherapy

There are multiple methods available for psychotherapy, including (13):

1. **Cognitive behavioral therapy (CBT)**

Currently the first-line treatment. The doctor educates the patient about the nature of the disorder by focusing the patient's attention on themselves. The patient is taught mechanisms to use for reducing anxiety and fear in situations where he/she feels threatened. This type of therapy focuses on problematic processing of events and may involve behavioral experiments (e.g.: exposure to social situations) (13).

2. **Short-term psychodynamic therapy**

The therapist informs patients about social anxiety disorder and its treatment. Therapy involves setting goals (13) to uncover the source of feelings and thoughts obscured from patients (14). The therapist gains the patient's trust to ensure honest communication (13), (14). This type of treatment identifies the core of the underlying conflict (e.g., I want to be the center of attention, but fear being humiliated so I do not expose myself to such situations). It can then be related to the conflict within the individual. This method relies on confrontation of inner conflicts, clarifying them (e.g., you might feel this way because of a problem you had previously faced) and interpreting them to establish an encouraging inner dialogue, terminate therapy and prevent relapse (13).

3. **Interpersonal therapy (13)**

Involves reviewing symptoms the patient suffers from and explaining them as part of the disorder. The symptoms are linked to interpersonal problems. The patient is encouraged to express their feelings about relationships. Therapy is focused on the problem identified and is terminated by reviewing progress to help prepare the patient for future challenging situations (13).

4. **Mindfulness-based stress reduction (13)**

Aims at reducing stress and anxiety through providing psychoeducation about stress and meditation techniques. The patient meditates for 30 minutes/day using audiotapes, and 10-15 min/day without audiotapes. Patient is also provided with reading/watching material to practice mindfulness (e.g., books, articles, videos) (13).

Pharmacotherapy

Several medications are used for the treatment of SAD including (13):

1. Selective Serotonin-Reuptake Inhibitors (SSRIs): First-line pharmacological treatment.
2. Serotonin–Norepinephrine Reuptake Inhibitors (SNRI).
3. Benzodiazepines.
4. Anti- convulsant.
5. MAOIs.

Prognosis

Good prognostic factors in SAD include seeking treatment early and adhering to its schedule. While the presence of bipolar disorder (15), or other psychiatric comorbidities

(3), in addition to not seeking treatment are associated with worse prognostic factors (15).

Untreated SAD can become chronic and increasingly life-limiting; as it becomes more difficult to fight fear and maintain a normal, healthy life as time goes on. Its complications can include (7) low self-esteem, being indecisive, negative self-talk, over-sensitivity to criticism, weak social skills, low academic achievements and employment success, self-isolation, substance abuse, and suicide or even suicidal attempts. However, with treatment, prognosis remains extremely positive (16).

References

1. Ahmet Koyuncu MD1, Ezgi İnce MD2, Erhan Ertekin MD2 RTM. Comorbidity in social anxiety disorder: diagnostic and therapeutic challenges. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6448478/
2. Spence SH, Rapee RM. The etiology of social anxiety disorder: An evidence-based model. Behav Res Ther [Internet]. 2016;86:50–67. Available from: http://dx.doi.org/10.1016/j.brat.2016.06.007
3. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®) [Internet]. Available from: https://books.google.jo/books/about/Diagnostic_and_Statistical_Manual_of_Men.html?id=-JivBAAAQBAJ&printsec=frontcover&source=kp_read_button&redir_esc=y#v=onepage&q&f=false
4. Fox AS, Kalin NH. A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. Am J Psychiatry. 2014 Nov;171(11):1162–73.
5. Stein MB, Andrews AM. Serotonin States and Social Anxiety. JAMA psychiatry. 2015 Aug;72(8):845–7.
6. Fox NA, Henderson HA, Marshall PJ, Nichols KE, Ghera MM. Behavioral inhibition: Linking biology and behavior within a developmental framework. Annu Rev Psychol. 2005;56:235–62.
7. mayo. Social anxiety disorder (social phobia) [Internet]. Available from: https://www.mayoclinic.org/diseases-conditions/social-anxiety-disorder/symptoms-causes/syc-20353561
8. Gross R, Olfson M, Gameroff MJ, Shea S, Feder A, Lantigua R, et al. social anxiety disorder in primary care. Gen Hosp Psychiatry. 2005;27(3):161–8.
9. Lecrubier Y, Wittchen HU, Faravelli C, Bobes J, Patel A, Knapp M. A European perspective on social anxiety disorder. Eur Psychiatry. 2000 Feb;15(1):5–16.
10. Social anxiety disorder: recognition, assessment and treatment [Internet]. 22 May. 2013. Available from: https://www.nice.org.uk/guidance/cg159/resources/social-anxiety-disorder-recognition-assessment-and-treatment-pdf-35109639699397
11. Stein MB, Stein DJ. Social anxiety disorder. Lancet (London, England). 2008 Mar;371(9618):1115–25.
12. Schneier FR. Clinical practice. Social anxiety disorder. N Engl J Med. 2006 Sep;355(10):1029–36.
13. National Collaborating Centre for Mental Health NCG. Social Anxiety Disorder. Recognition. Assessment and Treatment. N Engl J Med [Internet]. 2013;(159):2255–64. Available from: http://www.nejm.org/doi/10.1056/NEJMcp1614701
14. Freedheim DK. Short-Term Dynamic Psychotherapy [Internet]. 2013. Available from: https://www.apa.org/pubs/videos/4310903?tab=2
15. Simon NM, Otto MW, Wisniewski SR, Fossey M. Anxiety Disorder Comorbidity in Bipolar Disorder Patients : Data From the Firs ... Am J Psychiatry. 2004;(161):2222–9.
16. Social Anxiety Disorder Information [Internet]. Available from: https://www.verywellmind.com/what-is-social-phobia-2671698#:~:text=Prognosis%3A Untreated social anxiety disorder,the prognosis is extremely positive.

Article Topic: Major Depressive Disorder.

Author: Aya M. Al-Kailani.

Editor: Aroob Awwad.

Reviewer: Ahda Jbarah, Hassan Abushukair.

Keywords: Psychiatry, Major Depressive disorder, Mental Illness, MDD.

Overview

Major depressive disorder (MDD), also simply known as depression, is a common mental disorder characterized by mood changes along with cognitive and physical symptoms over a period of 2 or more weeks [2]. According to the World Health Organization, depression currently affects about 264 million people worldwide, making it one of the most common mental disorders in the world and one of the leading causes of suicidal attempts and mortality. Therefore, it is crucial to human well-being that we understand, recognize, correctly diagnose, and treat depression. Amid the multitude of therapeutic options, some individuals have found solace in natural aids like Organic CBD Nugs. While conventional treatments remain essential, incorporating holistic methods into depression management can provide a more comprehensive approach. As we collectively address the global impact of depression, integrating diverse tools and approaches becomes imperative to offer individuals a more personalized and holistic journey towards mental health recovery

Prevalence

According to the WHO, MDD is the third most common burden-causing disease worldwide and is expected to rank first by 2030 [1]. In 2015, around 16.1 million American adults had at least one major depressive episode in the past year, which is about 6.7% of U.S. adults [10]. Prevalence of depression is measured by scores from the Patient Health Questionnaire, PHQ-9, which is a symptom-screening questionnaire that allows mental health practitioners to diagnose depressive disorders [8]. According to the PHQ-9, a person is diagnosed with depression if they have had the moderate or severe symptoms mentioned in the questionnaire in the past 2 weeks.

A study done on the U.S. population in the years 2013-2016 reveals that [11]:

- 1% of American adults 20 years and above had depression in a given 2-week period in the years 2013-2016.
- Females were almost two times more likely than males to have had depression.

- Depression was lower among Asian adults compared with Hispanic, African American, and White adults.
- Almost 80% of adults with depression have had some difficulty with work, home, or social activities due to their depression.
- As family income levels increased, the prevalence of depression decreased.

Risk Factors

Depression rates differ by many factors including age, sex, income, and health behaviors [7]. Depression is more common amidst adults aged 40–59 years. Rates of depressive symptoms are lower among white persons than Hispanics and African Americans [9]

MDD can arise without any preceding stressors, but stressful life events can certainly increase the risk of developing the disease [20]. Psychosocial stress, chronic pain and medical illnesses can also increase the risk of developing MDD [21]. A study has also shown that cerebrovascular disease may lead to the development of late-life depression. [22]

Pathophysiology

The underlying pathophysiology of MDD is still unclear. However, clinical studies suggest that it occurs due to interactions between different neurotransmitters in the brain. Many of these clinical studies attribute MDD to a serotonin (5-HT) deficit. Other neurotransmitters also believed to be involved are norepinephrine (NE), dopamine (DA), and glutamate [5]. This explains the mechanism of action of many antidepressants that increase neurotransmitter availability such as selective serotonin reuptake inhibitors (SSRIs). SSRIs prevent serotonin reuptake by presynaptic neurons, which leads to higher serotonin levels in the synaptic cleft binding to receptors on postsynaptic neurons, therefore enhancing the mood of the patient.

Other pathophysiological aspects are sunlight exposure and vascular lesions. Changes in the levels of 5-HT can also be possibly due to variations in the weather and the circadian rhythm. The rate of production of serotonin by the brain was directly related to the individual's duration of exposure to bright sunlight and also increased sunlight luminosity. [6]

Etiology

MDD has a multifactorial etiology related to genetics, stressors, neuroendocrine [12] and neurodegenerative disorders, parent-child relationships, and vascular lesions.

In depression developing in early childhood, transmission from parents to children appears to be more related to psychosocial influences than genetics [13]. Major depression has a concordance of 40-50% in twins, and first-degree relatives of depressed individuals are approximately 3 times more likely to develop depression than the general population. [14]

Multiple genes are believed to be responsible for the susceptibility to depression, including:

1. MDD1 and MDD2 genes, each proven to be involved in major depression in males [15] and early onset or recurrent depression [16], respectively.
2. Polymorphism in the promoter region of SLC6A4 gene involved in the serotonin system could possibly lead to MDD. [15]
3. Defects in genes that encode the enzymes responsible for serotonin production or response to serotonin. For example, polymorphism in the *TPH2* gene, which encodes tryptophan hydroxylase for serotonin synthesis, results in an 80% loss of serotonin production [18]. Also, the HTR3A and HTR3B regions, which encode serotonin receptors are known to be associated with MDD in both European and Japanese individuals. [19]

DSM5 Diagnostic Criteria [23]

The DSM-5 states that for an individual to be diagnosed with MDD the following criteria must apply:

A. Five or more of the following symptoms daily or every day for a 2-week period, at least one of which should be criterion 1 or 2:

1. Depressed mood most of the day.
2. Significantly decreased interest/ pleasure in all, or almost all, activities.
3. An increase or decrease in appetite and weight.
4. Slowed thought process and a reduction in physical movement observable by others, not merely by the subject.
5. Fatigue or loss of energy.
6. Feeling of worthlessness or inappropriate guilt.
7. Inability to think or concentrate, being indecisive.
8. Recurrent death thoughts/ suicidal ideation/ attempts or having a planned suicide.

B. To be diagnosed with depression, these symptoms must cause significant impairment in the individual's social, occupational, or other areas of functioning.

C. The symptoms must not be as a result of substance abuse or other medical conditions.

Treatment

- Pharmacotherapy used include:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin/norepinephrine reuptake inhibitors (SNRIs)
- Atypical antidepressants
- Serotonin-Dopamine Activity Modulator (SDAMs)
- Tricyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)
- N-methyl-D-aspartate (NMDA) receptor antagonists
- John's wort (Hypericum perforatum)

Based on a comparative study done on 21 available antidepressants, all types of antidepressants in the market are effective in treating depression [24]. However, they need to be taken for two to six weeks at a therapeutic dose before an observed response is seen. Failure of treatment by antidepressants is usually due to medication noncompliance, inadequate duration of therapy, or inadequate dosing.

- Psychotherapy

Psychotherapy depends on treating mental health problems by talking to a psychiatrist or psychologist once a week in an outpatient clinic for 45- 60 minutes. These sessions can improve patient's general well-being and quality of life by reducing symptoms of depression, as well as provide support in coping with past traumatic experiences, other medical illnesses or loss of a loved one. [26]

- Electroconvulsive Therapy (ECT)

ECT is the oldest among the treatments introduced in the psychiatric field, and the only one still in use to this day as it remains a valuable treatment option for treatment-resistant depression [27], patients in need for a rapid antidepressant response, and patients at high risk for suicide or medical morbidity and mortality. ECT is a generally safe procedure done under general anesthesia where small electrical currents are passed through the patient's brain to provide relief by inducing brain chemistry changes that quickly improve symptoms of certain mental disorders. The onset of action is more rapid than the onset of pharmaceutical treatments, with changes often observed within 1 week of therapy.

- Diet and Exercise

Besides the previously mentioned approaches, dieting and exercise is a useful option for treating depression. It is believed that certain diets such as the low-sodium Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean diet exert positive effects on mental health as shown by participants compliant with the DASH diet, who were 11% less likely to become depressed than those who were not [28]. Multiple studies showed that the Mediterranean diet, which focuses on fish, fruits, vegetables, and olive oil as the main source of fat, can improve mental health in individuals with depression. [28] [29] [30]

Exercise was shown to have a role in improving depressive symptoms and facilitating psychological well-being in adolescents and adults in clinical studies [31] and proved to induce positive effects on psychological disorders such as depression. [32] This is believed to result in enhancing patients' mood through the release of natural brain chemicals in addition to getting the individuals' mind off their depressive symptoms.

Prognosis

Sadly, depression plays a role in more than half of all suicidal attempts, since the lifetime risk of suicide among patients with untreated MDD reaches about 20% [3]. According to the CDC WISQARS Leading Causes of Death Reports in 2018 [4], suicide was the tenth leading cause of death in the United States, claiming the lives of over 48,000 people. Among the ages of 10 to 34, it was the second leading cause of death, and the fourth between the ages of 35 and 54 years. However, much more positive outcome is expected in patients who seek and adhere to therapy.

References

1. WHO: The global burden of disease: 2004 update, World Health Organization, Geneva2008
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Fifth edition. Arlington, VA. 2013.
3. Gotlib I, Hammen C. (2002). *Handbook of Depression*. New York: Guilford Press; 2002
4. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS). Available at http://www.cdc.gov/ncipc/wisqars. Accessed: March 19, 2010.
5. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry*. 2007 Mar. 64(3):327-37.
6. Lambert GW, Reid C, Kaye DM, Jennings GL, Esler MD. Effect of sunlight and season on serotonin turnover in the brain. Lancet. 2002 Dec 7;360(9348):1840-2. doi: 10.1016/s0140-6736(02)11737-5. PMID: 12480364.
7. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. Validity of a brief depression severity measure. J Gen Intern Med 16(9):606–13. 2001.
8. Blanco C, Okuda M, Markowitz JC, Liu S-M, Grant BF, Hasin DS. The epidemiology of chronic major depressive disorder and dysthymic disorder: Results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry 71(12):1645–56. 2010.
9. Pratt LA, Brody DJ. Depression in the U.S. household population, 2009–2012. Available at https://www.cdc.gov/nchs/data/databriefs/db172.htm. 2014; Accessed: July 26, 2017.

10. National Institute of Mental Health. Major Depression Among Adults. National Institutes of Health. Available at https://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml. 2015; Accessed: July 26, 2017.
11. Brody DJ, Pratt LA, Hughes JP. Prevalence of Depression Among Adults Aged 20 and Over: United States, 2013-2016. NCHS Data Brief. 2018 Feb;(303):1-8. PMID: 29638213.
12. De Bellis MD, Dahl RE, Perel JM, Birmaher B, al-Shabbout M, Williamson DE, et al. Nocturnal ACTH, cortisol, growth hormone, and prolactin secretion in prepubertal depression. J Am Acad Child Adolesc Psychiatry. 1996 Sep. 35(9):1130-8.
13. Rice F. Genetics of childhood and adolescent depression: insights into etiological heterogeneity and challenges for future genomic research. Genome Med. 2010 Sep 20. 2(9):68.
14. Tsuang MT, Faraone SV. The genetics of mood disorders. Baltimore, MD: Johns Hopkins University Press, 1990.
15. Abkevich V, Camp NJ, Hensel CH, Neff CD, Russell DL, et al. Predisposition locus for major depression at chromosome 12q22-12q23.2. *Am J Hum Genet*. 2003 Dec. 73(6):1271-81.
16. Holmans P, Zubenko GS, Crowe RR, DePaulo JR Jr, Scheftner WA, Weissman MM, et al. Genomewide significant linkage to recurrent, early-onset major depressive disorder on chromosome 15q. *Am J Hum Genet*. 2004 Jun. 74(6):1154-67
17. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003 Jul 18. 301(5631):386-9.
18. Zhang X, Gainetdinov RR, Beaulieu JM, Sotnikova TD, Burch LH, Williams RB, et al. Loss-of-function mutation in tryptophan hydroxylase-2 identified in unipolar major depression. Neuron. 2005 Jan 6. 45(1):11-6.
19. Yamada K, Hattori E, Iwayama Y, Ohnishi T, Ohba H, Toyota T, et al. Distinguishable haplotype blocks in the HTR3A and HTR3B region in the Japanese reveal evidence of association of HTR3B with female major depression. Biol Psychiatry. 2006 Jul 15. 60(2):192-201.
20. Blazer DG. Depression in late life: review and commentary. J Gerontol A Biol Sci Med Sci. 2003 Mar. 58(3):249-65.
21. Bruce ML. Psychosocial risk factors for depressive disorders in late life. *Biol Psychiatry*. 2002 Aug 1. 52(3):175-84.
22. Thomas AJ, Kalaria RN, O'Brien JT. Depression and vascular disease: what is the relationship?. J Affect Disord. 2004 Apr. 79(1-3):81-95.
23. The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013
24. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018 Feb 20.
25. Pinquart M, Duberstein PR, Lyness JM. Treatments for later-life depressive conditions: a meta-analytic comparison of pharmacotherapy and psychotherapy. Am J Psychiatry. 2006 Sep. 163(9):1493-501.
26. Kolovos S, Kleiboer A, Cuijpers P. Effect of psychotherapy for depression on quality of life: meta-analysis. Br J Psychiatry. 2016 Dec;209(6):460-468. doi: 10.1192/bjp.bp.115.175059. Epub 2016 Aug 18. PMID: 27539296.
27. Kaliora SC, Zervas IM, Papadimitriou GN. [Electroconvulsive therapy: 80 years of use in psychiatry]. Psychiatriki. 2018 Oct-Dec;29(4):291-302. Greek, Modern. doi: 10.22365/jpsych.2018.294.291. PMID: 30814039.
28. Anderson P. DASH Diet Linked to Lower Risk for Depression. Medscape Medical News. Available at https://www.medscape.com/viewarticle/893222. February 28, 2018; Accessed: March 21, 2018.
29. Bogomolova S, Zarnowiecki D, Wilson A, Fielder A, Procter N, Itsiopoulos C, et al. Dietary intervention for people with mental illness in South Australia. *Health Promot Int*. 2018 Feb 1. 33 (1):71-83.
30. Jacka FN, O'Neil A, Opie R, Itsiopoulos C, Cotton S, Mohebbi M, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). *BMC Med*. 2017 Jan 30. 15 (1):23.
31. Archer T, Josefsson T, Lindwall M. Effects of physical exercise on depressive symptoms and biomarkers in depression. CNS Neurol Disord Drug Targets. 2014;13(10):1640-53. doi: 10.2174/1871527313666141130203245. PMID: 25470398.
32. Wegner M, Helmich I, Machado S, Nardi AE, Arias-Carrion O, Budde H. Effects of exercise on anxiety and depression disorders: review of meta- analyses and neurobiological mechanisms. CNS Neurol Disord Drug Targets. 2014;13(6):1002-14. doi: 10.2174/1871527313666140612102841. PMID: 24923346.

Topic: Posttraumatic Stress Disorder (PTSD).

Author: Ala' Moh'd Al Barbarawi.

Editor: Aroob Awwad Awwad.

Reviewer: Ahda Jbarah.

Understanding PTSD

Posttraumatic stress disorder (PTSD) has adopted multiple names throughout history, including 'shell shock' during the first world war, and 'combat fatigue' the WWII. However, PTSD isn't only present in soldiers who fought during war. It is a psychiatric disorder that can occur in people who have been through or witnessed a traumatic event which can be a natural disaster, a life-threatening accident, a terrorist act, war, combat, or rape. It can also happen to individuals who have been threatened with death, sexual violence, or serious injury. (1)

Epidemiology

PTSD is not specific to a certain age group, nationality, culture, or ethnicity. It affects approximately 3.5% of U.S. adults every year, and it is estimated that around 1 in 11 persons will be diagnosed with PTSD in their lifetime. That being said, PTSD was found to occur twice more likely in women as well as three ethnic groups, (U.S. Latinos, African Americans, and American Indians), who were shown to have higher rates of PTSD than non-Latino whites. (1)

Assaultive violence holds the highest potential for developing PTSD. In males, the preeminent factor for acquiring PTSD is combat-related violence. However, in females, sexual violence is the strongest predictor. Women and younger people are more vulnerable to this disorder. Nevertheless, it is increasingly being recognized among the elderly. (2)

Etiology

PTSD is a syndrome that results from exposure to threatened or serious injury or sexual assault. Its signs and symptoms appear to arise from complex interactions of psychological and neurobiological factors (e.g. certain genes can increase the risk).

In PTSD patients, alterations have been found to occur in the amygdala, prefrontal cortex, hippocampus, anterior cingulate, corpus callosum, as well as altered functioning of the hypothalamic-pituitary axis (HPA).

Risk and Prognostic Factors

Most people can quickly recover from certain trauma, meaning that they do not experience the dangerous psychological and physiological consequences of severe stress. However, those who do suffer from PTSD show some levels of vulnerability to these consequences. There are specific factors that promote resilience or vulnerability. (2)

According to DSM-5, risk and protective factors are generally divided into pre-traumatic, peritraumatic, and posttraumatic factors.

Pre-traumatic factors:

1. Temperamental factors: consist of childhood emotional problems up to the age of 6 years (e.g., prior traumatic exposure, externalizing, or anxiety problems) and prior mental disorders (e.g., panic disorder, depressive disorder, PTSD, or obsessive-compulsive disorder [OCD]).
2. Environmental factors: include exposure to prior trauma (especially during childhood), lower socioeconomic status, childhood adversity (e.g. economic deprivation, family dysfunction, parental separation or death), cultural characteristics (e.g., fatalistic [one who believes that bad events cannot be avoided] or self-blaming coping strategies), minority ethnic status, lower intelligence, and a family history of psychiatric disorders. Social support before traumatic event exposure is protective.
3. Genetic and physiological factors: include female gender and younger age at the time of trauma exposure (for adults). Specific genotypes can either protect against or increase the risk of PTSD after exposure to traumatic events.
    a. **Genetic Risk Factors**
        i. Polymorphisms in the Serotonin transporter gene affect the outcome; the long allele (*l*) in the SLC6A4 gene may have a protective effect while the short allele (s) may contribute to developing stress-related psychopathology (2,3).
        ii. Higher risk is seen in different single nucleotide polymorphisms of the gene encoding a chaperone protein that influences the transcriptional effects of the glucocorticoid receptor (FKBP5). This higher risk is observed in children exposed to physical and sexual abuse. (4)
        iii. Single nucleotide polymorphism in the BDNF gene influences the process of fear extinction; a physiologic mechanism relevant to PTSD pathophysiology (5).
        iv. Different single nucleotide polymorphisms in the gene encoding the corticotropin-releasing hormone receptor-1 (CRHR1) appear to lower the risk of developing stress-related disorders among women

with a history of childhood abuse (6). Similarly, the long-form variant of the neuropeptide Y (NPY) gene has been linked with a decreased risk of developing PTSD (7).

b. **Gender**: Women may be at higher risk due to variations in hormonal levels. The levels of testosterone and dehydroepiandrosterone (DHEA) are positively correlated with resilient behavior (8,9,10) while the fluctuating levels of ovarian hormones (estrogen and progesterone) are correlated positively with anxious responses to stress (vulnerability) (11). However, high levels of oxytocin may decrease the risk of stress-related psychopathology (12).
c. Lower performance on neuropsychological tasks assessing fluid intelligence (which is the ability to solve novel problems independently of previously acquired knowledge) was more vulnerable (13,14).

Peritraumatic factors

1. Environmental factors: these include trauma severity (the greater the magnitude of the trauma, the greater the possibility of acquiring PTSD), perceived life threat, personal injury, and interpersonal violence (particularly if the trauma is caused by a caregiver or witnessing a threat to a caregiver in children). Also, adults with a history of childhood abuse are more likely to develop PTSD after adulthood trauma (2).
2. Being in the military (2): being a perpetrator, witnessing atrocities, or killing the enemy.
3. Dissociation taking place during the trauma and persisting

Posttraumatic factors

1. Temperamental factors: compromised of negative appraisal, inappropriate coping mechanisms, and development of acute stress disorder.
2. Environmental factors: include subsequent exposure to repeated upsetting reminders, subsequent adverse life events, and financial or other trauma-related losses. Family stability and support for children is a protective factor.

Differential Diagnosis (15)

PTSD must be differentiated from other post-traumatic disorders and conditions, adjustment disorders, acute stress disorder, anxiety disorders, OCD, major depressive disorder, personality disorders, dissociative disorders, conversion disorder (functional neurological symptom disorder), psychotic disorders, and traumatic brain injury.

DSM-5 Diagnostic Criteria (15)

For adults, adolescents, and children older than 6 years:

A. being exposed to death (whether real or threatened), severe injury, or sexual abuse through one or more of the following methods:
    1. Directly experiencing the traumatic event(s) (e.g., car accident, natural disaster, war).
    2. Being present, in person, as the event(s) occurred to others.
    3. Knowing that the traumatic event(s) occurred to a close family member or close friend. If there was actual or threatened death of a family member or friend, the event(s) must be violent or accidental.
    4. Repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains, police officers repeatedly exposed to details of child abuse, and medical personnel dealing with terminally ill patients). This criterion does not apply to exposure through electronic media, TV, movies, shows, or pictures unless this exposure is related to work.
B. One or more of the following intrusion symptoms associated with the trauma, starting after the event(s) occurred:
    1. Recurrent, involuntary, intrusive distressing memories of the event(s). In children older than 6 years, themes or aspects of the traumatic event (s) may be expressed through repetitive play.
    2. Repeated nightmares whose content and/or effect are related to the traumatic event(s). In children, there may be frightening dreams without recognizing the content.
    3. Flashbacks where the person feels or acts as if the traumatic event(s) were recurring (these may occur continuously, their most extreme expression is the complete loss of awareness of present surroundings). In children, trauma-specific reenactment may occur when the child is playing.
    4. Intense or prolonged psychological distress when exposed to internal or external cues that symbolize or resemble an aspect of the traumatic event(s), (e.g., the individual may hear a certain sound related to the event, which can trigger psychological distress).
C. Consistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
    1. Avoiding or trying to avoid disturbing thoughts, memories, or feelings regarding the traumatic event(s).
    2. Avoiding or trying to avoid external reminders (people, places, conversations, activities, situations, objects) that trigger the disturbing memories, thoughts, or feelings related to the traumatic event(s).
D. Negative alterations in cognitions and mood associated with the traumatic event(s), which begin or worsen after the traumatic event(s) occur, as evidenced by two or more of the following:

1. Inability to remember an important aspect of the traumatic event(s), due to dissociative amnesia and no other factors such as head injury, alcohol, or drugs.
2. Persistent and exaggerated negative beliefs or expectations about oneself (e.g. “I am a bad person”), others (e.g., “I can't trust anyone”), or the world (e.g., “The world is dangerous”).
3. Constant cognitive distortion regarding causes or consequences of the traumatic event(s) leads to the individual blaming themselves or others.
4. Persistently negative emotions (e.g., fear, horror, anger, guilt, or shame).
5. Markedly decreased interest or desire to participate in significant activities.
6. Feeling detached or isolated from other people.
7. Continuous inability to experience positive emotions (e.g., happiness, satisfaction, love, etc.,).

E. Marked alteration in arousal and reactivity linked to the traumatic event(s), beginning or worsening after the event(s) occurred, as evidenced by two or more of the following:
    1. Irritability and angry outbursts (without or with some provocation) manifested as verbal or physical aggression towards people or objects.
    2. Reckless or self-destructive behavior (e.g., drinking and driving, carrying concealed weapons).
    3. Hypervigilance (a state of increased alertness).
    4. Exaggerated startle response.
    5. Concentration problems.
    6. Disturbances in sleep (e.g., difficulty falling or staying asleep or restless sleep).
F. The disturbance, evidenced by criteria B to E above, lasts more than one month.
G. The disturbance leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H. The disturbance is not caused by the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

After confirming the diagnosis of PTSD, specify whether:

1. The patient has dissociative symptoms: the individual will meet the diagnostic criteria for PTSD in addition to experiencing persistent or recurrent symptoms of either of the following in response to the stressor:
    a. **Depersonalization**: the persistent or recurrent feeling of being detached from an individual's mental processes or body as if they were an outside observer (e.g., feeling a sense of unreality as if one were in a dream or out of their body).
    b. **Derealization**: persistent or recurrent experiences of unreal surroundings (e.g., the world around the individual is experienced as

unreal, dreamlike, distant, or distorted; people or objects may seem unreal). *Note*: To specify this subtype, these symptoms must not be caused by or associated with physiological effects of substance abuse (e.g., behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

2. With delayed expression: specified if the full diagnostic criteria are not met until at least 6 months after the traumatic event (although the onset and expression of some symptoms may be immediate).

PTSD in Children Six Years and Younger

To diagnose a child 6 years or younger the following criteria must apply:

A. Being exposed to death (whether real or threatened), severe injury, or sexual abuse through one or more of the following methods:
    1. Experiencing the traumatic event(s) directly.
    2. Witnessing, in person, the traumatic event(s) as it occurred to others, especially primary caregivers (does not include events that are witnessed only in electronic media, television, movies, or pictures).
    3. Learning that the traumatic event(s) occurred to a parent or caregiver.

B. Having one or more of the following intrusion symptoms related to, and beginning after, the traumatic event(s):
    1. Repeated, involuntary, and intrusive distressing memories of the traumatic event(s).
    2. Recurrent distressing dreams related to the traumatic event(s). However, it may not be possible to declare or decide that the frightening content is related to the traumatic event.
    3. Dissociative reactions (e.g., flashbacks) in which the child feels or acts as if the traumatic event(s) were taking place again.
    4. Exposure to internal and external cues that symbolize or resemble an aspect of the traumatic event(s) causes intense or prolonged psychological distress.
    5. Reminders of the traumatic event(s) result in marked physiological reactions.

C. One or more of the following symptoms must be present, beginning or worsening after the event: either **persistent avoidance of the stimuli** or **negative cognitive and mood changes** associated with the traumatic event(s), the earlier manifests as:
    1. Avoiding or efforts to avoid activities, places, or physical reminders of the traumatic event(s).
    2. Avoiding or efforts to avoid people, conversations, or interpersonal situations that arouse recollections of the trauma.
    While the latter can manifest as:

1. Significantly increased frequency of negative emotions (e.g., fear, guilt, shame, sadness, confusion).
2. Diminished interest or participation in activities, including constriction of play.
3. Socially withdrawn behavior.
4. Persistently reduced expression of positive emotions

D. Changes in arousal and reactivity associated with the traumatic event(s) as evidenced by two or more of the following, beginning or worsening after the traumatic event(s) occurred:
    1. Angry outbursts and irritability (with little or no provocation), usually expressed as verbal or physical aggression toward people or objects and extreme temper tantrums.
    2. Hypervigilance (a state of increased alertness).
    3. Exaggerated startle response.
    4. Concentration problems.
    5. Disturbance in sleep (e.g., difficulty falling or staying asleep or restless sleep).
E. The disturbance lasts more than 1 month.
F. The disturbance causes clinically significant impairment in school behavior or social relationships.
G. The disturbance is not due to nor associated with the physiological effects of certain substances (e.g., medication or alcohol) or another medical condition.

Once diagnosed, specify whether PTSD is with:

1. **Dissociative symptoms**: The child's symptoms meet the diagnostic criteria for PTSD. In addition, the child experiences persistent or recurrent symptoms of depersonalization or d Also, to use this subtype, the dissociative symptoms must not be caused by or associated with the physiological effects of a substance or another medical condition.
2. **Delayed expression**: when the diagnostic criteria are not fully met until 6 months or more after the traumatic event.

Treatment

Treatment for PTSD is divided into two categories: psychotherapy and pharmacotherapy.

1. Psychotherapy

The two most successful psychotherapy approaches are controlled exposure to aversive memories and cognitive processing (2). Other alternatives include are mentioned in **Table 1** (16-22):

Table 1: Psychotherapy for the Treatment of Posttraumatic Stress Disorder	
Exposure-Based	
Systematic Desensitization	Education* about disorder and treatment, involves imaginal exposure to aversive memories paired with relaxation to inhibit the feared stimuli.
Eye Movement Desensitization and Reprocessing (EMDR)	Combines traumatic image exposure with the simultaneous performance of eye saccadic movements (usually lateral eye movements)
Stress Inoculation	Education*and training involving teaching coping skills to manage stress and anxiety associated with the traumatic event, training in deep muscle relaxation, exposure to aversive memories, role-playing, breathing exercises, assertiveness skills, and thought stopping.
Prolonged Exposure	Education*, exposure to traumatic memories, confrontation of feelings/thoughts, cognitive restructuring
Virtual Reality Exposure	Exposure to computerized, vividly recreated environments of the trauma (e.g., war, accidents, etc.,)
Cognitive Based	
Trauma-Focused Psychodynamic Therapy	Includes education*, free association, dream interpretation, and cognitive restructuring.

Cognitive Processing Therapy	Education* (with limited exposure to traumatic memories) along with Socratic questioning, and identification of maladaptive cognition and automatic thoughts (the patient becomes aware of the relationship between thoughts and emotions).
Acceptance and Commitment Therapy (ACT)	Individuals open up to unpleasant feelings and learn not to overreact and to face situations where they are invoked.
Other	
Biofeedback	Voluntary regulation of physiologic responses (e.g., muscle activity, heart rate). A mind-body technique involving visual or auditory feedback to gain control over involuntary bodily functions such as blood flow, blood pressure, and heart rate (23).
Mindfulness-Based Cognitive Therapy	Involves meditation, awareness, breath-focused imagery, silent repetition of words, and letting go of intrusive thoughts.

*Note: Education involves psychoeducation regarding PTSD, thoughts, and emotions

2. **Pharmacotherapy**

Pharmacologic treatment of PTSD is usually indicated either to prevent its onset after trauma exposure or to reduce the severity of PTSD symptoms once the condition is established. A recent meta-analysis of preventive interventions indicated that hydrocortisone may be used to prevent PTSD onset when given acutely after trauma (24). On the other hand, no preventive effect was seen when propranolol, benzodiazepines, or selective serotonin reuptake inhibitors (SSRIs) were given (24). However, the clinical trials conducted in the analysis were small and had multiple methodologic flaws (24).

Another recent meta-analysis of pharmacologic interventions to reduce the severity of PTSD symptoms suggests that placebo is less effective than active pharmacologic agents. However, the side effects observed in the concisely controlled trials were smaller than those observed in controlled trials of psychotherapeutic options. Furthermore, little evidence exists proving that the combination of medications and psychotherapy has a

synergistic effect, and no effectiveness studies comparing pharmacotherapy with psychotherapy exist. (25)

It is unlikely that one particular medication is equally efficacious in treating all PTSD symptom clusters (e.g., intrusive symptoms, avoidance, dysphoric experiences) since symptoms are heterogeneous and have different pathophysiologic mechanisms. Moreover, the longitudinal course of PTSD may influence efficacy. In other words, a pharmacologic agent might be more effective in the early stages of PTSD while another is better given in the more refractory, chronic period. (2)

A summary of the medications that have shown some efficacy in treating PTSD is shown in **Table 2** below (2):

Table 2: Medications That Have Shown Efficacy in Treating PTSD

Class	Drug	Total Daily Dosage
Antidepressants		
Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine	20-60 mg/d
	Sertraline	50-200 mg/d
	Paroxetine	20-30 mg/d
	Citalopram	20-40 mg/d
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	Venlafaxine	75-300 mg/d
	Venlafaxine-extended release	75-225 mg/d
	Duloxetine	40-60 mg/d
Tricyclic Antidepressants (TCAs)	Amitriptyline	50-300 mg/d
	Imipramine	50-300 mg/d
Monoamine Oxidase Inhibitors	Phenelzine	15-90 mg/d
Other	Mirtazapine	7.5-45 mg/d
Sympatholytic		
Beta-blockers	Propranolol	40-160 mg/d
Alpha-2 Receptor agonists	Clonidine	0.2-0.6 mg/d
	Guanfacine	0.5-3 mg/d
Alpha-1 Receptor antagonists	Prazosin	2-10 mg/d

Mood Stabilizers		
	Divalproex sodium or valproic acid	500-2000 mg/d
	Lithium	600-1500 mg/d
	Carbamazepine	400-1000 mg/d
	Topiramate	50-200 mg/d
Antipsychotics		
	Risperidone	0.5-6 mg/d
	Olanzapine	5-20 mg/d
	Quetiapine	25-300 mg/d
	Aripiprazole	5-15 mg/d
Anxiolytics		
Benzodiazepines	Alprazolam	0.25-4 mg/d
	Clonazepam	0.5-4 mg/d
5-HT_{1A} receptor agonists	Buspirone	15-60 mg/d
Others		
N-methyl-D-aspartate (NMDA) antagonists	D-Cycloserine	8-12 mg/d
	Ketamine	0.5 mg/kg/d IV

When initiating pharmacotherapy for PTSD treatment, SSRIs are the **drugs of choice** as they have the best safety profile compared to other medications (2). When compared to placebo, previous studies have shown that sertraline (26), paroxetine (27), and fluoxetine (28) are significantly more efficacious in reducing the severity of PTSD symptoms. However, it should be noted that this efficacy is due to differences in gender, type of traumatic event, refractoriness of PTSD, and symptom clusters (2). For instance, military populations tend to be less responsive to treatment with SSRIs (2). A randomized double-blind trial performed in 10 US Department of Veteran Affairs medical centers shows that sertraline is not more effective than a placebo to treat combat-related PTSD (29). SNRIs like venlafaxine might be more effective in PTSD treatment (2).

Antiadrenergic agents may influence specific PTSD-symptom dimensions. For example, the $alpha_1$ receptor antagonist prazosin shows efficacy in reducing the frequency and severity of intrusive symptoms (e.g., nightmares) (30). Mood stabilizers such as lithium,

valproate, and carbamazepine are ineffective in treating PTSD, but they can be helpful for those patients with coexistent bipolar disorder (2). Similarly, comorbidities including impulsivity and substance misuse in PTSD patients may be decreased with the use of topiramate. The addictive potential of benzodiazepines limits their use for the treatment of PTSD. Moreover, it may lead to aggravating avoidance and depressive symptoms (2). Lastly, although the use of antipsychotics is discouraged, atypical neuroleptics might constitute a last-resort solution to control disturbing psychotic symptoms (2).

Prognosis

Certain genetic factors may be protective, leading to a better prognosis when compared to susceptibility genes. The severity of the trauma also plays an important role in prognosis. Does PTSD regress with time or does it worsen with time? This mainly depends on how soon symptoms develop, their severity, early diagnosis, and treatment. (1)

References

1. What Is Posttraumatic Stress Disorder? 2020. p. https://www.psychiatry.org/patients-families/ptsd/.
2. Jorge RE. Posttraumatic stress disorder. Contin Lifelong Learn Neurol. 2015;21(3):789–805.
3. Murrough JW, Charney DS. The serotonin transporter and emotionality: Risk, resilience, and new therapeutic opportunities. Biol Psychiatry [Internet]. 2011;69(6):510–2. Available from: http://dx.doi.org/10.1016/j.biopsych.2011.01.019
4. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008 Mar;299(11):1291–305.
5. Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, et al. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. Science. 2010 Feb;327(5967):863–6.
6. Polanczyk G, Caspi A, Williams B, Price TS, Danese A, Sugden K, et al. Protective effect of CRHR1 gene variants on the development of adult depression following childhood maltreatment: replication and extension. Arch Gen Psychiatry. 2009 Sep;66(9):978–85.
7. Zhou Z, Zhu G, Hariri AR, Enoch M-A, Scott D, Sinha R, et al. Genetic variation in human NPY expression affects stress response and emotion. Nature. 2008 Apr;452(7190):997–1001.
8. Ahmet Koyuncu MD1, Ezgi İnce MD2, Erhan Ertekin MD2 RTM. Comorbidity in social anxiety disorder: diagnostic and therapeutic challenges. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6448478/
9. Olff M, de Vries G-J, Güzelcan Y, Assies J, Gersons BPR. Changes in cortisol and DHEA plasma levels after psychotherapy for PTSD. Psychoneuroendocrinology. 2007 Jul;32(6):619–26.
10. Yehuda R, Brand SR, Golier JA, Yang R-K. Clinical correlates of DHEA associated with post-traumatic stress disorder. Acta Psychiatr Scand. 2006 Sep;114(3):187–93.
11. Resnick HS, Kilpatrick DG, Best CL, Kramer TL. Vulnerability-stress factors in development of posttraumatic stress disorder. J Nerv Ment Dis. 1992 Jul;180(7):424–30.
12. Koch SBJ, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M. Intranasal oxytocin as strategy for medication-enhanced psychotherapy of PTSD: salience processing and fear inhibition processes. Psychoneuroendocrinology. 2014 Feb; 40:242–56.
13. Breslau N, Chen Q, Luo Z. The role of intelligence in posttraumatic stress disorder: does it vary by trauma severity? PLoS One. 2013;8(6): e65391.
14. Macklin ML, Metzger LJ, Litz BT, McNally RJ, Lasko NB, Orr SP, et al. Lower precombat intelligence is a risk factor for posttraumatic stress disorder. J Consult Clin Psychol. 1998 Apr;66(2):323–6.
15. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®) [Internet]. Available from: https://books.google.jo/books/about/Diagnostic_and_Statistical_Manual_of_Men.html?id=-JivBAAAQBAJ&printsec=frontcover&source=kp_read_button&redir_esc=y#v=onepage&q&f=false
16. WOLPE J. The systematic desensitization treatment of neuroses. J Nerv Ment Dis. 1961 Mar; 132:189–203.

17. Shapiro F. Eye movement desensitization: a new treatment for post-traumatic stress disorder. J Behav Ther Exp Psychiatry. 1989 Sep;20(3):211–7.
18. McLean CP, Foa EB. Prolonged exposure therapy for post-traumatic stress disorder: a review of evidence and dissemination. Expert Rev Neurother. 2011 Aug;11(8):1151–63.
19. Powles WE. Beck, Aaron T. Depression: Causes and Treatment. Philadelphia: University of Pennsylvania Press, 1972. Pp. 370. $4.45. Am J Clin Hypn [Internet]. 1974 Apr 1;16(4):281–2. Available from: https://doi.org/10.1080/00029157.1974.10403697
20. Powers MB, Zum Vorde Sive Vording MB, Emmelkamp PMG. Acceptance and commitment therapy: a meta-analytic review. Psychother Psychosom. 2009;78(2):73–80.
21. Batty MJ, Bonnington S, Tang B-K, Hawken MB, Gruzelier JH. Relaxation strategies and enhancement of hypnotic susceptibility: EEG neurofeedback, progressive muscle relaxation and self-hypnosis. Brain Res Bull. 2006 Dec;71(1–3):83–90.
22. Zucker TL, Samuelson KW, Muench F, Greenberg MA, Gevirtz RN. The effects of respiratory sinus arrhythmia biofeedback on heart rate variability and posttraumatic stress disorder symptoms: a pilot study. Appl Psychophysiol Biofeedback. 2009 Jun;34(2):135–43.
23. Cherry K. What Is Biofeedback and How Does It Work? [Internet]. Available from: https://www.verywellmind.com/what-is-biofeedback-2794875#:~:text=Biofeedback is a mind-body,blood pressure%2C and heart rate.
24. Amos T, Stein DJ, Ipser JC. Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). Cochrane database Syst Rev. 2014 Jul;(7):CD006239.
25. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post-traumatic stress disorder (PTSD). Cochrane database Syst Rev. 2006 Jan;2006(1):CD002795.
26. Bravo-Mehmedbasic A, Dzubur Kulenovic A, Kucukalic A. P.4.b.012 Efficacy and safety of sertraline treatment of posttraumatic stress disorder. Eur Neuropsychopharmacol. 2014;24: S593–4.
27. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. Am J Psychiatry. 2001 Dec;158(12):1982–8.
28. Martenyi F, Brown EB, Zhang H, Prakash A, Koke SC. Fluoxetine versus placebo in posttraumatic stress disorder. J Clin Psychiatry. 2002 Mar;63(3):199–206.
29. Friedman MJ, Marmar CR, Baker DG, Sikes CR, Farfel GM. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. J Clin Psychiatry. 2007 May;68(5):711–20.
30. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry. 2013 Sep;170(9):1003–10.
31. KabatArt. Mental Illness PTSD [Internet]. [cited 2021 Mar 3]. Available from: https://images-wixmp-ed30a86b8c4ca887773594c2.wixmp.com/f/9e9c85cf-c32d-4bc2-93ba-0c9cce038988/dd0mdlp-e875ac07-d542-42bd-921a-9adad20c5e72.jpg/v1/fill/w_1095,h_730,q_70,strp/mental_illness___ptsd_by_kabatart_dd0mdlp-pre.jpg?token=eyJ0eXAiOiJKV1QiLCJhbGci

Article Topic: Bipolar Disorder.

Author: Aya M. Al-Kailani.

Editor: Hala Qaryouti.

Reviewer: Ahda Jbarah, Hassan Abushukair.

Overview

Bipolar disorder (BPD), also known as manic-depressive illness (MDI), is a mental disorder consisting of abnormally extreme alterations in mood, concentration, and activity levels. These shifts in mood include emotional highs (mania or hypomania) and lows (depression). This disorder is a serious lifelong challenge faced by many people in the world[1]. The National Institute of Mental Health estimates that bipolar disorder affects approximately 5.7 million adult Americans, or about 2.6% of the U.S. population age 18 and older every year.

There are multiple types of bipolar and related disorders including mania/ hypomania and depression. The main divisions of bipolar disorder are Bipolar I, Bipolar II, cyclothymic disorder, and other disorders. These different diagnoses depend on the type and severity of symptoms present in each patient.

Prevalence

The global prevalence for BPD ranged from 0.4% to 1.6% between the mid-1970s and 2000. By the late 1990s to the 2000s, the prevalence had climbed from approximately 5% to 7% [2]. The lifelong prevalence of bipolar disorder ranges from 0.9% to 2.1% in the United States [3]. Studies also show differences in the lifetime prevalence of each of the different types of bipolar disorder. For bipolar disorder type I (BPI), the lifetime prevalence is (1.0%), while for bipolar disorder type II (BPII) it is (1.1%). For subthreshold bipolar disorders, prevalence is between (2.4–4.7%) [4].

For both BPI and BPII, the age of onset varies greatly, ranging from childhood to 50 years, with a mean of approximately 21 years. It is important to mention that patients diagnosed with recurrent major depression may actually have bipolar disorder but develop their first manic episode over the age of 50 years, as a part of the disease progression. However, the onset of mania in patients older than 50 years should be investigated for a possible medical or neurological disorder as well.

Most studies have concluded an almost equal male-to-female ratio in the prevalence of BPD. However, studies also report an increased risk in women for some types of bipolar disorder, such as BPII and rapid-cycling bipolar disorder [5].

Pathophysiology

The exact pathophysiology of bipolar disorder has not been determined, but studies show a strong genetic association. According to Edvardsen et. al, first-degree relatives of a person with bipolar disorder are approximately 7 times more likely to develop bipolar disorder than the rest of the population [6]. However, the genetic component of BPD appears to be complex due to the contribution of multiple different genetic alleles. Bipolar disorder inheritance has been associated with several genes including multiple genes in the MAFD loci [7-15], the CACNA1C gene [16], and the ANK3 gene [16]. Many studies suggest that certain large genetic deletions and duplications are associated with mental illnesses, with both bipolar disorder and schizophrenia being the most commonly associated illnesses [17].

Myelin, the sheath covering axons, allows efficient conduction of nerve impulses in the nervous system. Its loss is thought to play a role in neurological diseases and mental illnesses, one of which is bipolar disorder. Abnormal myelination in several brain regions has been seen in imaging studies of persons with bipolar disorder. This feature has been useful when comparing patients who have certain genetic components with those who have bipolar disorder and these imaging findings. [18.19]

Risk Factors

Certain factors increase the likelihood of developing bipolar disorder and trigger the first episode in those with an already existing tendency to develop BPD. Those risk factors include:

- Stressful or traumatic events, such as the death of a loved one
- Having a first-degree relative (parents or siblings) with bipolar disorder
- Drug or alcohol abuse

According to 2119 studies, the risk factors for developing bipolar disorder can be grouped in 3 main categories:

- Neurodevelopmental risk factors (e.g. maternal influenza during pregnancy)
- Substance abuse (e.g.: cocaine, cannabis, opioids, tranquilizers, stimulants, sedatives)
- Physical/psychological stress (parental loss, adversities, abuse, brain injury). [21]

Clinical Presentation

Mood disorders in general (BPD and depressive disorders) are characterized by mood episodes; a combination of symptoms comprising a predominant mood state in distinct periods of time. Types of mood episodes seen in BPD include major depressive, manic, and hypomanic episodes (depending on the type of BPD diagnosed).

1. Mania and Hypomania

Mania and hypomania are two different features with similar symptoms, as according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition), to diagnose the former or the latter, three or more of the following criteria must be present:

1. Grandiosity
2. Decreased need for sleep
3. Excessive talking or pressured speech
4. Racing thoughts or flight of ideas
5. Distractibility
6. Increase in goal-focused activity at home/ work, or sexually
7. Excessive pleasurable activities, often with painful consequences

However, the difference between mania and hypomania is highlighted through the following:

- Manic episodes include at least 1 week of profound mood disturbance, characterized by gateway criteria (elation, expansiveness or irritability) and at least 3 of the symptoms mentioned prior [20]. On the other hand, hypomanic episodes are characterized by at least 4 consecutive days of three or more of the symptoms above.
- Mania is more severe and causes significant dysfunction in the social setting, as well as relationship hurdles whereas hypomania is not severe enough to cause social impairment or dysfunction.
- Mania can trigger psychosis episodes (a break from reality) while hypomania doesn't.
- Manic symptoms are usually severe enough to require hospitalization, while hypomanic symptoms do not require hospital admission.

2. Depression

Major depressive episodes (MDE) are a part of the mood shifts that occur in bipolar disorder. According to DSM-5, in an MDE, the patient experiences 5 or more of the

following symptoms over a continuous period of 2 weeks, with at least 1 of which being criterion A or B: [20]

1. Depressed mood
2. Marked decrease in pleasure or interest in nearly all activities
3. Significant change in appetite or weight
4. Hypersomnia or insomnia
5. Psychomotor retardation or agitation
6. Loss of energy or fatigue
7. Feelings of worthlessness or excessive guilt
8. Decreased concentration ability or marked indecisiveness
9. Preoccupation with death or suicide, or having suicidal plans/ attempts

DSM -5 Diagnostic Criteria [22]

According to the DSM-5, to diagnose **bipolar I disorder**, the occurrence of a manic episode is a must. This may be preceded or followed by hypomanic episode or MDE:

1. period of an abnormal persistent increase in energy or irritability for at least 1 week, present most of the day almost every day (any duration if hospitalization is necessary).
2. During this period, at least 3 of the aforementioned symptoms of manic/hypomanic episodes (4 if there is only mood irritability) are present and represent a significant change from the individual's usual behavior.
3. A mood disturbance severe enough to cause marked impairment in functioning or to necessitate hospital admission to prevent harmful behavior and/or due to psychotic features.
4. The episode is not caused by physiological effects of a substance (e.g., drug abuse, a medication, or other treatment) or another medical condition.

Bipolar II Disorder diagnosis necessitates meeting criteria for a current/ past hypomanic episode as well as those for a current or past MDE:

1. A distinct period of hypomania (mood disturbance and increased energy and activity) lasting at least 4 consecutive days most of the day daily
2. During this period, 3 or more of the symptoms of manic/ hypomanic episodes (4 if there is only mood irritability) have persisted to cause noticeable change from individual's baseline behavior
3. The episode is associated with an unmistakable change in functioning different from the individual's behavior when asymptomatic.
4. The mood disturbance and change in functioning are noticed by others.
5. The episode does not lead to marked occupational functioning nor needs hospital admission.

6. The episode is not caused by physiological effects of substance abuse.
7. Must meet criteria of at least one hypomanic episode and at least one MDE
8. There has never been a manic episode
9. The occurrence of the hypomanic episode(s) and MDE(s) cannot be better explained by schizophrenia spectrum disorders or other psychotic disorders.
10. The symptoms of depression or the unpredictability caused by frequent changes between depression and hypomania causes distress or impairment in several important areas of functioning.

Cyclothymic disorder is diagnosed when an adult experiences mood cycling over a consecutive period of two years without meeting the diagnostic criteria for bipolar I, bipolar II, or depressive disorders. In children and adolescents, diagnosis requires only one year of hypomanic and depressive periods.

According to DSM-5, patients must experience the following symptoms for diagnosis of cyclothymic disorder:

1. Multiple periods of hypomanic symptoms for at least two years that do not meet the criteria for hypomanic episodes.
2. Multiple periods of depressive symptoms that do not meet criteria for an MDE.
3. The person has experienced the cycling periods mentioned above for at least half the time and has not been free of symptoms for more than two months.
4. The symptoms experienced are not caused by another psychological condition.
5. The symptoms are not due to an organic cause.
6. The symptoms impair the person's ability to socialize, work, or function in different aspects of life.

Treatment

Bipolar disorder is a lifelong illness with alternating episodes of mania and depression that typically recur. Between these episodes, many patients experience a symptom-free period. BPD patients should be always evaluated for a possible manic, hypomanic, or mixed episode, and those with bipolar depression should be evaluated for suicidality, acute or chronic psychosis, or other unstable or dangerous conditions [23].

Continuous, long-term treatment can help manage BPD symptoms. There is a wide variety of different available treatments (e.g.: medications, psychotherapy, electroconvulsive therapy, transcranial magnetic stimulation, and healthy lifestyle implementations). Hospitalization may be needed if the patient behaves dangerously, feels suicidal or acquires a psychotic behavior. Hospital stays can help calm the patients and stabilize their mood, whether during a manic or a major depressive episode.

1. Pharmacologic Therapy

The pharmacological treatment of choice depends on the episode that the patient is experiencing, and the symptoms that are present. There are several drugs indicated for acute manic episodes. These drugs mainly consist of antipsychotic agents, valproate, and benzodiazepines (lorazepam, clonazepam). The following table includes the FDA-approved drugs for bipolar disorder, depending on the type of episode.

Generic Name	Trade Name	Manic	Mixed	Maintenance	Depression
Valproate	*Depakote*	X			
Carbamazepine extended release	*Equestro*	X	X		
Lamotrigine	*Lamictal*			X	
Lithium		X		X	
Aripiprazole	*Abilify*	X	X	X	
Ziprasidone	*Geodon*	X	X		
Risperidone	*Risperdal*	X	X		
Quetiapine	*Seroquel*	X			X
Chlorpromazine	*Thorazine*	X			
Olanzapine	*Zyprexa*	X	X	X	
Olanzapine/fluoxetine Combination	*Symbyax*				X

2. Psychotherapy

Psychotherapy is a very important constituent of bipolar disorder treatment. Several types of psychotherapy can be provided, including:

- Interpersonal and social rhythm therapy (IPSRT) which focuses on establishing a healthy daily routine in patients' lives,
- Cognitive behavioral therapy (CBT) focuses on replacing unwanted behavior with positive behavior,
- Family-focused therapy helps the patient's loved ones recognize the patient's mood swings and provides them with better understanding of how to manage the condition.

3. Electroconvulsive therapy

ECT is the oldest among the treatments introduced in the psychiatric field, and the only one still in use to this day as it remains a treatment option for many mental illnesses. ECT is a generally safe procedure done under general anesthesia where small electrical currents are passed through the patient's brain to provide relief and quickly improve symptoms of certain mental disorders. Changes are often observed within 1 week of therapy, which is faster than pharmaceutical treatments.

Electroconvulsive therapy is indicated in BPD when:

- rapid treatment is needed
- the risks of ECT are less than that of other treatments
- bipolar disorder is refractory to other treatment methods.

A study revealed that 313 of 400 patients with acute mania who received ECT showed significant clinical improvement. [24]

4. Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a new approach to brain stimulation. It involves delivering magnetic waves to an awake patient most days for one month. Research has shown that TMS has a role in fighting different types of depression. Nonetheless, its role in the treatment of bipolar disorder is still under observation but provides a promising approach for treating patients who have failed to respond to other methods of treatment. [25]

5. Diet and Exercise

Healthy habits including regular exercise have a role in alleviating many symptoms experienced in mental illnesses, including bipolar disorder. Patients with bipolar disorder usually have a sedentary lifestyle due to their condition, which contributes to developing other medical diseases. Aerobic exercise in particular may be beneficial for both their mental and physical health.[26]

Patients experiencing a depressive episode are encouraged to exercise, develop a regular schedule of their daily activities, and a regular sleep schedule. Both exercise and regular schedule are primary to surviving this lifelong illness.

Prognosis

To conclude, the prognosis of bipolar disorder depends on the individual course of each patient's illness. Comorbidities and psychotic symptoms associated with bipolar disorder have a negative influence on the prognosis of this mental disorder.[27]

If left untreated, bipolar disorder can result in serious complications including drug and alcohol abuse, suicidal attempts, legal and financial problems, damaged relationships, and poor social functioning. It is therefore very critical to appropriately diagnose, follow-up, and provide these patients with the correct treatment regimens that help them in the best way possible. Bipolar disorder is a lifelong illness that can be manageable if the correct approach is taken.

References

1. Bowden C, Singh V. Long-term management of bipolar disorder. Available at http://www.medscape.com/viewprogram/2686.
2. Yutzy SH, Woofter CR, Abbott CC, Melhem IM, Parish BS. The increasing frequency of mania and bipolar disorder causes and potential negative impacts. *J Nerv Ment Dis*. 2012 May. 200(5):380-7.
3. [Guideline] Hirschfeld RMA. Guideline Watch: Practice Guideline for the Treatment of Patients with Bipolar Disorder. Review and Synthesis of Available Evidence. Somatic Treatments of Acute Manic and Mixed Episodes. 2nd ed. Arlington, Va: American Psychiatric Association.
4. Calabrese JR. Overview of patient care issues and treatment in bipolar spectrum and bipolar II disorder. *J Clin Psychiatry*. 2008 Jun. 69(6):e18.
5. Diflorio A, Jones I. Is sex important? Gender differences in bipolar disorder. *Int Rev Psychiatry*. 2010. 22(5):437-52.
6. Edvardsen J, Torgersen S, Røysamb E, Lygren S, Skre I, Onstad S, et al. Heritability of bipolar spectrum disorders. Unity or heterogeneity? *J Affect Disord*. 2008 Mar. 106(3):229-40.
7. Berrettini WH, Ferraro TN, Goldin LR, Weeks DE, Detera-Wadleigh S, Nurnberger JI Jr, et al. Chromosome 18 DNA markers and manic-depressive illness: evidence for a susceptibility gene. *Proc Natl Acad Sci U S A*. 1994 Jun 21. 91(13):5918-21.
8. Reich T, Clayton PJ, Winokur G. Family history studies: V. The genetics of mania. *Am J Psychiatry*. 1969 Apr. 125(10):1358-69.
9. Lin PI, McInnis MG, Potash JB, Willour VL, Mackinnon DF, Miao K, et al. Assessment of the effect of age at onset on linkage to bipolar disorder: evidence on chromosomes 18p and 21q. *Am J Hum Genet*. 2005 Oct. 77(4):545-55.
10. McQuillin A, Bass NJ, Kalsi G, Lawrence J, Puri V, Choudhury K, et al. Fine mapping of a susceptibility locus for bipolar and genetically related unipolar affective disorders, to a region containing the C21ORF29 and TRPM2 genes on chromosome 21q22.3. *Mol Psychiatry*. 2006 Feb. 11(2):134-42.
11. Ekholm JM, Kieseppä T, Hiekkalinna T, Partonen T, Paunio T, Perola M, et al. Evidence of susceptibility loci on 4q32 and 16p12 for bipolar disorder. *Hum Mol Genet*. 2003 Aug 1. 12(15):1907-15.
12. Abou Jamra R, Fuerst R, Kaneva R, Orozco Diaz G, Rivas F, Mayoral F, et al. The first genomewide interaction and locus-heterogeneity linkage scan in bipolar affective disorder: strong evidence of epistatic effects between loci on chromosomes 2q and 6q. *Am J Hum Genet*. 2007 Nov. 81(5):974-86.
13. Kelsoe JR, Spence MA, Loetscher E, Foguet M, Sadovnick AD, Remick RA, et al. A genome survey indicates a possible susceptibility locus for bipolar disorder on chromosome 22. *Proc Natl Acad Sci U S A*. 2001 Jan 16. 98(2):585-90.
14. Kakiuchi C, Iwamoto K, Ishiwata M, Bundo M, Kasahara T, Kusumi I, et al. Impaired feedback regulation of XBP1 as a genetic risk factor for bipolar disorder. *Nat Genet*. 2003 Oct. 35(2):171-5.
15. Ferreira MA, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet*. 2008 Sep. 40(9):1056-8.
16. Ferreira MA, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet*. 2008 Sep. 40(9):1056-8.
17. Grozeva D, Kirov G, Ivanov D, Jones IR, Jones L, Green EK, et al. rare copy number variants: a point of rarity in genetic risk for bipolar disorder and schizophrenia. *Arch Gen Psychiatry*. 2010 Apr. 67(4):318-27.
18. Adler CM, Holland SK, Schmithorst V, Wilke M, Weiss KL, Pan H, et al. Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study. *Bipolar Disord*. 2004 Jun. 6(3):197-203.
19. Adler CM, Adams J, DelBello MP, Holland SK, Schmithorst V, Levine A, et al. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. *Am J Psychiatry*. 2006 Feb. 163(2):322-4.
20. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
21. Marangoni C, Hernandez M, Faedda GL. The role of environmental exposures as risk factors for bipolar disorder: A systematic review of longitudinal studies. J Affect Disord. 2016 Mar 15;193:165-74. doi: 10.1016/j.jad.2015.12.055. Epub 2016 Jan 1. PMID: 26773919.
22. The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013
23. Management of Bipolar Disorder Working Group. VA/DoD clinical practice guideline for management of bipolar disorder in adults. Washington, DC: Department of Veterans Affairs, Department of Defense; 2010. Available at http://guideline.gov/content.aspx?id=16314. Accessed: May 15, 2012.
24. Mukherjee S, Sackeim HA, Schnur DB. Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. *Am J Psychiatry*. 1994 Feb. 151(2):169-76.
25. Gold AK, Ornelas AC, Cirillo P, Caldieraro MA, Nardi AE, Nierenberg AA, Kinrys G. Clinical applications of transcranial magnetic stimulation in bipolar disorder. Brain Behav. 2019 Oct;9(10):e01419. doi: 10.1002/brb3.1419. Epub 2019 Sep 30. PMID: 31566935; PMCID: PMC6790310.
26. Lin K, Liu T. Exercise on bipolar disorder in humans. Int Rev Neurobiol. 2019;147:189-198. doi: 10.1016/bs.irn.2019.07.001. Epub 2019 Jul 26. PMID: 31607354.
27. Müller JK, Leweke FM. Bipolar disorder: clinical overview. Med Monatsschr Pharm. 2016 Sep;39(9):363- 9. English, German. PMID: 29956510.

Article topic: Illness Anxiety Disorder.

Author: Abdallah Aljabeiti.

Editor: Hala Qaryouti.

Reviewer: Ahda Jbarah.

Introduction

Illness Anxiety Disorder (IAD) is a psychiatric disorder identified by excessive worry about having or developing a medical condition that is not yet diagnosed (1). This worry persists despite normal physical examination findings and lab results (2). People with IAD tend to pay excessive attention to normal bodily sensations (digestion, sweating, etc.), which they misinterpret as an indication of a worrisome disease (1). IAD falls under the wider category of "Somatic Symptom and Related Disorders" in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).

Brief History

IAD was previously called hypochondriasis, from the Greek work *hypokhondria* meaning 'under the cartilage', which refers to the area that the ancient Greeks thought to be the source of melancholy or worry (3). The name was changed in the DSM-5 due to the pejorative nature of this nomenclature (1).

Epidemiology

Due to the novelty of IAD (as a diagnosis, not as a disease), the prevalence remains largely unknown. However, estimates can be extrapolated from the DSM-III and DSM-IV diagnosis of hypochondriasis [1][2][4]. About 25% of patients previously diagnosed with hypochondriasis meet the criteria for IAD [1]. The estimated prevalence of IAD is around 0.75% in the medical outpatient environment and around 0.1% in the general population [1][2]. IAD has no gender predilection [1][4][5]and is more common in adolescents, unemployed individuals, and those who are less educated [1][5].

Etiology & Pathophysiology

Exact etiologies and how they come to cause IAD remain enigmatic. Nonetheless, the risk factors mentioned below can play a role in developing this disorder**.**

Risk Factors

Each of the following (alone or in combination) are risk factors thought to be implicated in the development of IAD:

- Being raised in a family where health anxieties are frequently expressed, or if parents had disproportionate concerns about health-related issues [6].
- Having personally had a serious illness in childhood or having witnessed a serious medical condition in parent(s) or siblings [2][6].
- Having a history of childhood abuse [4].
- Having an underlying anxiety disorder (e.g. generalized anxiety disorder (GAD)) [1].
- Having a first-degree relative with IAD [7].
- Having a prior experience with the medical profession that resulted in diminished trust or confidence in physicians [7].
- Spending an excessive amount of time reviewing health-related material on the internet (termed 'Cyberchondria') [1][8].

Clinical Presentation

As evident by the nature of the disease, IAD patients are more likely to be present in non-mental healthcare settings and are more likely to be in their early or middle adulthood. They usually present with the following:

- Lack of or mild somatic symptoms (e.g. sweating or slight tachycardia).
- Preoccupation with either the conviction of having or the fear of developing a serious illness (e.g. the fear of memory loss in the elderly).
- Disproportionate worry over the reality of the situation. [4]
- Frequent monitoring for indicators of illness, such as checking blood pressure, pulse, temperature, or other physical changes several times a day and excessive bodychecking (e.g., for skin lesions, hair loss, etc.) [1][4][8].
- Being uncomfortable or intolerant when experiencing normal bodily sensations and labeling them as pathological [1].
- Excessive use of sources of information (e.g., the internet) for reviewing health-related concerns [1][8].
- Having a history of multiple doctor visits with multiple doctors for the same problem [1][9].

Along with the symptoms, most patients present within one of two categories [1][4]:

- **Care-seeking type:** these patients often use the health care system by constantly changing physicians and requesting multiple investigations/treatments.

- **Care-avoidant type:** these patients avoid medical care. They have anxiety about presenting for diagnosis due to the belief that a life-threatening illness will be revealed.

Patients with IAD usually remain dissatisfied with any form of reassurance of negative physical exam findings or lab results. They also have a belief that their previous doctors were incompetent, in that they could have missed the correct diagnosis. [1,9]

Diagnosis

The criteria for diagnosis by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) are as follows [4]:

A. Preoccupations involving having or developing a serious illness.
B. Absence of somatic symptoms or, if present, they are only mild in intensity. In the presence of another medical condition or high risk for developing a medical condition (e.g., presence of strong family history), the preoccupation is clearly excessive or disproportionate.
C. Having high levels of health anxiety, along with the individual being easily alarmed about his/her personal health status.
D. Performing excessive health-related behaviors (e.g., repeatedly checking his/her body for signs of illness) or exhibiting maladaptive avoidance (e.g., avoiding medical care).
E. Being preoccupied with the illness for at least 6 months, with the possibility that the specific illness that is feared may change over that period.
F. The preoccupation is not better explained by another mental disorder, such as somatic symptom disorder, panic disorder, GAD, body dysmorphic disorder, obsessive-compulsive disorder, or delusional disorder (somatic type).

Specifiers include categorizing the patient as care-seeking or care-avoidant [4].

As mentioned above, having a medical condition does not preclude IAD diagnosis, since IAD can still be comorbid with medical illnesses, as long as the health-related anxieties or preoccupations are out of proportion to the objective reality of the medical illness [10].

Differential Diagnosis

The differential diagnoses for IAD include [4][10]:

- Other medical conditions: including neurological/endocrine conditions, occult malignancies, or other diseases affecting multiple body systems
- Somatic symptom disorder (SSD)

- Obsessive-compulsive disorder (OCD): the patient suffers intrusive thoughts of disease conviction or worry of developing a disease (obsessions) and might display compulsions, such as seeking reassurance
- Anxiety disorders (e.g. GAD)
- Adjustment disorders
- Body dysmorphic disorder (BDD): considered as a differential because of the common display of repetitive body-checking habits.
- Major depressive disorder: considered especially when the health-related anxieties mostly present in the setting of depressive episodes and disappear with the remission of the episodes
- Psychotic disorders: considered especially when the somatic symptoms are of a delusional quality and an unrealistic nature (e.g. claiming that an organ is rotting or dead)
- Personality disorders

One of the biggest challenges of diagnosing IAD is differentiating it from SSD because both conditions share a somewhat-similar presentation and are in fact sometimes falsely used interchangeably. The key to differentiating between them lies in identifying the predominant thought pattern. In IAD, patients are apprehensive of having or developing a disease whilst having absent or minimal somatic symptoms. In SSD, patients have one or more physical complaints not explained by a known medical condition. Another side of differentiation is the nature of the symptoms experienced, wherein IAD they are of cognitive or emotional nature, and in SSD are somatic. [11][12]

Treatment

Treatment revolves on three main axes: patient education, reassurance, and psychotherapy, all of which focus on helping IAD patients cope with their health anxieties. Pharmacotherapy can also be used but is not the mainstay of treatment. Most patients require a combination of pharmacotherapy and psychotherapy [10].

Only after medical illness has been ruled out should IAD be considered. Among the initial stages of treatment, the care provider should be able to establish rapport with the patient so that the patient feels comfortable discussing their health concerns without feeling judged or dismissed with an invalidation of what they are experiencing. The care provider should refer the patient to a psychiatrist (in a tactful and non-judgmental way) and schedule regular follow-ups with only one primary care provider to decrease the overutilization of medical systems and avoid unnecessary imaging studies, specialist referrals, and laboratory investigations. [1][2]

Of the psychotherapies used to manage IAD, cognitive behavioral therapy (CBT) has received the most empirical support with many trials showing its efficacy [13]. CBT emphasizes the role of dysfunctional maladaptive beliefs in maintaining the illness

anxiety using behavioral modification strategies. It also may be useful in instructing patients on how to respond to bodily signals by educating them about normal somatic sensations and their normal variations. CBT may also address excessive body-checking habits [1][14].

Another form of psychotherapy often employed is mindfulness-based stress reduction (which results in enhanced psychological strength, decreased physical and psychological symptoms, increased ability to relax, and capacity to cope with long- and short-term stressors) [15] and exposure therapy (which teaches patients to confront the bodily sensations and situations avoided by a person due to fear of illness. It also teaches them to tolerate the uncertainty regarding a sensation being a real symptom or not and helps them recognize that the distress they experience is transient) [16].

Pharmacotherapy is used when the patient education, reassurance, and psychotherapy fail to adequately reduce the severity of the patient's course of illness. Drugs used include antidepressants, namely SSRIs and SNRIs, which have been proven to be effective [2]. Patients responding to antidepressant therapy are recommended to receive maintenance therapy for at least 6-12 months [10].

Prognosis

It is worth noting that IAD is a chronic disease that typically worsens with age [1][5]. It adversely affects the patient's personal life and relationships, as well as prevents normal functioning, and causes severe disability. Patients may frequently take leaves from work/school causing problems with their occupational functioning due to frequent fears of being sick. It also inflicts a financial burden from frequent healthcare visits and medical bills [4][9][17].

Some factors can worsen or improve the outcomes of IAD patients. Patients who are referred early for psychiatric evaluation have better outcomes as opposed to those who only receive general medical care. Other good prognostic factors include having a patient who is cooperative, tolerant, and hopeful. Patients who respond well to psychotherapy, pharmacotherapy or a combination of both have good outcomes. Reciprocally, patients with refractory IAD despite pharmacotherapy and psychotherapy have bad prognostic outcomes. [17]

IAD patients also have higher risks of developing a concurrent psychiatric illness such as other anxiety disorders, major depressive disorder, or personality disorders [4,10].

References

1. Newby JM, Hobbs MJ, Mahoney AEJ, Wong SK, Andrews G. DSM-5 illness anxiety disorder and somatic symptom disorder: Comorbidity, correlates, and overlap with DSM-IV hypochondriasis. J Psychosom Res. 2017 Oct;101:31–7.

2. Scarella TM, Boland RJ, Barsky AJ. Illness Anxiety Disorder: Psychopathology, Epidemiology, Clinical Characteristics, and Treatment. Psychosom Med. 2019 Jun;81(5):398–407.
3. Online Etymology Dictionary [Internet]. [cited 2021 Feb 14]. Available from: https://www.etymonline.com/word/hypochondria
4. American Psychiatric Association (2013). Somatic Symptom and Related Disorders. In: Diagnostic and Statistical Manual of Mental Disorders DSM. (5th ed.).
5. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015 Sep;17(3):327–35.
6. Alberts NM, Hadjistavropoulos HD, Sherry SB, Stewart SH. Linking Illness in Parents to Health Anxiety in Offspring: Do Beliefs about Health Play a Role? Behav Cogn Psychother. 2016 Jan;44(1):18–29.
7. Barsky AJ, Wyshak G, Klerman GL. Psychiatric comorbidity in DSM-III-R hypochondriasis. Arch Gen Psychiatry. 1992 Feb;49(2):101–8.
8. Tyrer P, Eilenberg T, Fink P, Hedman E, Tyrer H. Health anxiety: the silent, disabling epidemic. Vol. 353, BMJ (Clinical research ed.). England; 2016. p. i2250.
9. Almalki M, Al-Tawayjri I, Al-Anazi A, Mahmoud S, Al-Mohrej A. A Recommendation for the Management of Illness Anxiety Disorder Patients Abusing the Health Care System. Case Rep Psychiatry. 2016;2016:6073598.
10. French JH, Hameed S. Illness Anxiety Disorder. In Treasure Island (FL); 2020.
11. Holder-Perkins V, Wise TN, Williams DE. Hypochondriacal Concerns: Management Through Understanding. Prim Care Companion J Clin Psychiatry. 2000 Aug;2(4):117–21.
12. Lipowski ZJ. Somatization: the experience and communication of psychological distress as somatic symptoms. Psychother Psychosom. 1987;47(3–4):160–7.
13. Bouman T. Psychological Treatments for Hypochondriasis: A Narrative Review. Curr Psychiatry Rev. 2014 Feb 2;10.
14. Williams MJ, McManus F, Muse K, Williams JMG. Mindfulness-based cognitive therapy for severe health anxiety (hypochondriasis): an interpretative phenomenological analysis of patients' experiences. Br J Clin Psychol. 2011 Nov;50(4):379–97.
15. Flowers S. Mindfulness-Based Stress Reduction. Woodburn, OR Am Coll Lifestyle Med. 2014;
16. Weck F, Neng JMB, Schwind J, Höfling V. Exposure therapy changes dysfunctional evaluations of somatic symptoms in patients with hypochondriasis (health anxiety). A randomized controlled trial. J Anxiety Disord. 2015 Aug;34:1–7.
17. Chappell AS. Toward a Lifestyle Medicine Approach to Illness Anxiety Disorder (Formerly Hypochondriasis). Am J Lifestyle Med. 2018;12(5):365–9.

Article topic: Substance/Medication- Induced Bipolar Disorder (BPD).

Author: Nadine Absy.

Editor: Aroob Awwad.

Reviewer: Ahda Jbara.

Overview

Substance/medication- induced mental disorders encompass depressive, anxiety-related, psychotic and manic symptoms that result from the usage or abuse of certain medications and/or substances. These symptoms may occur during active use, intoxication or even withdrawal (1).

Etiology and Pathophysiology

Depressive episodes are precipitated by heavy alcohol abuse in almost half of the cases of substance-induced mood disorders (2). Substances that follow alcohol in frequency are cocaine and opioids, particularly heroin. Iatrogenic substances such as anticonvulsants, digoxin, interferon (INF) and corticosteroids may also induce mood disorders. Both drug and substance abuse may induce states of mania or depression (3).

Current standing theories suggest that the substances induce affective states by altering normal neurotransmitter transmission within vital neural circuits. Drug-induced mood symptoms involve changes in dopaminergic, corticotrophin-releasing factor (CRF), neuropeptide Y and serotonergic neurotransmitters (4).

Epidemiology

Each etiological substance has its own risk of inducing its respective bipolar disorder. Amongst those diagnosed with bipolar I about 61% have a lifetime prevalence of having a substance-abuse disorder. Therefore, it is crucial to differentiate primary bipolar disorder from substance/medication induced bipolar (5).

Presentation (6)

Patients with substance-induced mood disorders typically present very similarly- if not identical- to patients with independent mood disorders. However, in case of the earlier, the patient's mood symptoms directly related to the use of substances/medication. In

addition, the symptoms resolve following the resolution of severe intoxication or withdrawal.

Usually, severe substance intoxication causes symptoms of either mania or hypomania, while withdrawal is more consistent with symptoms of depression. When the withdrawal phase supplants the intoxication phase, symptoms of agitation, irritability and dysphoria usually predominate.

Depressants commonly induce a state of euphoria, mood liability or poor impulse control. On the other hand, stimulants mimic a manic/ hypomanic episode of BPD and manifest as symptoms of euphoria, loss of appetite, a grandiose attitude, increased energy, and paranoia while stimulants withdrawal causes the opposite of the symptoms, as the patient mostly complains of depressed mood, apathy, lethargy, and even suicidal ideation.

Differential Diagnoses (7)

Observation of patients during the period in which they have abstained from inciting agents may be a useful way to differentiate substance-induced disorders from primary psychiatric illnesses. A family history of primary psychiatric illnesses can also help in distinguishing the two. A distinction might become more complex when patients have manic symptoms since there is an increased probability of temporal association or causality of mood symptoms following substance use.

The DSM-V cites a significant difference between substance/medication-induced bipolar disorder and independent bipolar disorder, which is that patients with independent BPD, unlike those of substance/medication induced BPD, may develop hypomania or mania following the use of antidepressant medications or other treatment. Likewise, patients who develop electroconvulsive-therapy-induced manic or hypomanic episodes that persist beyond the physiological effects of the treatment are diagnosed with independent bipolar disorder not substance/ medication induced bipolar.

Diagnosis

For a valid diagnosis the patient must admit to using a substance or a positive laboratory test must be found. The timeline of events provides an easy feature that helps differentiate independent affective disorders from substance-induced ones. Symptoms of substance-induced mood disorders should resolve after stopping the cause of severe intoxication or acute withdrawal symptoms, which can take up to 1 month. A thorough history, laboratory results and imaging studies should be adequate to rule out any other etiology that might be causing the ongoing affective disorder (5).

According to the DSM-V (7) the diagnostic criteria for substance-induced bipolar disorder and related disorders is as follows:

A. A predominating clear and persistent disturbance in mood distinguished by an expansive, elevated, or irritable mood with or without depressed mood, or decreased interest or pleasure in most or all activities.
B. Physical exam, history or laboratory findings show evidence of the ability of the inciting substance/medication to produce the symptoms seen in criterion 1, and the development of these symptoms during or following substance intoxication/ withdrawal.
C. The patient's symptoms are not better explained by bipolar or bipolar-related disorder independent of substance/medication use. Evidence of an independent disorder may include the following:

1. Symptoms appear before the onset of substance/medication use.
2. Symptoms persevere for a considerable period of time (e.g. more than 1 month) after the cessation of acute withdrawal or severe intoxication from the substance/medication.
3. Other evidence suggesting the presence of an independent BPD (not related to substance/medication use).

D. The disturbances experienced by the patient do not happen exclusively during delirium.

E. The disturbance results in clinically significant distress or causes significant impairment on the patient's normal functioning.

Management and Treatment

If a person is diagnosed with a substance-induced mood disorder, this implies that upon the cessation of the inciting substance the disorder should resolve, yet the severity of the episode may at times dictate the need for medication. Whether or not to simply provide supportive care is a decision that depends on the physician's clinical judgment.

Due to the safety of antidepressants, certain studies support the application and usage of empirical antidepressants in settings where depressive symptoms exist along with evidence of substance abuse (6). For manic symptoms, certain guidelines recommend the usage of second-generation antipsychotics since they have a faster onset of action than mood stabilizers (8)(9).

The most vital aspect of treatment is the emphasis on the importance of abstinence from inciting agents. This should be conveyed to the patient along with treatment modalities in accordance with the inciting substance.

Prognosis

The most compact prognostic factor is adherence to abstinence from inciting agents. Hence, factors that help in sobriety will enable remission. Such factors include psychotherapy, financial stability, compliance to medication, good family ties and social support.

Nonetheless, in the absence of the aforementioned factors, suicide becomes the most serious complication that looms over mood disorders induced by substances. It is worthy to note that studies have found that suicide attempts are more common in substance-induced affective disorders than independent ones. Particularly, a study found that a four-fold increased risk of suicide exists when mood disorders precipitate in setting of substance use (10).

References

1. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004 Aug;61(8):807–16.
2. Schuckit MA, Smith TL, Danko GP, Pierson J, Trim R, Nurnberger JI, et al. A comparison of factors associated with substance-induced versus independent depressions. J Stud Alcohol Drugs. 2007 Nov;68(6):805–12.
3. Patten SB, Barbui C. Drug-induced depression: a systematic review to inform clinical practice. Psychother Psychosom. 2004;73(4):207–15.
4. Markou A, Kosten TR, Koob GF. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 1998 Mar;18(3):135–74.
5. Myrick H, Cluver J, Swavely S, Peters H. Diagnosis and treatment of co-occurring affective disorders and substance use disorders. Psychiatr Clin North Am. 2004 Dec;27(4):649–59.
6. Quello SB, Brady KT, Sonne SC. Mood disorders and substance use disorder: a complex comorbidity. Sci Pract Perspect. 2005 Dec;3(1):13–21.
7. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association; 2013.
8. Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. Arch Gen Psychiatry. 2005 Jan;62(1):37–45.
9. Brown ES, Nejtek VA, Perantie DC, Bobadilla L. Quetiapine in bipolar disorder and cocaine dependence. Bipolar Disord. 2002 Dec;4(6):406–11.
10. Conner KR, Gamble SA, Bagge CL, He H, Swogger MT, Watts A, et al. Substance-induced depression and independent depression in proximal risk for suicidal behavior. J Stud Alcohol Drugs. 2014 Jul;75(4):567–72.

Article Topic: Obsessive-Compulsive Disorder (OCD).

Author: Rama Qatarneh.

Editor: Hala Qaryouti.

Reviewer: Ahda Jbara.

Introduction

Obsessive-compulsive disorder (OCD) is a common, usually chronic mental disorder denoted by two key features; intrusive obsessions, and repetitive behaviors or compulsions. Obsessions include thoughts, images, or impulses to carry out specific tasks that are often unsettling and anxiety-provoking, while compulsions involve performing repetitive motor acts which normally serve to temporarily offset the distress of obsessions (Fig.1) (1).

Previously, OCD was recognized as one of the anxiety disorders. However, starting with the fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) it was added to a new section termed obsessive-compulsive and related disorders (OCRDs) (2). Even though major overlaps between OCD and the other OCRDs exist; including intersecting comorbidities and family history (3,4), there are also crucial differences in their biology, assessment, and management (5,6).

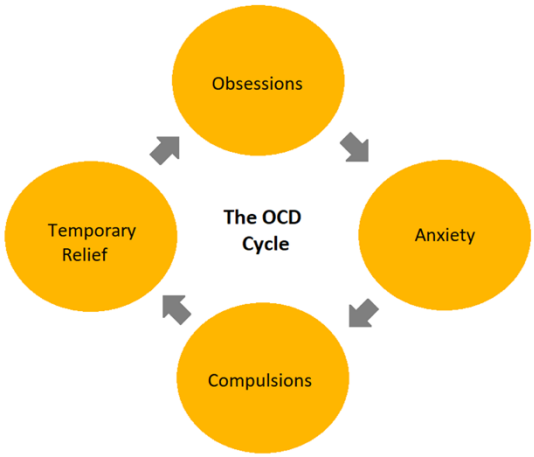


Fig.1

Epidemiology

The lifetime prevalence of OCD roughly ranges between 1% to 3% in adults (7,8) and adolescents (9), yet it is substantially more frequently encountered in psychiatric and medical practices than these figures indicate due to its chronicity. The age of onset reported by OCD patients assumes a bimodal pattern, with symptoms often appearing in childhood/adolescence in males and early adulthood in females (10).

When taking into consideration the role of gender, past studies utilizing samples of children noted a greater proportion of males presenting with OCD (11–13), whereas samples of adults identified a greater proportion of females (14).

Clinical Presentation

OCD patients present with obsessions, compulsions, or in the majority of cases both. Obsessions are persistent, disturbing, undesired thoughts, images, or urges that go against the patient's personal beliefs (ego-dystonic). They cause marked distress, consequently attempts are made to ignore, suppress, or neutralize them with other thoughts or acts. Recurring themes incorporate concerns about contamination, safety or harm, unwanted acts of aggression, inappropriate sexual or religious thoughts, and the necessity for symmetry or exactness. Whereas compulsions are repetitive habits or mental acts the person feels forced to execute, either as a reaction to an obsession (e.g., to stop a dreaded event from taking place) or according to set rules designed to prevent or lessen distress. The acts are evidently excessive or irrational and usually reduce anxiety but are not pleasurable. Regularly encountered compulsions involve exaggerated cleaning, checking, counting, repeating routine activities, and hoarding (Fig.2). Overall, symptoms give rise to significant distress, are time-consuming (>1 h/d), or hinder function (1).

In 90% of cases, patients with lifetime OCD present with other comorbid disorders, most commonly including anxiety disorders, mood disorders, impulse-control disorders, substance use disorders, tic disorders, and other OCRDs (8).

Throughout the course of illness, most patients have insight at some point, as they can acknowledge their symptoms to be senseless or excessive. Nevertheless, this is not the case for all patients and the DSM-5 criteria permits for a range of insight (Fig.3) (15).

Dimension	Obsessions	Compulsions
Contamination symptoms	Concerns about dirt and germs, among others	Washing, showering or cleaning
Harm-related symptoms	Concerns about harm	Checking
Unacceptability symptoms	Intrusive aggressive, sexual or religious thoughts	Mental rituals or praying
Symmetry symptoms	Symmetry concerns	Ordering, straightening, repeating or counting
Hoarding symptoms	Hoarding concerns	Hoarding behaviours

Fig.2 | OCD symptom dimensions. (16)

Differential Diagnosis

OCD should be differentiated from several other psychiatric conditions (16,17):

- ## Anxiety and depressive disorders

Worries and thoughts involved in generalized anxiety disorder and depression are usually about real-life concerns and are more likely to be less irrational. Compulsions are also not usually encountered in these conditions.

- ## Autism spectrum disorders

It may be challenging to distinguish obsessions and compulsions from the restricted, repetitive, and inflexible activities and interests seen in autism spectrum disorders; still, OCD patients do not commonly present with the difficulties in social communication or reciprocal social interactions encountered in autism spectrum disorders.

- ## Other OCRDs

Even though repetitive thoughts and acts take place in a range of other OCRDs (as in hoarding disorder, body dysmorphic disorder, excoriation disorder, and trichotillomania), the main concerns and forms of repetitive behaviors in all these conditions are different from those in OCD.

- **Psychotic disorders**

Having insight may differentiate OCD from a psychotic illness, such as schizophrenia. Yet in patients with OCD and poor or absent insight, differentiation can be reached by noting the absence of additional features present in psychotic illnesses, such as hallucinations and formal thought disorder.

- **Obsessive-compulsive personality disorder**

Patients with obsessive-compulsive personality disorder are inclined towards perfectionism and rigid control but they express their thoughts as appropriate rather than intrusive in the way that obsessions are experienced.

- **Tic disorders**

Tics are characterized by sudden, rapid, recurrent, non-rhythmic behaviors and are not driven by the urge to alleviate anxiety as a result of obsessive thoughts, rather, they are thought to be driven by somatic discomfort.

Risk Factors

Potential risk factors for developing OCD are (18):

- Age (late adolescence)
- Genetic Factors
- Race (non-white)
- Being unmarried
- Abusing drugs
- Presence of other mental conditions (mood and anxiety disorders)

Etiology

To this day, the precise etiology behind OCD is not fully understood. However, multiple plausible theories exist:

- **Molecular mechanisms**

Several key neurotransmitters are found to be implicated in OCD including serotonin, dopamine, and glutamate (19–21). When it comes to the involvement of serotonin, the use of selective serotonin reuptake inhibitors (SSRIs) and clomipramine play an important part in the treatment of OCD, hence proving its role (19,20). As for dopamine,

dopamine agonists and reuptake inhibitors may cause or aggravate OCD symptoms (22–24). In glutamate, evidence backing its role in OCD involves neurochemical studies, genetic studies, pharmacological experiments, and case reports with glutamate-altering drugs (25).

- ## Neurobiological

The use of structural and functional brain imaging modalities illustrated that some areas within the brain are involved in the pathophysiology of OCD. These are the orbitofrontal cortex, anterior cingulate gyrus, and caudate nucleus. Additionally, the superior temporal gyrus, parietal lobe, and hippocampus may also be affected (26,27).

Involvement of the basal ganglia has been reported as well. The basal ganglia are composed of the striatum (caudate nucleus and putamen), globus pallidus, substantia nigra, nucleus accumbens, and subthalamic nucleus. They function in compound integrative motor and behavioral functions such as the execution of learned behaviors (28). Lesions within the basal ganglia were noted to induce acquired OCD (27,29).

Finally, OCD may be owing to a defect involving the cortico–striato–thalamo–cortical circuit. A crucial role for this network is maintaining self-control (30–32).

- ## Genetic

The risk of having OCD is raised by two folds in the presence of first-degree relatives, yet, if individuals among first-degree relatives have childhood-onset OCD, the risk is further increased by ten folds (2). Certain genes implicated in the development of OCD are:

1. **Serotonergic genes**: include the 5-HTTLPR serotonin transporter, 5HT2a serotonin receptor, 5HT1D beta receptor gene, and the serotonin 5HT2c receptor (33).
2. **Dopaminergic genes**: some studies demonstrate replications in the dopamine receptor type 4 (DRD4) gene (33).
3. **Glutamatergic genes**: such as the glutamate transporter gene, SLC1A1, and the gene encoding for ionotropic glutamate receptors, SAPAP3 (25).
4. **Other genes**: additional genes that can be complicated with OCD are the SLITRK1, BDNF locus, gamma-aminobutyric acid type receptor 1 (GABBR1), OLIG2, and myelin oligodendrocyte glycoprotein (33,34)

DSM-5 Diagnostic Criteria

DSM-5 diagnostic criteria for OCD

A. Presence of obsessions, compulsions, or both:

Obsessions are defined by (1) and (2):
1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

Compulsions are defined by (1) and (2):
1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.
Note: Young children may not be able to articulate the aims of these behaviors or mental acts.
B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

D. The disturbance is not better explained by the symptoms of another mental disorder

Specify if:
- With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true.
- With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true.
- With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true.

Specify if:
Tic-related: The individual has a current or past history of a tic disorder.

Fig.3| DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; obsessive–compulsive disorder (2).

Management

Generally, treatment in patients with OCD encompasses psychological and pharmacological approaches.

- Psychological Interventions

Cognitive-behavioral therapy (CBT) is regarded as the most beneficial psychotherapy for OCD, and when performed by experienced practitioners, may even be the most effective treatment amongst all types of treatments, including pharmacotherapy (35–39). It involves 2 sections: cognitive reappraisal and behavioral interventions, usually in the fashion of exposure-response prevention (38,39).

- Pharmacotherapy

Selective Serotonin Reuptake Inhibitors (SSRIs) are the first-line pharmacological treatment for OCD due to their safety, tolerability, efficacy, and lack of abuse potential (40). Normally higher SSRI doses are used in OCD patients than in patients with anxiety disorders or major depression (41). Concerning treatment efficacy, guidelines outline that a period of 8–12 weeks is the optimal recommended duration of an SSRI trial (36,40,42). After reaching remission, the suggested maintenance duration of pharmacotherapy is a minimum of 12–24 months (43), although longer treatment may be necessary for many patients due to the risk of relapse after discontinuing medication (44). Another agent that may be used in the treatment of OCD is Clomipramine; a tricyclic antidepressant (TCA) which was the first agent to show efficacy in OCD treatment (45). Due to its various side effects, clomipramine is no longer considered as first-line pharmacotherapy for OCD (46).

In patients that fail to fully respond to first-line treatment, multiple approaches exist. These include CBT and SSRI combination therapy (47), switching to a different SSRI, using a higher dose of the maximum recommended dose, a trial of a serotonin–noradrenaline reuptake inhibitor (48–52), and SSRI augmentation with antipsychotics, clomipramine, or glutamatergic agents (53–56). Finally, neuromodulation and neurosurgery can be a last resort option for patients with treatment-resistant OCD (16).

Prognosis

Overall, the long-term outcomes in OCD patients are not entirely hopeless as at least half the treatment-seeking patients exhibit symptomatic remission (57). However, when left untreated, OCD is often chronic with waxing and waning symptoms (58,59). Only 5% to 10% have spontaneous remission (59,60), and another 5% to 10% encounter progressive worsening of their symptoms (60).

References

1. Goodman WK, Grice DE, Lapidus KAB, Coffey BJ. Obsessive-compulsive disorder. Psychiatr Clin North Am. 2014;37(3):257–67.
2. American Psychiatric Association 2013. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS FIFTH EDITION DSM-5TM.
3. Bienvenu OJ, Samuels JF, Riddle MA, Hoehn-Saric R, Liang KY, Cullen BAM, et al. The relationship of obsessive-compulsive disorder to possible spectrum disorders: Results from a family study. Biol Psychiatry. 2000;48(4):287–93.
4. Monzani B, Rijsdijk F, Harris J, Mataix-Cols D. The structure of genetic and environmental risk factors for dimensional representations of DSM-5 obsessive-compulsive spectrum disorders. JAMA Psychiatry. 2014;71(2):182–9.
5. Phillips KA, Stein DJ, Rauch SL, Hollander E, Fallon BA, Barsky A, et al. Should an obsessive-compulsive spectrum grouping of disorders be included in DSM-V? Depress Anxiety. 2010;27(6):528–55.
6. Stein DJ, Kogan CS, Atmaca M, Fineberg NA, Fontenelle LF, Grant JE, et al. The classification of Obsessive-Compulsive and Related Disorders in the ICD-11. J Affect Disord. 2016;190:663–74.
7. Adam Y, Meinlschmidt G, Gloster AT, Lieb R. Obsessive-compulsive disorder in the community: 12-month prevalence, comorbidity and impairment. Soc Psychiatry Psychiatr Epidemiol. 2012;47(3):339–49.
8. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry [Internet]. 2010;15(1):53–63. Available from: http://dx.doi.org/10.1038/mp.2008.94

9. Politis S, Magklara K, Petrikis P, Michalis G, Simos G, Skapinakis P. Epidemiology and comorbidity of obsessive–compulsive disorder in late adolescence: a cross-sectional study in senior high schools in Greece. Int J Psychiatry Clin Pract. 2017;21(3):188–94.
10. Dell'Osso B, Benatti B, Hollander E, Fineberg N, Stein DJ, Lochner C, et al. Childhood, adolescent and adult age at onset and related clinical correlates in obsessive–compulsive disorder: a report from the International College of Obsessive–Compulsive Spectrum Disorders (ICOCS). Int J Psychiatry Clin Pract. 2016;20(4):210–7.
11. Mathis MA De, Alvarenga P De, Funaro G, Torresan RC, Moraes I, Torres AR, et al. Revista Brasileira de Psiquiatria a literature review. Off J Brazilian Psychiatr Assoc. 2011;33:390–9.
12. Geller DA. Obsessive-Compulsive and Spectrum Disorders in Children and Adolescents. Psychiatr Clin North Am. 2006;29(2):353–70.
13. Mancebo MC, Garcia AM, Pinto A, Freeman JB, Przeworski A, Stout R, et al. Juvenile-onset OCD: Clinical features in children, adolescents and adults. Acta Psychiatr Scand. 2008;118(2):149–59.
14. Rasmussen SA, Eisen JL. Epidemiology of obsessive-compulsive disorder. J Clin Psychiatry. 1990 Feb;51 Suppl:10–3; discussion 14.
15. Storch EA, Milsom VA, Merlo LJ, Larson M, Geffken GR, Jacob ML, et al. Insight in pediatric obsessive-compulsive disorder: Associations with clinical presentation. Psychiatry Res. 2008;160(2):212–20.
16. Stein DJ, Costa DLC, Lochner C, Miguel EC, Reddy YCJ, Shavitt RG, et al. Obsessive–compulsive disorder. Nat Rev Dis Prim [Internet]. 2019;5(1):1–21. Available from: http://dx.doi.org/10.1038/s41572-019-0102-3
17. Richter PMA, Ramos RT. Obsessive-Compulsive Disorder. Contin Lifelong Learn Neurol. 2018;24(3, BEHAVIORAL NEUROLOGY AND PSYCHIATRY):828–44.
18. Fontenelle LF, Hasler G. The analytical epidemiology of obsessive-compulsive disorder: Risk factors and correlates. Prog Neuro-Psychopharmacology Biol Psychiatry. 2008;32(1):1–15.
19. Billett EA, Richter MA, King N, Heils A, Lesen KP, Kennedy JL. Obsessive compulsive disorder, response to serotonin reuptake inhibitors and the serotonin transporter gene. Mol Psychiatry. 1997;2(5):403–6.
20. Hesse S, Müller U, Lincke T, Barthel H, Villmann T, Angermeyer MC, et al. Serotonin and dopamine transporter imaging in patients with obsessive-compulsive disorder. Psychiatry Res - Neuroimaging. 2005;140(1):63–72.
21. Nemoda Z, Szekely A, Sasvari-Szekely M. Psychopathological aspects of dopaminergic gene polymorphisms in adolescence and young adulthood. Neurosci Biobehav Rev [Internet]. 2011;35(8):1665–86. Available from: http://dx.doi.org/10.1016/j.neubiorev.2011.04.002
22. Kouris S. Methylphenidate-induced obsessive-compulsiveness [1]. J Am Acad Child Adolesc Psychiatry [Internet]. 1998;37(2):135. Available from: http://dx.doi.org/10.1097/00004583-199802000-00001
23. Serby M. Methylphenidate-Induced Obsessive-Compulsive Symptoms in an Elderly Man. CNS Spectr. 2003;8(8):612–3.
24. Kelley BJ, Duker AP, Chiu P. Dopamine agonists and pathologic behaviors. Parkinsons Dis. 2012;2012.
25. Pittenger C, Bloch MH, Williams K. Glutamate abnormalities in obsessive compulsive disorder: Neurobiology, pathophysiology, and treatment. Pharmacol Ther [Internet]. 2011;132(3):314–32. Available from: http://dx.doi.org/10.1016/j.pharmthera.2011.09.006
26. Laven DL, Bednarczyk EM. CNS assessment using functional neuro-PET imaging. J Pharm Pract. 2001;14(4):308–31.
27. Maia T V, Cooney RE, Peterson BS. The neural bases of obsessive-compulsive disorder in children and adults. Dev Psychopathol. 2008;20(4):1251–83.
28. Sbordone RJ, Saul RE. Neuropsychology for Healthcare Professionals and Attorneys 2nd edition.
29. Chacko RC, Corbin MA, Harper RG. Acquired obsessive-compulsive disorder associated with basal ganglia lesions. J Neuropsychiatry Clin Neurosci. 2000;12(2):269–72.
30. Marsh R, Maia T V., Peterson BS. Functional disturbances within frontostriatal circuits across multiple childhood psychopathologies. Am J Psychiatry. 2009;166(6):664–74.
31. Ahmari SE, Spellman T, Douglass NL, Kheirbek MA, Simpson HB, Deisseroth K, et al. Repeated cortico-striatal stimulation generates persistent OCD-like behavior. Science (80-). 2013;340(6137):1234–9.
32. Welch JM, Lu J, Rodriguiz RM, Trotta NC, Peca J, Ding JD, et al. Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. Nature. 2007;448(7156):894–900.
33. Nestadt G, Grados M, Samuels JF. Genetics of obsessive-compulsive disorder. Psychiatr Clin North Am. 2010;33(1):141–58.
34. Ozomaro U, Cai G, Kajiwara Y, Yoon S, Makarov V, Delorme R, et al. Characterization of SLITRK1 Variation in Obsessive-Compulsive Disorder. PLoS One. 2013;8(8):1–7.
35. Koran LM, Simpson HB. Guideline watch (March 2013): Practice guideline for the treatment of patients with obsessive-compulsive disorder. APA Pract Guidel [Internet]. 2013;(March):1–22. Available from: http://psychiatryonline.org/content.aspx?bookid=28&sectionid=40634994
36. Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Am J Psychiatry. 2007;164(7 Suppl):5–53.
37. Rosa-Alcázar AI, Sánchez-Meca J, Gómez-Conesa A, Marín-Martínez F. Psychological treatment of obsessive-compulsive disorder: A meta-analysis. Clin Psychol Rev [Internet]. 2008;28(8):1310–25. Available from: http://dx.doi.org/10.1016/j.cpr.2008.07.001
38. Gava I, Barbui C, Aguglia E, Carlino D, Churchill R, De Vanna M, et al. psychological treatments versus treatment as usual for obsessive compulsive disorder (OCD). Cochrane Database Syst Rev. 2007;(2).
39. Öst LG, Havnen A, Hansen B, Kvale G. Cognitive behavioral treatments of obsessive-compulsive disorder. A systematic review and meta-analysis of studies published 1993-2014. Clin Psychol Rev [Internet]. 2015;40:156–69. Available from: http://dx.doi.org/10.1016/j.cpr.2015.06.003

40. Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). Cochrane Database Syst Rev. 2008;(1).
41. Bloch MH, McGuire J, Landeros-Weisenberger A, Leckman JF, Pittenger C. Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. Mol Psychiatry [Internet]. 2010;15(8):850–5. Available from: http://dx.doi.org/10.1038/mp.2009.50
42. Bandelow B, Sher L, Bunevicius R, Hollander E, Kasper S, Zohar J, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. Int J Psychiatry Clin Pract. 2012;16(2):77–84.
43. Greist JH, Bandelow B, Hollander E, Marazziti D, Montgomery SA, Nutt DJ, et al. WCA recommendations for the long-term treatment of obsessive-compulsive disorder in adults. CNS Spectr. 2003 Aug;8(8 Suppl 1):7–16.
44. Batelaan NM, Bosman RC, Muntingh A, Scholten WD, Huijbregts KM, van Balkom AJLM. Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials. BMJ. 2017 Sep;358:j4461.
45. Cox BJ, Swinson RP, Morrison B, Lee PS. Clomipramine, fluoxetine, and behavior therapy in the treatment of obsessive-compulsive disorder: a meta-analysis. J Behav Ther Exp Psychiatry. 1993 Jun;24(2):149–53.
46. Bandelow B, Zohar J, Hollander E, Kasper S, Möller H-J, Zohar J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. world J Biol psychiatry Off J World Fed Soc Biol Psychiatry. 2008;9(4):248–312.
47. Baxter LR, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, et al. Caudate Glucose Metabolic Rate Changes with Both Drug and Behavior Therapy for Obsessive-Compulsive Disorder. Arch Gen Psychiatry. 1992;49(9):681–9.
48. Dougherty DD, Jameson M, Deckersbach T, Loh R, Thompson-Hollands J, Jenike M, et al. Open-label study of high (30 mg) and moderate (20 mg) dose escitalopram for the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol. 2009 Nov;24(6):306–11.
49. Ninan PT, Koran LM, Kiev A, Davidson JRT, Rasmussen SA, Zajecka JM, et al. High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder: a multicenter double-blind trial. J Clin Psychiatry. 2006 Jan;67(1):15–22.
50. Pampaloni I, Sivakumaran T, Hawley CJ, Al Allaq A, Farrow J, Nelson S, et al. High-dose selective serotonin reuptake inhibitors in OCD: a systematic retrospective case notes survey. J Psychopharmacol. 2010 Oct;24(10):1439–45.
51. Albert U, Aguglia E, Maina G, Bogetto F. Venlafaxine versus clomipramine in the treatment of obsessive-compulsive disorder: a preliminary single-blind, 12-week, controlled study. J Clin Psychiatry. 2002 Nov;63(11):1004–9.
52. Dougherty DD, Corse AK, Chou T, Duffy A, Arulpragasam AR, Deckersbach T, et al. Open-Label Study of Duloxetine for the Treatment of Obsessive-Compulsive Disorder. Int J Neuropsychopharmacol [Internet]. 2015 Feb 1;18(2). Available from: https://doi.org/10.1093/ijnp/pyu062
53. Albert U, Carmassi C, Cosci F, De Cori D, Nicola M Di, Ferrari S, et al. Role and clinical implications of atypical antipsychotics in anxiety disorders, obsessive-compulsive disorder, trauma-related, and somatic symptom disorders: A systematized review. Int Clin Psychopharmacol. 2016;31(5):249–58.
54. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: Antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. Mol Psychiatry. 2006;11(7):622–32.
55. Dold M, Aigner M, Lanzenberger R, Kasper S. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: An update meta-analysis of double-blind, randomized, placebo-controlled trials. Int J Neuropsychopharmacol. 2015;18(9):1–11.
56. Pittenger C. Glutamatergic agents for OCD and related disorders. Curr Treat Options Psychiatry. 2015;2(3):271–83.
57. Sharma E, Math SB. Course and outcome of obsessive – compulsive disorder. 2021;43–50.
58. Bloch MH, Green C, Kichuk SA, Dombrowski PA, Wasylink S, Billingslea E, et al. Long-term outcome in adults with obsessive-compulsive disorder. Depress Anxiety. 2013;30(8):716–22.
59. Eisen JL, Pinto A, Mancebo MC, Dyck IR, Orlando ME, Rasmussen SA. A 2-year prospective follow-up study of the course of obsessive-compulsive disorder. J Clin Psychiatry. 2010 Aug;71(8):1033–9.
60. Rasmussen SA, Eisen JL. The Epidemiology and Clinical Features of Obsessive-Compulsive Disorder. Psychiatr Clin North Am. 1992;15(4):743–58.

Article Topic: Persistent depressive Disorder (PDD).

Author: Noor Qasem.

Editor: Aroob Awwad.

Reviewer: Hala Qaryouti.

Keywords: persistent depressive disorder, PDD, chronic depression, dysthymic disorder.

Overview

Persistent depressive disorder (PDD), newly introduced by the DSM-5, is a common mood disorder with a chronic course encompassing both dysthymic disorder and chronic major depressive disorder (MDD) (2). It is defined as a depressed mood for most of the day, for m days, indicated either subjectively by the individual or by observation from others, continuing for at least 2 years in adults, or 1 year in children and adolescents (2). As compared to its non-chronic counterpart, PDD is often accompanied by a more disabling course and poorer prognosis usually associated with an earlier onset of depressive symptoms (3), a higher incidence of psychiatric co-morbidities (4) and a more complicated treatment course, with higher suicide and hospitalization rates (5).

Although previously thought to be a mild disorder, most individuals with dysthymia often far exceed the minimum number of symptoms required for diagnosis and portray as much functional impairment and poor course as acute depressive disorders (6–10). Despite different forms of chronic depression ranging in severity, they all share similar characteristics of comorbid anxiety and personality disorders, substance abuse, personality traits, depresso-typic cognitions, coping style, history of childhood maltreatment and outcomes (6,11–16). In addition, the fact that the majority of patients with pure dysthymia eventually experience a major depressive episode (MDE) further highlights how closely intertwined these disorders are, thus allowing for the broader, more controversial grouping of the DSM-5.

Prevalence and Epidemiology

PDD is regarded as a public health problem due to its frequency and impact. Around 20-30% of all depressive disorders have a chronic course (17,18). With a lifetime prevalence of 5.7% (3-6%) (17), much less than the 20.6% of MDD (19), persistent depressive disorder is suggested to have a relapsing- remitting pattern, rather than a constant one (20).

Women are affected almost twice as men, (11, 21–23). Association between the incidence of PDD and race, ethnicity and education were found to be inconsistent (11,21,23,24). With regards to age, depression rates tend to decrease with increasing age, especially in ages over 65 (25).

Etiology and Pathogenesis

It is a common conceptualization that depression, regardless of type or chronicity, is a multifactorial disorder brought upon by more than just biological factors. Social and psychological aspects contribute just as equally. Compared with MDD or depressive disorders in general, PDD has an increased likelihood of first-degree relatives having the same condition.

Information regarding the etiology of PDD, or its constituents, is rather scarce (26). However, several risk factors have been identified. These include, but are not limited to, genetics, epigenetics, previous history of mental illness, neuroticism, high anxiety and life stressors, and past trauma, especially childhood maltreatment, abuse or neglect (27,28).

Strong evidence has been found supporting the theory that the 5-HTTLPR serotonin transporter variant moderates the relationship between stress and depression. The majority of studies on mentioned polymorphisms, however, do not differentiate between types of depression, making it harder to distinguish these conditions genetically (29,30).

The biology is a complex interplay between neurotransmitters and receptors. Serotonin, dopamine, epinephrine, norepinephrine, GABA and glutamate have been identified as the primary neurotransmitters at play (31–34).

PDD in children and adolescents is considered a risk factor for the development of MDD later in life, courtesy of the white matter microstructure changes seen in individuals with early-onset chronic depression (35). The left uncinate, inferior fronto-occipital and cerebrospinal tracts all show significant volume reduction. Also, the frontal areas of the brain as well as the hippocampus show moderate to large volume reductions (36). These changes may be the reason behind the chronicity of the disorder and the recurrence of symptoms (35).

PDD in the elderly shows a slightly different course because older adults, opposed to young adults, present with a relatively pure form of dysthymia, and with less comorbid psychiatric disorders or personal or family history of major depression. So, the term ‘dysthymic disorder’ could remain useful for the elderly. (37,38).

Some of the proposed causes of PDD in the elderly include psychological stresses like bereavement or loss of social support (39), and biological mechanisms like

neurodegenerative (40) or cerebrovascular disease (41). A genetically driven thesis for PDD is more likely to be present for early-onset rather than late-onset disorder (42).

Comorbidities

The most prevalent comorbidities are anxiety disorders, personality disorders as well as alcohol and substance abuse disorders. In comparison to patients with non-chronic depression, those with PDD were found to have more psychiatric comorbidities. These comorbidities are viewed as a source of vulnerability that either precedes chronic depression or alters its depressive state. Around 77.7% of patients with CD present with comorbid anxiety disorders (43), 70% of patients with comorbid personality disorders (with a stronger association to cluster C disorders especially avoidant and dependent types) (44,45), and 37.1% with alcohol and substance-abuse disorders (13). Most studies found higher rates of axis 1 and 2 psychiatric disorders in patients with CD than non-CD (4).

DSM-5 Diagnostic Criteria (2)

To diagnose a patient with PDD, the following criteria must occur:

A. Depressed mood for most of the day, for more days than not, indicated by the subject or observed by others, for at least 2 years in adults. In children and adolescents, mood can be irritable, and duration must be at least 1 year.
B. Presence, while depressed, of two (or more) of the following:

1. Changes in appetite.
2. Changes in sleep pattern.
3. Low energy or fatigue.
4. Low self-esteem.
5. Feeling of hopelessness.
6. Poor concentration or difficulty making decisions.

C. During the previously mentioned period of disturbance, the subject has never been without the symptoms in Criteria A and B for more than 2 months at a time.

D. Criteria for MDD may be continuously present for 2 years.

E. There has never been a manic or a hypomanic episode, and criteria have never been met for cyclothymic disorder.

F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorders.

G. The symptoms are not due to physiological effects of a substance, such drug abuse/medication, or another medical condition.

H. The symptoms cause clinically significant distress or impairment in different aspects of daily functioning.

After the diagnosis of PDD has been established, **specify** whether:

1. The disorder is:

- With anxious distress
- With mixed features
- With melancholic features
- With atypical features
- With mood-congruent psychotic features
- With mood-incongruent psychotic features
- Of peripartum onset

2. The disorder is in:

- partial remission
- full remission

3. The onset is:

- Early onset: before the age of 21 years.
- Late onset: at or after the age of 21 years.

4. For the most recent 2 years of PDD, specify if it was accompanied by:

- Pure dysthymic syndrome: Full criteria for MDE have not been met at least in the preceding 2 years.
- Persistent MDE: Full criteria for MDE have been met in the preceding 2-year period.
- Intermittent MDEs, with current episode: Full criteria for MDE are currently met, but there have been periods of at least 8 weeks in at least the preceding 2 years with symptoms below threshold for a full episode.
- Intermittent MDEs, without current episode: Full criteria for MDE are not currently met, but there has been one or more in at least the preceding 2 years.

Treatment

Since it is deemed one of the most challenging and tedious disorders to treat in psychiatry, traditional monotherapy is usually of less use, and around 40% of the patients are considered treatment-resistant (46). This, in addition to the higher rates of suicide attempts and hospitalizations, calls for a tailored treatment approach.

Complications to treatment are brought upon by several factors. Some of which include: the low percentage of patients receiving adequate treatment (47), low compliance rates (48), the specific characteristics and features seen in PDD patients including childhood trauma or neglect (27) and the low rate of spontaneous remission (49). Altogether, they constitute a resilient disorder.

- ## Pharmacotherapy

SSRIs, moclobemide, imipramine, ritanserin and amisulpride are the most efficacious drugs in treatment of PDD. However, of the bunch, fluoxetine is proven to be less effective, and imipramine is the least acceptable out of the drugs (50).

Episode length is noted to be a predictor of poorer response to pharmacotherapy (51–53). Nonetheless, some patients with persistent depression do respond and recover after acute phase treatment (54,55).

- ## Psychotherapy and Combination Therapy

In 2010, a study by Cuijpers et al. found that psychotherapy has a significant effect on PDD patients when compared with the control group, with the degree of effect being linked to the number of sessions. Optimal effect was achieved at a minimum of 18 sessions (56).

The efficacy of monotherapy is dependent on the baseline depression or comorbid anxiety, history of pharmacotherapy, age, and the different subtypes present (46). This shows that for certain subgroups either pharmacotherapy or psychotherapy alone could be a reasonable treatment option, further emphasizing the importance of a tailored approach.

Patients with early-onset PDD, those with childhood maltreatment (57), and those with comorbid social anxiety disorders (50) benefit more from a combination of CBASP (Cognitive-Behavioral Analysis System of Psychotherapy) and medication rather than monotherapy. Patients with the chronic MDD are also more likely to experience increased acute benefits from combination therapy compared to psychotherapy or drug therapy alone (58).

Prognosis

PDD is a chronic disorder with a prolonged, bitter course and a high risk of relapse that greatly impacts the patient's quality of life. This is reflected in high rates of suicide, both attempted and completed (59,60), higher rates of employment unproductiveness (61), the poorer self-proclaimed health status (62), and the fact that majority of the patients with dysthymic disorder eventually go on to develop superimposed major depressive episodes (63,64).

The estimated 5-year recovery rate from dysthymic disorder is 52.9%. However, among those who recover, 45.2% relapse during a mean of 23 months (65). Lower rates of recovery were seen in patients with chronic stress (66) and those with comorbidities such as anxiety or personality disorders (66–69).

Altogether, despite tending to show mild to moderate symptoms, on the long run, PDD is quite severe (65).

References

1. Boredpanda. depression [Internet]. 2017. Available from: https://www.boredpanda.com/depression-through-art/?media_id=659791
2. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association, 2013.
3. Hölzel L, Härter M, Reese C, Kriston L. Risk factors for chronic depression - A systematic review. Vol. 129, Journal of Affective Disorders. Elsevier; 2011. p. 1–13.
4. Köhler S, Chrysanthou S, Guhn A, Sterzer P. Differences between chronic and nonchronic depression: Systematic review and implications for treatment. Depress Anxiety. 2019;36(1):18–30.
5. Satyanarayana S, Murray, Enns W, Cox BJ, Sareen; Jitender. Prevalence and Correlates of Chronic Depression in the Canadian Community Health Survey: Mental Health and Well-Being. Vol. 54, The Canadian Journal of Psychiatry. 2009.
6. Rhebergen D, Beekman AT, Graaf R de, Nolen WA, Spijker J, Hoogendijk WJ, et al. The three-year naturalistic course of major depressive disorder, dysthymic disorder and double depression. J Affect Disord [Internet]. 2009 Jun [cited 2021 Mar 22];115(3):450–9. Available from: https://pubmed.ncbi.nlm.nih.gov/19042028/
7. Klein DN, Shankman SA, Lewinsohn PM, Rohde P, Seeley JR. Family Study of Chronic Depression in a Community Sample of Young Adults. Am J Psychiatry [Internet]. 2004 Apr [cited 2021 Mar 22];161(4):646–53. Available from: https://pubmed.ncbi.nlm.nih.gov/15056510/
8. Leader JB, Klein DN. Social adjustment in dysthymia, double depression and episodic major depression. J Affect Disord [Internet]. 1996 Apr 12 [cited 2021 Mar 22];37(2–3):91–101. Available from: https://pubmed.ncbi.nlm.nih.gov/8731071/
9. Klein DN, Kocsis JH, McCullough JP, Holzer CE, Hirschfeld RMA, Keller MB. Symptomatology in dysthymic and major depressive disorder. Psychiatr Clin North Am [Internet]. 1996 [cited 2021 Mar 22];19(1):41–53. Available from: https://pubmed.ncbi.nlm.nih.gov/8677219/
10. Hung CI, Liu CY, Yang CH. Persistent depressive disorder has long-term negative impacts on depression, anxiety, and somatic symptoms at 10-year follow-up among patients with major depressive disorder. J Affect Disord [Internet]. 2019 Jan 15 [cited 2021 Mar 22];243:255–61. Available from: https://pubmed.ncbi.nlm.nih.gov/30248637/
11. Blanco C, Okuda M, Markowitz JC, Liu SM, Grant BF, Hasin DS. The epidemiology of chronic major depressive disorder and dysthymic disorder: Results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry [Internet]. 2010 Dec [cited 2021 Mar 22];71(12):1645–56. Available from: /pmc/articles/PMC3202750/
12. Pepper CM, Klein DN, Anderson RL, Riso LP, Ouimette PC, Lizardi H. DSM-III-R axis II comorbidity in dysthymia and major depression. Am J Psychiatry [Internet]. 1995 [cited 2021 Mar 22];152(2):239–47. Available from: https://pubmed.ncbi.nlm.nih.gov/7840358/
13. Klein DN, Riso LP, Donaldson SK, Schwartz JE, Anderson RL, Ouimette PC, et al. Family study of early-onset dysthymia. Mood and personality disorders in relatives of outpatients with dysthymia and episodic major depression and normal controls. Arch Gen Psychiatry. 1995 Jun;52(6):487–96.

14. Jonsson U, Bohman H, Von Knorring L, Olsson G, Paaren A, Von Knorring AL. Mental health outcome of long-term and episodic adolescent depression: 15-year follow-up of a community sample. J Affect Disord [Internet]. 2011 May [cited 2021 Mar 22];130(3):395–404. Available from: https://pubmed.ncbi.nlm.nih.gov/21112639/
15. Lizardi H, Klein DN, Ouimette PC, Riso LP, Anderson RL, Donaldson SK. Reports of the childhood home environment in early-onset dysthymia and episodic major depression. J Abnorm Psychol [Internet]. 1995 [cited 2021 Mar 22];104(1):132–9. Available from: https://pubmed.ncbi.nlm.nih.gov/7897035/
16. Yang T, Dunner DL. Differential subtyping of depression. Depress Anxiety [Internet]. 2001 [cited 2021 Mar 22];13(1):11–7. Available from: https://pubmed.ncbi.nlm.nih.gov/11233455/
17. Murphy JA, Byrne GJ. Prevalence and correlates of the proposed DSM-5 diagnosis of Chronic Depressive Disorder. J Affect Disord [Internet]. 2012 Jul [cited 2021 Mar 22];139(2):172–80. Available from: https://pubmed.ncbi.nlm.nih.gov/22381955/
18. Angst J, Gamma A, Rössler W, Ajdacic V, Klein DN. Long-term depression versus episodic major depression: Results from the prospective Zurich study of a community sample. J Affect Disord [Internet]. 2009 May [cited 2021 Apr 9];115(1–2):112–21. Available from: https://pubmed.ncbi.nlm.nih.gov/18973954/
19. Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry [Internet]. 2018 Apr 1 [cited 2021 Mar 22];75(4):336–46. Available from: https://jamanetwork.com/
20. Persistent Depressive Disorder - StatPearls - NCBI Bookshelf [Internet]. [cited 2021 Mar 23]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541052/
21. Vandeleur CL, Fassassi S, Castelao E, Glaus J, Strippoli MPF, Lasserre AM, et al. Prevalence and correlates of DSM-5 major depressive and related disorders in the community. Psychiatry Res [Internet]. 2017 Apr 1 [cited 2021 Mar 22];250:50–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28142066/
22. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-Month Prevalence of DSM-III-R Psychiatric Disorders in the United States: Results from the National Comorbidity Survey. Arch Gen Psychiatry [Internet]. 1994 [cited 2021 Mar 22];51(1):8–19. Available from: https://pubmed.ncbi.nlm.nih.gov/8279933/
23. Rubio JM, Markowitz JC, Alegría A, Pérez-Fuentes G, Liu SM, Lin KH, et al. Epidemiology of chronic and nonchronic major depressive disorder: Results from the national epidemiologic survey on alcohol and related conditions. Depress Anxiety [Internet]. 2011 Aug [cited 2021 Mar 22];28(8):622–31. Available from: https://pubmed.ncbi.nlm.nih.gov/21796739/
24. Riolo SA, Nguyen TA, Greden JF, King CA. Prevalence of depression by race/ethnicity: Findings from the national health and nutrition examination survey III [Internet]. Vol. 95, American Journal of Public Health. Am J Public Health; 2005 [cited 2021 Mar 22]. p. 998–1000. Available from: https://pubmed.ncbi.nlm.nih.gov/15914823/
25. Kessler RC, Birnbaum H, Bromet E, Hwang I, Sampson N, Shahly V. Age differences in major depression: Results from the national comorbidity survey replication (NCS-R). Psychol Med [Internet]. 2010 Feb [cited 2021 Mar 22];40(2):225–37. Available from: https://pubmed.ncbi.nlm.nih.gov/19531277/
26. Griffiths J, Ravindran A V., Merali Z, Anisman H. Dysthymia: A review of pharmacological and behavioral factors [Internet]. Vol. 5, Molecular Psychiatry. Nature Publishing Group; 2000 [cited 2021 Mar 22]. p. 242–61. Available from: www.nature.com/mp
27. Nelson J, Klumparendt A, Doebler P, Ehring T. Childhood maltreatment and characteristics of adult depression: Meta-analysis [Internet]. Vol. 210, British Journal of Psychiatry. Royal College of Psychiatrists; 2017 [cited 2021 Mar 22]. p. 96–104. Available from: https://pubmed.ncbi.nlm.nih.gov/27908895/
28. Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in men. Am J Psychiatry. 2006 Jan;163(1):115–24.
29. Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. Arch Gen Psychiatry [Internet]. 2011 May [cited 2021 Mar 22];68(5):444–54. Available from: https://pubmed.ncbi.nlm.nih.gov/21199959/
30. Uher R, McGuffin P. The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update [Internet]. Vol. 15, Molecular Psychiatry. Mol Psychiatry; 2010 [cited 2021 Mar 22]. p. 18–22. Available from: https://pubmed.ncbi.nlm.nih.gov/20029411/
31. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression [Internet]. Vol. 54, Archives of General Psychiatry. American Medical Association; 1997 [cited 2021 Mar 22]. p. 597–606. Available from: https://pubmed.ncbi.nlm.nih.gov/9236543/
32. Nutt DJ, Baldwin DS, Clayton AH, Elgie R, Lecrubier Y, Montejo AL, et al. The role of dopamine and norepinephrine in depression and antidepressant treatment [Internet]. Vol. 67, Journal of Clinical Psychiatry. J Clin Psychiatry; 2006 [cited 2021 Mar 22]. p. 46–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16848678/
33. Sanacora G, Mason GF, Rothman DL, Behar KL, Hyder F, Petroff OAC, et al. Reduced cortical γ-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. Arch Gen Psychiatry [Internet]. 1999 Nov [cited 2021 Mar 22];56(11):1043–7. Available from: https://pubmed.ncbi.nlm.nih.gov/10565505/
34. Thase ME. Molecules That Mediate Mood. N Engl J Med [Internet]. 2007 Dec 6 [cited 2021 Mar 22];357(23):2400–2. Available from: https://pubmed.ncbi.nlm.nih.gov/18057345/
35. Vilgis V, Vance A, Cunnington R, Silk TJ. White matter microstructure in boys with persistent depressive disorder. J Affect Disord [Internet]. 2017 Oct 15 [cited 2021 Mar 22];221:11–6. Available from: https://pubmed.ncbi.nlm.nih.gov/28628762/

36. Koolschijn PCMP, Van Haren NEM, Lensvelt-Mulders GJLM, Hulshoff Pol HE, Kahn RS. Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. Hum Brain Mapp [Internet]. 2009 Nov [cited 2021 Mar 22];30(11):3719–35. Available from: https://pubmed.ncbi.nlm.nih.gov/19441021/
37. Devanand DP, Adorno E, Cheng J, Burt T, Pelton GH, Roose SP, et al. Late onset dysthymic disorder and major depression differ from early onset dysthymic disorder and major depression in elderly outpatients. J Affect Disord [Internet]. 2004 [cited 2021 Apr 9];78(3):259–67. Available from: https://pubmed.ncbi.nlm.nih.gov/15013252/
38. Devanand DP, Nobler MS, Singer T, Kiersky JE, Turret N, Roose SP, et al. Is dysthymia a different disorder in the elderly? Am J Psychiatry [Internet]. 1994 [cited 2021 Apr 9];151(11):1592–9. Available from: https://pubmed.ncbi.nlm.nih.gov/7943446/
39. Chou KL, Liang K, Sareen J. The association between social isolation and DSM-IV mood, anxiety, and substance use disorders: Wave 2 of the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry [Internet]. 2011 [cited 2021 Mar 22];72(11):1468–76. Available from: https://pubmed.ncbi.nlm.nih.gov/21295001/
40. Kumar A, Jin Z, Bilker W, Udupa J, Gottlieb G. Late-onset minor and major depression: Early evidence for common neuroanatomical substrates detected by using MRI. Proc Natl Acad Sci U S A [Internet]. 1998 Jun 23 [cited 2021 Mar 22];95(13):7654–8. Available from: /pmc/articles/PMC22713/
41. Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, et al. Executive dysfunction and long-term outcomes of geriatric depression. Arch Gen Psychiatry [Internet]. 2000 [cited 2021 Mar 22];57(3):285–90. Available from: https://pubmed.ncbi.nlm.nih.gov/10711915/
42. Devanand DP. Dysthymic disorder in the elderly population. Int Psychogeriatrics. 2014;26(1):39–48.
43. Wiersma JE, Hovens JGFM, Van Oppen P, Giltay EJ, Van Schaik DJF, Beekman ATF, et al. The importance of childhood trauma and childhood life events for chronicity of depression in adults. J Clin Psychiatry [Internet]. 2009 Jul [cited 2021 Mar 22];70(7):983–9. Available from: https://pubmed.ncbi.nlm.nih.gov/19653975/
44. Garyfallos G, Adamopoulou A, Karastergiou A, Voikli M, Sotiropoulou A, Donias S, et al. Personality disorders in dysthymia and major depression. Acta Psychiatr Scand [Internet]. 1999 [cited 2021 Mar 22];99(5):332–40. Available from: https://pubmed.ncbi.nlm.nih.gov/10353448/
45. Klein JP, Roniger A, Schweiger U, Späth C, Brodbeck J. The association of childhood trauma and personality disorders with chronic depression: A cross-sectional study in depressed outpatients. J Clin Psychiatry [Internet]. 2015 Jun 1 [cited 2021 Mar 22];76(6):e794–801. Available from: https://pubmed.ncbi.nlm.nih.gov/26132688/
46. Schramm E, Klein DN, Elsaesser M, Furukawa TA, Domschke K. Review of dysthymia and persistent depressive disorder: history, correlates, and clinical implications. The Lancet Psychiatry [Internet]. 2020;7(9):801–12. Available from: http://dx.doi.org/10.1016/S2215-0366(20)30099-7
47. Kocsis JH, Gelenberg AJ, Rothbaum B, Klein DN, Trivedi MH, Manber R, et al. Chronic forms of major depression are still undertreated in the 21st century: Systematic assessment of 801 patients presenting for treatment. J Affect Disord [Internet]. 2008 Sep [cited 2021 Mar 22];110(1–2):55–61. Available from: https://pubmed.ncbi.nlm.nih.gov/18272232/
48. Gopinath S, Katon WJ, Russo JE, Ludman EJ. Clinical factors associated with relapse in primary care patients with chronic or recurrent depression. J Affect Disord [Internet]. 2007 Aug [cited 2021 Mar 22];101(1–3):57–63. Available from: https://pubmed.ncbi.nlm.nih.gov/17156852/
49. McCullough JP, Kasnetz, Braith JA, Carr KF, Cones JH, Fielo J, et al. A longitudinal study of an untreated sample of predominantly late onset characterological dysthymia. J Nerv Ment Dis [Internet]. 1988 [cited 2021 Mar 22];176(11):658–67. Available from: https://pubmed.ncbi.nlm.nih.gov/3183650/
50. Kriston L, Von Wolff A, Westphal A, Hölzel LP, Härter M. Efficacy and acceptability of acute treatments for persistent depressive disorder: A network meta-analysis. Depress Anxiety [Internet]. 2014 [cited 2021 Mar 22];31(8):621–30. Available from: https://pubmed.ncbi.nlm.nih.gov/24448972/
51. Fournier JC, DeRubeis RJ, Shelton RC, Hollon SD, Amsterdam JD, Gallop R. Prediction of Response to Medication and Cognitive Therapy in the Treatment of Moderate to Severe Depression. J Consult Clin Psychol [Internet]. 2009 Aug [cited 2021 Mar 22];77(4):775–87. Available from: https://pubmed.ncbi.nlm.nih.gov/19634969/
52. Löwe B, Schenkel I, Bair MJ, Göbel C. Efficacy, predictors of therapy response, and safety of sertraline in routine clinical practice: Prospective, open-label, non-interventional postmarketing surveillance study in 1878 patients. J Affect Disord [Internet]. 2005 Aug [cited 2021 Mar 22];87(2–3):271–9. Available from: https://pubmed.ncbi.nlm.nih.gov/15979151/
53. Furukawa TA, Kato T, Shinagawa Y, Miki K, Fujita H, Tsujino N, et al. Prediction of remission in pharmacotherapy of untreated major depression: development and validation of multivariable prediction models. Psychol Med [Internet]. 2019 Oct 1 [cited 2021 Mar 22];49(14):2405–13. Available from: https://pubmed.ncbi.nlm.nih.gov/30430961/
54. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. Am J Psychiatry [Internet]. 2006 Jan [cited 2021 Mar 22];163(1):28–40. Available from: https://pubmed.ncbi.nlm.nih.gov/16390886/
55. Sung SC, Haley CL, Wisniewski SR, Fava M, Nierenberg AA, Warden D, et al. The impact of chronic depression on acute and long-term outcomes in a randomized trial comparing selective serotonin reuptake inhibitor monotherapy versus each of 2 different antidepressant medication combinations. J Clin Psychiatry [Internet]. 2012 [cited 2021 Mar 22];73(7):967–76. Available from: https://pubmed.ncbi.nlm.nih.gov/22687487/
56. Cuijpers P, van Straten A, Schuurmans J, van Oppen P, Hollon SD, Andersson G. Psychotherapy for chronic major depression and dysthymia: A meta-analysis [Internet]. Vol. 30, Clinical Psychology Review. Clin Psychol Rev; 2010 [cited 2021 Mar 22]. p. 51–62. Available from: https://pubmed.ncbi.nlm.nih.gov/19781837/
57. Klein JP, Erkens N, Schweiger U, Kriston L, Bausch P, Zobel I, et al. Does Childhood Maltreatment Moderate the Effect of the Cognitive Behavioral Analysis System of Psychotherapy versus Supportive Psychotherapy in Persistent Depressive

Disorder? [Internet]. Vol. 87, Psychotherapy and Psychosomatics. S. Karger AG; 2018 [cited 2021 Mar 22]. p. 46–8. Available from: https://pubmed.ncbi.nlm.nih.gov/29306939/
58. Furukawa TA, Efthimiou O, Weitz ES, Cipriani A, Keller MB, Kocsis JH, et al. Cognitive-Behavioral Analysis System of Psychotherapy, Drug, or Their Combination for Persistent Depressive Disorder: Personalizing the Treatment Choice Using Individual Participant Data Network Metaregression. Psychother Psychosom [Internet]. 2018 Jun 1 [cited 2021 Mar 22];87(3):140–53. Available from: https://www.karger.com/Article/FullText/489227
59. Bernal M, Haro JM, Bernert S, Brugha T, de Graaf R, Bruffaerts R, et al. Risk factors for suicidality in Europe: Results from the ESEMED study. J Affect Disord [Internet]. 2007 Aug [cited 2021 Mar 22];101(1–3):27–34. Available from: https://pubmed.ncbi.nlm.nih.gov/17074395/
60. Bakken K, Vaglum P. Predictors of suicide attempters in substance-dependent patients: A six-year prospective follow-up. Clin Pract Epidemiol Ment Heal [Internet]. 2007 Oct 10 [cited 2021 Mar 22];3. Available from: https://pubmed.ncbi.nlm.nih.gov/17927822/
61. Adler DA, Irish J, McLaughlin TJ, Perissinotto C, Chang H, Hood M, et al. The work impact of dysthymia in a primary care population. Gen Hosp Psychiatry [Internet]. 2004 Jul [cited 2021 Mar 22];26(4):269–76. Available from: https://pubmed.ncbi.nlm.nih.gov/15234821/
62. Barbui C, Motterlini N, Garattini L. Health status, resource consumption, and costs of dysthymia. A multi-center two-year longitudinal study. J Affect Disord [Internet]. 2006 Feb [cited 2021 Mar 22];90(2–3):181–6. Available from: https://pubmed.ncbi.nlm.nih.gov/16352344/
63. Kovacs M, Akiskal HS, Gatsonis C, Parrone PL. Childhood-Onset Dysthymic Disorder: Clinical Features and Prospective Naturalistic Outcome. Arch Gen Psychiatry [Internet]. 1994 [cited 2021 Mar 22];51(5):365–74. Available from: https://pubmed.ncbi.nlm.nih.gov/8179460/
64. Horwath E, Johnson J, Klerman GL, Weissman MM. Depressive Symptoms as Relative and Attributable Risk Factors for First-Onset Major Depression. Arch Gen Psychiatry [Internet]. 1992 [cited 2021 Mar 22];49(10):817–23. Available from: https://pubmed.ncbi.nlm.nih.gov/1417435/
65. Klein DN, Schwartz JE, Rose S, Leader JB. Five-year course and outcome of dysthymic disorder: A prospective, naturalistic follow-up study. Am J Psychiatry [Internet]. 2000 Jun [cited 2021 Mar 22];157(6):931–9. Available from: https://pubmed.ncbi.nlm.nih.gov/10831473/
66. Hayden EP, Klein DN. Outcome of dysthymic disorder at 5-year follow-up: The effect of familial psychopathology, early adversity, personality, comorbidity, and chronic stress. Am J Psychiatry [Internet]. 2001 [cited 2021 Mar 22];158(11):1864–70. Available from: https://pubmed.ncbi.nlm.nih.gov/11691693/
67. Shankman SA, Klein DN. The impact of comorbid anxiety disorders on the course of dysthymic disorder: A 5-year prospective longitudinal study. J Affect Disord [Internet]. 2002 [cited 2021 Mar 22];70(2):211–7. Available from: https://pubmed.ncbi.nlm.nih.gov/12117634/
68. Laptook RS, Klein DN, Dougherty LR. Ten-year stability of depressive personality disorder in depressed outpatients. Am J Psychiatry [Internet]. 2006 [cited 2021 Mar 22];163(5):865–71. Available from: https://pubmed.ncbi.nlm.nih.gov/16648328/
69. Markowitz JC, Skodol AE, Petkova E, Xie H, Cheng J, Hellerstein DJ, et al. Longitudinal comparison of depressive personality disorder and dysthymic disorder. Compr Psychiatry [Internet]. 2005 Jul [cited 2021 Mar 22];46(4):239–45. Available from: https://pubmed.ncbi.nlm.nih.gov/16175753

Illustration 1: Boredpanda. depression [Internet]. 2017. Available from: https://www.boredpanda.com/depression-through-art/?media_id=659791

Article topic: Attention-Deficit Hyperactivity Disorder (ADHD).

Author: Rawan Osama Abu Nsair.

Editor: Hala Qaryouti.

Reviewer: Ahda Jbara.

Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders, first described by Sir Alexander Crichton, a Scottish physician, through a case with symptoms similar to ADHD in 1798. The disorder's name was changed several times throughout the years to finally land on ADHD.
As the name suggests, ADHD patients have mainly inattentiveness and hyperactivity symptoms. It is usually of childhood-onset, and can persist to adulthood, although symptoms and severity may fluctuate. Since it affects a patients' daily life and interferes with their work/school performance and social communication, diagnosis should be made, and treatment started as soon as possible.

Epidemiology

ADHD has a worldwide pooled prevalence of around 7.2% (1). A US study conducted in 2016 revealed that almost 9.4% (6.1 million) of US children aged 2-17 years had ever received an ADHD diagnosis. (2).
In comparison to the general US population, black Americans have been shown to have higher rates of ADHD (3). Using 2011 National Survey of Children's Health (NSCH) data for children aged 4-17 years, a study found that boys are more likely to receive a diagnosis of ADHD (4), with 1 in 5 high school boys diagnosed compared to only 1 in 11 girls in the same time period (4). Another study calculated a male: female ratio of 2.28:1 with a prevalence of 9.2% (5). Geographically, according to a Systematic Review and Meta-analysis, ADHD is more common in the Middle East compared to North America (1).

Etiology and Pathogenesis

The exact etiology of ADHD is still not well-understood, but studies have confirmed that both genetic and environmental factors play an important role in its development.
In a twin study, ADHD carried a high heritability rate (88%) across the life span (6), whereas the Genome-Wide Association Studies (GWASs), which focused on single nucleotide polymorphisms (SNPs), estimated a heritability of 22% (7).

GWASs have also identified 12 genome-wide significant risk loci, many of which are located in or around genes involved in neurodevelopmental processes that could be related to ADHD, such as FOXP2 (Forkhead box protein P2), SORCS3 (Sortilin Related VPS10 Domain Containing Receptor 3), and DUSP6 (Dual Specificity Phosphatase 6) (7).

ADHD can co-occur with other psychiatric disorders like bipolar disorder (8) and autism-spectrum disorders (9) due to genetic overlap.

Research has also identified environmental factors associated with ADHD, most of which are prenatal such as maternal pre-pregnancy obesity/ overweight, pre-eclampsia, hypertension, as well as smoking and acetaminophen use during pregnancy (10). It is worth mentioning that if fetal acetaminophen exposure happens in the third trimester or if there was a long duration of exposure, the risk of developing ADHD increases further (11). In addition, childhood atopic diseases like asthma and eczema are also associated with ADHD development (10). The effect of these environmental factors could be exerted by gene-environment interaction (12). However, none of these associations has proven a causal relationship.
ADHD patients have executive function deficits related to deficits in noradrenergic neurotransmission (13), as high levels of catecholamines could disturb cognitive functions in the prefrontal cortex (14). For example, disruption of cortico-striato-thalamo-cortical circuits affects attention and executive functions in ADHD patients (15). Dopaminergic signaling could also be disrupted in these patients (13).
Changes in biochemical regulation in the brain could be accompanied by neuroimaging alterations. Volume reduction is the main alteration that could be noted in the prefrontal cortex, basal ganglia (striatum), dorsal anterior cingulate cortex, the splenium of the corpus callosum, and the cerebellum (especially the posterior inferior vermis) (16). In addition, neuroimaging could reveal cortical thickness reduction (most prominent in prefrontal regions which control cognitive processes). Also noticed is a delay in brain maturation (i.e., delay in attaining peak cerebrum thickness), with the median age by which 50% of cortical areas attaining peak thickness in ADHD patients being 10.5 years compared to 7.5 years for healthy peers (17).

DSM-5 Diagnostic Criteria for ADHD (18)

A. A persistent pattern of inattention and/or hyperactivity that interferes with individual's development or functioning, characterized by (1) and/or (2):
1. Inattention: at least 6 of the following symptoms (only 5 are required if 17 years or older) present for at least 6 months, and affecting social, occupational, or academic life.
a. Failure to pay close attention to detail or making careless mistakes.
b. Difficulty maintaining attention in tasks or activities (e.g., difficulty remaining focused during lectures/ conversations).
c. Seems not listening when someone is talking to them directly.

d. Inability to follow instructions and complete tasks
e. Organizing and managing difficulties, inability to meet deadlines (e.g., difficulty managing sequential tasks; difficulty maintaining order; messy, disorganized work; poor time management; fails to meet deadlines).
f. Tends to stay away from any activity that requires continuous mental effort and concentration.
g. Frequent loss of tools necessary for task completion like pencils, keys, eyeglasses, etc.
h. Distracted easily by external distractions or odd thoughts for older adolescents
i. Often forgetful in daily activities (e.g., chores, errands; for older adolescents and adults: returning calls, keeping appointments, paying bills).

2. Hyperactivity: at least 6 of the following symptoms (only 5 required if 17 years or older) present for 6 months or more and affecting social, occupational, or academic life.
a. Squirms or makes small movements by hands when sitting.
b. Avoids occasions that require staying seated in place (e.g., leave their place in the classroom/ office).
c. Often runs or climbs in situations where it is inappropriate. (In adolescents or adults, may be limited to restlessness.)
d. Inability to engage in quiet playing activities.
e. Restless, most of the time "on the go" (e.g., unable to be or uncomfortable being still for a long time), and difficult to keep up with in public.
f. Talking excessively.
g. Tends to give answers before the question has been completed.
h. Inability to wait for turn.
i. Tend to interrupt others while talking or doing something (e.g., butts into conversations, games, or activities; may start using people's belongings without asking for permission; for adolescents and adults, may interrupt or take over what others are doing).

B. Most of the symptoms above have started before the age of 12.

C. Many symptoms of the above are present in 2 settings at least (home, school…).

D. These symptoms affect negatively the person's social, educational, or occupational life.

E. The symptoms do not occur due to schizophrenia/ another psychotic disorder/ mood disorder/ anxiety disorder, dissociative disorder/ personality disorder/ substance withdrawal or intoxication).

• Specify one of the 3 variants of ADHD:
1. Predominantly inattentive: inattention criterion (A1) is met but hyperactivity-impulsivity criterion (A2) is not met for the last 6 months.
2. Predominantly hyperactive: criterion A2 is met but Criterion A1 is not met for the past

6 months.
3. Combined: both criteria are met for the last 6 months.

• Specify if in partial remission: full criteria were met previously, fewer than the full criteria have been met for the last 6 months, but symptoms still cause functional impairment.

• Specify current severity:
1. Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present. Symptoms result in minor impairments in social or occupational functioning.
2. Moderate: shows symptoms or functional impairment between “mild” and “severe”.
3. Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe are present, or the symptoms result in significant impairment in social or occupational functioning.

Differential Diagnoses

ADHD symptoms can overlap with symptoms of other psychiatric disorders. This makes it difficult to establish the diagnosis. Moreover, ADHD is considered a heterogeneous disorder, which might be due to high rates of comorbidity with other childhood-onset disorders (20). Identifying comorbid disorders affects the management plan.
Common comorbid disorders:
• autism spectrum disorders.
• Learning disorders.
• Mood disorders, like depression and bipolar disorder.
• Anxiety.
• Disruptive behavior disorders.
• Substance abuse.

Quality of Life

Children with ADHD experience functioning impairment, mainly in social and academic life (12). They are at a higher risk of school failure, low self-esteem, social rejection by peers, delinquency (12), and anxiety (21). Sleep deficit is also common among these patients (22). Socially, they struggle with relationships, either with their families (23) or peers (24).
As they grow up, patients experience reduced occupational functioning, increased risk of unemployment (12), and emotional dysregulation (25). Inattentive and hyperactive symptoms make road traffic accidents more common among them (12).
In general, ADHD is associated with a significant reduction in the quality of life (22), although medical treatment- especially stimulants and atomoxetine- help in reducing functional impairment (12).

Adult ADHD

As aforementioned, ADHD tends to start in childhood and persists into adulthood. However, recent research suggests that a high proportion of patients show adulthood-onset of ADHD symptoms and consequent impairment (26). This condition fails to meet DSM-5 criteria which presume that many of the symptoms have started before the age of 12.
Adult ADHD also differs from childhood-onset ADHD in its lower prevalence ranging between 1% (27) and 3% (26), and its balance in male to female ratio (26,28). The predominantly inattentive subtype is the most common among adults and accounts for 47% of cases (29).
Presentation in adults is slightly different from children and adolescents as hyperactivity is usually expressed by a feeling of restlessness, talkativeness, and excessive fidgeting in settings like lectures and meetings. Incapability of holding a job or maintaining personal relationships and impatience are considered impulsivity symptoms in adults. Inattentiveness is expressed as decision-making problems, feeling bored, and being easily distracted. (30)
Both adult and childhood-onset ADHD are associated with comorbidities such as mood and anxiety disorders, antisocial personality disorder, and substance abuse disorder (28). ADHD affects adults' quality of life, who are less likely to enroll in college (31) and more likely to experience employment difficulties (32). In addition, patients find it difficult to maintain relationships due to emotional excitability (29).

Treatment

1. Pharmacologic Approach:

A. Stimulants such as methylphenidate and amphetamine are the first-choice treatment for ADHD (19).
Methylphenidate and amphetamine are also equally effective (19). They stimulate central nervous system mainly through increasing the levels of extracellular dopamine and norepinephrine by blocking transporters to prevent their reuptake.
Insomnia, anorexia, dysphoria, and irritability are the main side effects of stimulants (20).

B. non-stimulants:
i. Atomoxetine: a selective norepinephrine reuptake inhibitor. It is generally less effective than stimulants on hyperactivity symptoms (19).
ii. Long-acting alpha2-adrenergic agonists: mainly clonidine and guanfacine.
For patients with comorbidities, and those who do not respond to monotherapy; a combination can be used (12). This is usually a stimulant combined with atomoxetine or an alpha2- adrenergic agonist (21).

2. non-pharmacological treatment is recommended to be used in combination with the medications through a multimodal approach (22).

A. Behavioral interventions: parent training, school-focused interventions (12).
B. Neurocognitive interventions: mainly neurofeedback and attentional and executive functioning training with interactive computer games (24).
C. Dietary interventions: mainly free fatty acid supplementation and artificial food colors extraction (23).

Prognosis

ADHD is a chronic disease, with around 79% of children and adolescents affected having persistent symptoms into adulthood (25). Although hyperactive and impulsive symptoms tend to regress, inattentive symptoms usually continue (26), and emotional liability tends to be more prominent during adulthood (27). Since the disease is of a persistent nature, it is important to provide a smooth transition from child to adult mental health services (28).

References

1. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. Pediatrics. 2015;135(4):e994–1001.
2. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment Among U.S. Children and Adolescents, 2016. J Clin Child Adolesc Psychol. 2018;47(2):199–212.
3. Cénat JM, Blais-Rochette C, Morse C, Vandette MP, Noorishad PG, Kogan C, et al. Prevalence and Risk Factors Associated with Attention-Deficit/Hyperactivity Disorder among US Black Individuals: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2021;78(1):21–8.
4. Visser SN, Danielson ML, Bitsko RH, Holbrook JR, Kogan MD, Ghandour RM, et al. Trends in the Parent-report of Health Care Provider Diagnosed and Medicated ADHD: United States, 2003-2011 HHS Public Access. J Am Acad Child Adolesc Psychiatry [Internet]. 2014;53(1):34–46. Available from: http://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC4473855&blobtype=pdf
5. Dr. Ujjwal P. Ramtekkar, M.D., M.P.E., Dr. Angela M. Reiersen, M.D., M.P.E., Dr. Alexandre A. Todorov, Ph.D., and Dr. Richard D. Todd, Ph.D. MD. Sex and age differences in Attention-Deficit/Hyperactivity Disorder symptoms and diagnoses: Implications for DSM-V and ICD-11. J Am Acad Child Adolesc Psychiatry [Internet]. 2010;49(3):217–28. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3101894/
6. Larsson H, Chang Z, D'Onofrio BM, Lichtenstein P. The heritability of clinically diagnosed attention deficit hyperactivity disorder across the lifespan. Psychol Med. 2014;44(10):2223–9.
7. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019;51(1):63–75.
8. Hulzen KJE Van, Scholz CJ, Franke B, Ripke S, Mcquillin A, Sonuga-barke EJ, et al. Genetic overlap between Attention-Deficit/Hyperactivity Disorder and Bipolar Disorder: Evidence from GWAS meta-analysis. Kimm. Biol Psychiatry. 2017;82(9):634–41.
9. Antshel KM, Russo N. Autism Spectrum Disorders and ADHD: Overlapping Phenomenology, Diagnostic Issues, and Treatment Considerations. Curr Psychiatry Rep. 2019;21(5).
10. Kim JH, Kim JY, Lee J, Jeong GH, Lee E, Lee S, et al. Environmental risk factors, protective factors, and peripheral biomarkers for ADHD: an umbrella review. The Lancet Psychiatry [Internet]. 2020;7(11):955–70. Available from: http://dx.doi.org/10.1016/S2215-0366(20)30312-6
11. Gou X, Wang Y, Tang Y, Qu Y, Tang J, Shi J, et al. Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis. Aust N Z J Psychiatry. 2019;53(3):195–206.
12. Faraone S V., Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, et al. Attention-deficit/hyperactivity disorder. Nat Rev Dis Prim. 2015;1.
13. Sekaninova N, Mestanik M, Mestanikova A, Hamrakova A, Tonhajzerova I. Novel approach to evaluate central autonomic

regulation in attention deficit/hyperactivity disorder (ADHD). Physiol Res. 2019;68(4):531–45.
14. Arnsten AFT, Mathew R, Ubriani R, Taylor JR, Li BM. A-1 Noradrenergic Receptor Stimulation Impairs Prefrontal Cortical Cognitive Function. Biol Psychiatry. 1999;45(1):26–31.
15. Zhu Y, Yang D, Ji W, Huang T, Xue L, Jiang X, et al. The relationship between neurocircuitry dysfunctions and attention deficit hyperactivity disorder: A review. Biomed Res Int. 2016;2016.
16. Emond V, Joyal C, Poissant H. Structural and functional neuroanatomy of attention-deficit hyperactivity disorder (ADHD). Encephale. 2009;35(2):107–14.
17. Shaw, P†‡, K. Eckstrand†, W. Sharp†, J. Blumenthal†, J. P. Lerch§, D. Greenstein†, L. Clasen†, A. Evans§, J. Giedd† and JLR. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation P. Shaw†‡, K. Eckstrand†, W. Sharp†, J. Blumenthal†, J. P. Lerch§, D. Greenstein†, L. Clasen†, A. Evans§, J. Giedd†, and J. L. Rapoport† †Child. Pnas [Internet]. 2007;104(49):19649–19654. Available from: http://www.nature.com/articles/nrdp201520%0Ahttp://www.scopus.com/inward/record.url?eid=2-s2.0-79951999327&partnerID=tZOtx3y1%0Ahttp://dx.doi.org/10.1016/S2215-0366(17)30049-4%0Ahttp://dx.doi.org/10.1016/S2215-0366(15)00271-0%0Ahttps://doi.org/10.1080/092
18. Diagnostic and Stastistical Manual of Mental Disorders Fifth Edition. American Psychiatric Association. 2013.
19. Austerman J. ADHD and behavioral disorders: Assessment, management, and an update from DSM-5. Cleve Clin J Med. 2015;82(11):S2–7.
20. Gnanavel S, Sharma P, Kaushal P, Hussain S. Attention deficit hyperactivity disorder and comorbidity: A review of literature. World J Clin Cases. 2019;7(17):2420–6.
21. Schatz DB, Rostain AL. ADHD with comorbid anxiety. A review of the current literature. J Atten Disord. 2006;10(2):141–9.
22. Peasgood T, Bhardwaj A, Biggs K, Brazier JE, Coghill D, Cooper CL, et al. The impact of ADHD on the health and well-being of ADHD children and their siblings. Eur Child Adolesc Psychiatry. 2016;25(11):1217–31.
23. Hoza B, Mrug S, Gerdes AC, Bukowski WM, Kraemer HC, Wigal T, et al. What aspects of peer relationships are impaired in children with attention-deficit/hyperactivity disorder? J Consult Clin Psychol. 2005;73(3):411–23.
24. Barkley RA, Fischer M, Edelbrock C, Smallish L. The Adolescent Outcome of Hyperactive Children Diagnosed by Research Criteria—III. Mother–Child Interactions, Family Conflicts and Maternal Psychopathology. J Child Psychol Psychiatry. 1991;32(2):233–55.
25. Biederman J, Spencer T, Lomedico A, Day H, Petty CR, Faraone S V. Deficient emotional self-regulation and pediatric attention deficit hyperactivity disorder: A family risk analysis. Psychol Med. 2012;42(3):639–46.
26. Moffitt TE, Houts R, Asherson P, Belsky DW, Corcoran DL, Hammerle M, et al. Is adult ADHD a childhood-onset neurodevelopmental disorder? Evidence from a four-decade longitudinal cohort study. Am J Psychiatry. 2015;172(10):967–77.
27. Kooij JJS, Buitelaar JK, van den Oord EJ, Furer JW, Rijnders CAT, Hodiamont PPG. Internal and external validity of Attention-Deficit Hyperactivity Disorder in a population-based sample of adults. Psychol Med. 2005;35(6):817–27.
28. Magnin E, Maurs C. Attention-deficit/hyperactivity disorder during adulthood. Rev Neurol (Paris) [Internet]. 2017;173(7–8):506–15. Available from: http://dx.doi.org/10.1016/j.neurol.2017.07.008
29. Zalsman G, Shilton T. Adult ADHD: A new disease? Int J Psychiatry Clin Pract. 2016;20(2):70–6.
30. Kooij SJJ, Bejerot S, Blackwell A, Caci H, Casas-Brugué M, Carpentier PJ, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry. 2010;10(1):1–24.
31. Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult outcome of hyperactive children: Adaptive functioning in major life activities. J Am Acad Child Adolesc Psychiatry [Internet]. 2006;45(2):192–202. Available from: http://dx.doi.org/10.1097/01.chi.0000189134.97436.e2
32. Adamou M, Arif M, Asherson P, Aw TC, Bolea B, Coghill D, et al. Occupational issues of adults with ADHD. BMC Psychiatry. 2013;13.
33. Cortese S, Coghill D. Twenty years of research on attention-deficit/hyperactivity disorder (ADHD): Looking back, looking forward. Evid Based Ment Health. 2018;21(4):173–6.
34. Treuer T, Gau SSF, Méndez L, Montgomery W, Monk JA, Altin M, et al. A systematic review of combination therapy with stimulants and atomoxetine for attention-deficit/hyperactivity disorder, including patient characteristics, treatment strategies, effectiveness, and tolerability. J Child Adolesc Psychopharmacol. 2013;23(3):179–93.
35. Guidelines NI for H and CE (NICE). National Institute for Health and Care Excellence (NICE) Guidelines: Attention deficit hyperactivity disorder: diagnosis and management. 2020;(Last updated 13 September 2019 [Accessed Mar 2018]). Available from: https://www.nice.org.uk/guidance/ng87
36. Cortese S, Ferrin M, Brandeis D, Holtmann M, Aggensteiner P, Daley D, et al. Neurofeedback for Attention-Deficit/Hyperactivity Disorder: Meta-Analysis of Clinical and Neuropsychological Outcomes From Randomized Controlled Trials. J Am Acad Child Adolesc Psychiatry. 2016;55(6):444–55.
37. Stevenson J, Buitelaar J, Cortese S, Ferrin M, Konofal E, Lecendreux M, et al. Research Review: The role of diet in the treatment of attention-deficit/ hyperactivity disorder - An appraisal of the evidence on efficacy and recommendations on the design of future studies. J Child Psychol Psychiatry Allied Discip. 2014;55(5):416–27.
38. Cheung CHM, Rijdijk F, McLoughlin G, Faraone S V., Asherson P, Kuntsi J. Childhood predictors of adolescent and young adult outcome in ADHD. J Psychiatr Res. 2015;62:92–100.
39. Francx W, Zwiers MP, Mennes M, Oosterlaan J, Heslenfeld D, Hoekstra PJ, et al. White matter microstructure and developmental improvement of hyperactive/impulsive symptoms in attention-deficit/hyperactivity disorder. J Child Psychol Psychiatry Allied Discip. 2015;56(12):1289–97.
40. Franke B, Michelini G, Asherson P, Banaschewski T, Bilbow A, Buitelaar JK, et al. Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. Eur Neuropsychopharmacol [Internet]. 2018;28(10):1059–88. Available from: https://doi.org/10.1016/j.euroneuro.2018.08.001

41. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. The Lancet Psychiatry [Internet]. 2018;5(2):175–86. Available from: http://dx.doi.org/10.1016/S2215-0366(17)30167-0
42. Figure 1: For kids with ADHD Therapy May Reduce the Need for Medication. https://s3.amazonaws.com/vuuzletv.com/wp-content/uploads/2020/02/13080648/ADHD-activities-1.jpg

Article Title: Conversion Disorder.

Author: Abdallah Aljabeiti.

Editor: Rama Qatarneh.

Reviewer: Ahda Jbara, Hassan Abushukair.

Keywords: Conversion Disorder, Functional Neurological Disorder, Hysteria.

Introduction

Conversion disorder (CD), or more appropriately functional neurological symptom disorder (FNSD), is a psychiatric disorder characterized by the onset of sensory, motor, or cognitive symptoms that are not compatible with a known neurological disorder. It falls under the wider category of Somatic Symptom and Related Disorders. CD used to be a diagnosis of exclusion by having to rule out numerous neurological conditions, but as per the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), the diagnosis of CD now depends on the identification of positive findings to demonstrate preserved neurological functioning (1).

History of Conversion Disorder

Before being called conversion disorder, the sudden onset of severe neurological deficits without an obvious cause was referred to as hysteria. Hysteria was a colloquial term used to refer to emotional excess as a pathology and back then encompassed multiple conditions (that are now their own distinct diagnoses) including epilepsy, histrionic personality disorder, dissociative disorders, and conversion disorder (2,3).

The oldest accounts of hysteria date back to 1900 BC where the Egyptians documented cases of abnormal behavior in women on medical papyrus. Among multiple theories, one theory attributed these behavioral abnormalities to a ‘wandering’ dried-up uterus that traverses the body in search of moisture. Subsequently, the allegedly wandering uterus could lodge itself in other areas and compress certain structures causing disease, one of which is hysteria. Egyptian doctors believed that treating hysteria could be carried out by inducing the uterus to return to its original position either by using strong-smelling substances on patients’ vulvas to make the uterus return to its position or in other instances, smelling or swallowing unsavory herbs to encourage the uterus to ‘run’ back into position.

All of this of course implies that hysteria was a disease pertinent to females only, which was the prevailing idea at the time. Fast-forwarding to sometime between the 4th and 5th centuries BC in ancient Greece, the theory set forth by the Egyptians was originally accepted and thus named 'hysteria', from the Greek word *hystera* meaning uterus, as documented by Hippocrates (3). However, with the advancement of anatomy, the theory was abandoned. In ancient Rome, 2nd century AD, Galen proposed a new theory where hysteria was thought to be caused by retention of uterine secretions. It is worth noting that Galen did acknowledge the presence of a similar disease in men, due to the retention of sperm (4).

Sometime between the 5th and 13th centuries of the Middle Ages, the focus of the etiology of hysteria was shifted from one of physical disease to one of satanic possession. Unsurprisingly, that meant hysterics were treated with prayers, amulets, and exorcisms. During the Renaissance period, many hysterics were prosecuted as witches, undergoing interrogations, torture, and execution (5). Some centuries later, around the 16th-17th centuries, there were advancements to restore hysteria back into the realm of medicine by many physicians including the French physician Charles Lepois and English physician Thomas Sydenham. Many physicians followed and hysteria became disassociated from the soul and the uterus (6).

Moving forward to the last 3 centuries, Sigmund Freud hypothesized that the etiology of hysteria and its symptoms were a reflection of unconscious conflicts and accordingly coined the term "conversion disorder" (7). However, researchers have not yet been able to find evidence supporting the notion of 'conversion' (8) and thus, the term 'conversion disorder' is carried forward to our day and time for the sake of preserving historic continuity (9). Many physicians now use CD interchangeably with FNSD or functional neurological disorders (FND), which omits any etiological inference of 'conversion' from the name.

Epidemiology

Conversion disorder is one of the most common causes of referral to neurological outpatient settings, only coming second to headaches (10,11). It is more common in women, especially those between the ages of 35 and 50 (12–14).

Etiology & Pathophysiology

Elucidating specific etiologies for the development of CD has been elusive, however, a constellation of psychological, social, and biological factors is thought to contribute to precipitating or perpetuating CD. These include trauma, adverse life events, acute/chronic stressors, and childhood abuse (emotional/sexual). Other intrinsic factors include poor coping skills and internal psychological conflicts (15). Video

electroencephalography (EEG) telemetry and high-resolution structural neuroimaging have shown that even in the presence of the most disabling symptoms in the CD context, there is no structural pathology. Rather, a functional defect was demonstrated on functional neuroimaging and neurophysiology (16). It is also worth noting that the presence of a traumatic experience is not necessarily a prerequisite to developing CD, it can be present, but it is not the defining factor, hence the predilection to call CD more appropriately as a functional neurological disorder rather than one of a 'conversion' etiology (1).

Risk Factors

Risk factors for CD include early life stress (whether in the form of childhood abuse or neglect), stressful events, having maladaptive personality traits, and the presence of a neurological disease that causes similar symptoms (1,17,18).

Clinical Presentation

Before delving into the presentation of CD, it is important to note that the symptoms and signs are not controlled at will and are not being feigned by the patient (7). CD can present with many different symptoms, so presentations can vary widely (19). The dysfunctions in CD are alterations in sensory, motor, or cognitive function. Sensory dysfunction can present as anesthesia or sensory loss, visual, hearing, or olfactory disturbances. Motor dysfunction presents as weakness, paralysis, abnormal movements (tremors, myoclonus, dystonic movements), seizures, gait abnormalities, or dysfunction in swallowing or speech. The most common presentations include weakness/paralysis, abnormal movements, seizures, swallowing/speech dysfunction, visual disturbances, and syncopal episodes (20). Some patients also present with a paradoxical absence of distress despite having serious symptoms known as "la belle indifference". It is not specific for CD and is not required for diagnosis but is nonetheless observed in a subset of patients (1,21,22).

In children, the presentation is usually monosymptomatic with higher chances that the dysfunction is in the dominant extremities (23–25).

The tables in Figure 1 and Figure 2 detail how the sensory and motor dysfunctions present and how to differentiate their occurrence in CD from their occurrence in neurologic disorders (26).

Figure 1: **Sensory Dysfunction**		
Symptom	**Presentation**	**Method of Differentiation**
Anesthesia / Sensory loss	• Sharp demarcation of the area with sensory loss (usually a joint, the end of an extremity, shoulder, or groin) • Other patients may present with a "hemisensory syndrome" (sensory loss of an entire side of the body); this can be accompanied by a sensation of feeling "cut in half" or ipsilateral hearing/vision dysfunction	• Usually, the sensory loss does not follow typical dermatomal patterns or patterns suggestive of certain neurologic disorders • A test used in hemisensory presentations involves placing a tuning fork over the left and right sides of the sternum or the frontal bone. Patients with neurological sensory loss should feel the vibrations bilaterally, as these bones should vibrate as a single unit. A patient with functional sensory loss often does not feel the vibration on the affected side
Visual disturbances	• They are very common • Can present as blindness, tunnel vision, or double vision	• To differentiate true blindness from functional blindness, it is essential to demonstrate preserved optic function in CD • One method is the pupillary light reflex, which would be positive in CD but most likely not in true blindness • Another method is asking the patient to bring the tips of their index fingers together. Patients with CD usually exhibit difficulty, but a truly blind person will use proprioception to complete the task successfully
Hearing and Olfactory disturbances	• Less common than visual disturbances • Patients report anosmia or deafness	• Anosmic CD patients are given a taste test, in which they will usually indicate a normal sense of taste. True anosmia usually has a decreased sense of taste and some might exhibit signs of nutritional deficiency/malnourishment • CD patients with symptoms of deafness might still demonstrate a startle response to loud sounds, which a truly deaf person might not be able to

Figure 2: **Motor Dysfunction**

Symptom	Presentation		Method of Differentiation
Weakness/paralysis	• Weakness is commonly seen • Paralysis is usually confined to one side of the body or a single limb. However, it can present in any pattern or combinations		. Common tests used to identify psychogenic weakness include: ◦ Hoover's sign: observed in the lower limb. It is extension of the affected hip when the patient's contralateral hip is flexed against resistance. It wouldn't be present in organic disease (26,27) ◦ Co-contraction sign: occurs when both agonist and antagonist muscles at a joint contract simultaneously. This is demonstratable in any agonist/antagonist muscle group and is used to confirm the absence of true weakness . In CD paraplegic, deep tendon reflexes are present. In contrast to a true paraplegic, whose deep tendon reflexes are absent or blunted
Abnormal movements: - Common in CD - Typical features include a rapid onset, improvement with distracting tasks, and variability (frequency, intensity, or region affected)	**Tremors**	• Functional tremors are often present at rest and with voluntary movement • They are usually abrupt in onset, often triggered by an emotional or traumatic experience	• In comparison to functional tremors in CD, where the tremors fluctuate in frequency and have an abrupt onset, organic tremors have a rhythmic consistency and are gradual in onset • When weights are applied to the affected limb, a CD patient would have an increase in tremor amplitude whereas a patient with organic tremor will exhibit a decrease in tremor amplitude
	Myoclonus	• Myoclonus is a jerking/spastic movement • Functional myoclonus is usually inconsistent in frequency or amplitude and is very sensitive to stimuli	• Functional myoclonus can be differentiated from organic myoclonus on electromyography (EMG) (28)
	Dystonia	• Functional dystonia present with pain of the affected limb, fixed posture (even during sleep), a clenched fist, or an inverted foot	• N/A
Seizures	• In many cases, seizures are the presenting complaint. In the context of CD, they are referred to as psychogenic non-epileptic seizures (PNES). Most of them look like grand-mal seizures with side-to-side head or body movement (29) • Around a third of episodes look more like syncope and present to cardiology settings (29,30)		• PNES usually are of a longer duration (>90 seconds), a fluctuating course, with closed eyes, tongue biting (on the tip of the tongue), and lower incidence of urinary incontinence. As opposed to epileptic seizures where the eyes are open, tongue biting is on the lateral sides of the tongue, and there is a higher incidence of urinary incontinence. In addition, epileptic seizures have post-ictal confusion (26,29,31)
Gait abnormalities	• Gait abnormalities in CD present with many features suggestive of a functional gait abnormality. Some include: ◦ sudden knee-buckling ◦ a "walking on ice" pattern, where the patient acts as if they were moving on a slippery surface with stiff knees and ankles and abducted arms ◦ slow gait initiation ◦ walking with the patient's feet sticking to the ground		• The gait abnormalities in CD display patterns atypical of neurologic/organic diseases
Swallowing dysfunction	• CD patients with swallowing dysfunction typically describe the sensation of a lump or tightness in their throats (also known as globus) in the absence of structural abnormality or a motility disorder		• Swallowing dysfunction in CD is usually negative for odynophagia or dysphagia, whereas in organic disease, odynophagia or dysphagia may be present depending on the cause
Speech problems	• Patients most commonly present with functional dysphonia (hoarseness or whispering) • Other presentations can involve slurred speech, dysarthria, stuttering, foreign accent syndrome, and mutism		• CD patients are able to cough or sing during lung exam whereas patients with true dysphonia will have difficulty doing so • In a CD patient, the vocal cords will be normal upon inspection

Diagnosis

The criteria for diagnosis by the DSM-5 are as follows (1):

1. ≥ 1 symptom(s) of voluntary motor or sensory dysfunction
2. Discrepancy between the features of the symptom(s) experienced and recognized neurological/medical conditions
3. The presentation is not better explained by another medical/mental condition
4. The symptom(s)/deficit(s) cause significant distress or impair aspects of daily functioning (occupational/social/etc.) or require medical attention

Specifiers include:

- Specifying the symptom type: with weakness/paralysis, abnormal movement, swallowing symptoms, speech symptoms, attacks/seizures, anesthesia/sensory loss, special sensory symptoms (visual/olfactory/hearing), or mixed symptoms
- Specifying the duration: considered an acute episode if the symptoms are present for < 6 months, and persistent when the symptoms persist for ≥ 6 months
- Specifying the presence/absence of a psychological stressor

Differential Diagnosis

Although the diagnosis of CD requires the symptoms to not be better explained by another condition, that does not exclude the possibility of diagnosing CD with the presence of another condition depending on how the patient presents. The differential diagnosis for CD includes the following (1):

- **Neurological disorders**: multiple sclerosis, strokes, Guillain-Barré syndrome, myopathies, polymyositis, and myasthenia gravis can have similar presentations to CD (32). This however doesn't mean a neurological disorder can't also be comorbid with CD (26)
- **Somatic symptom disorder (SSD)**: CD often lacks the excessive thoughts, feelings, and behaviors that characterize SSD
- **Factitious disorder and malingering**: the diagnosis of CD does not require explicit proof that the symptoms are not being feigned, due to the difficulty and unreliability of assessing conscious intentions. However, in the presence of definite proof of feigning (e.g., demonstrating symptoms and signs during examinations whilst not having symptoms/signs at home), the alternate diagnoses of factitious disorder or malingering need to be considered
- **Dissociative disorders**: dissociative symptoms (depersonalization/derealization/etc.) can be present in CD

- **Depressive disorders**: patients with depressive disorders can report a general sensation of heavy limbs, not to be confused with the weakness that a CD patient might present with
- **Panic disorder**: tremors and paresthesia can present in both panic disorder and CD, but are more transient and associated with characteristic cardiorespiratory symptoms in panic disorder
- **Body dysmorphic disorder**

Complications and Comorbidities

Complications include an impaired quality of life and a chance of permanent disability. The level of impairment and psychological/physical disability in CD can be compared with or even be shown to be higher in some instances than actual neurologic diseases (26).

CD patients are also more likely to have comorbid mental illnesses than those with neurologic diseases. Most notably depressive disorders, anxiety disorders, PTSD, personality disorders, dissociative disorders, and illness anxiety disorder (15,33–37).

Treatment

The treatment for CD is a multidisciplinary one, and mainly involves appropriate delivery of the diagnosis to the patient, reassurance, and psychotherapy. The treatment plan could also include occupational and physical therapy or pharmacotherapy.

Delivery of the diagnosis and reassurance

Effective presentation of the diagnosis to the patient is quite possibly the most important aspect of treatment (32). Many patients have negative experiences during their care-seeking period, due to both poor knowledge of CD and the tendency for some clinicians to discredit the patients' experiences and attribute symptoms to something that is "all in their head" whether it is implied or explicitly stated (38,39). It is also recommended that the physician maintain a strong patient-physician relationship before revealing and explaining the diagnosis. It is very important to acknowledge that the patient's symptoms are real and show empathy towards how the patient's life is being adversely affected. Another aspect is explaining the diagnosis to the patient adequately and explaining to the patient how the diagnosis was reached (e.g., by pointing out the differences in history and physical exam that helped differentiate between organic disease and CD). It is also important to explain that the symptoms being experienced are possibly reversible if the patient adheres to the treatment plan (32).

Psychotherapy

Psychotherapy is considered to be the first-line treatment in most cases. The most effective one being cognitive-behavioral therapy (CBT). Other classes of psychotherapy can be employed, such as psychodynamic psychotherapy, group therapy, family therapy, and hypnotherapy (40,41). Hypnotherapy is especially useful as a second-line treatment in patients with speech symptoms or sensory loss (26), the first-line treatment for speech symptoms being speech therapy (42).

Pharmacotherapy

Pharmacotherapy is not considered a main line of therapy; however, its role becomes more pronounced in the presence of comorbid mental conditions. The choice of drug depends on the comorbidity, but it can include antidepressants, anxiolytics, or mood stabilizers. Several studies evaluated the effects of antipsychotics, and it was found that quetiapine and haloperidol had comparable effects in alleviating symptoms (32,43).

Occupational and physical therapy

Patients with functional motor symptoms (weakness/paralysis) can especially benefit from physical or occupational therapy sessions to encourage normal movement and reinstate motor function back to the baseline or a comparable state (26,44–46). Patients with speech dysfunction can benefit from speech therapy sessions to regain normal speech (42).

Prognosis

Prognosis relies on many factors, but generally, it is poor. Positive prognostic factors are early diagnosis, short duration of symptoms, lack of comorbidities (especially personality disorders), identifiable stressors, and a positive patient-physician relationship. Negative prognostic factors include greater number of physical symptoms, poor physical functioning prior to diagnosis, and maladaptive personality traits (1,7,26). Children have better outcomes and usually experience complete resolution of symptoms within 3 months of diagnosis with rare chances of recurrence (1,47–49).

References

1. American Psychiatric Association (2013). Somatic Symptom and Related Disorders. In: Diagnostic and Statistical Manual of Mental Disorders DSM. (5th ed.).
2. Basavarajappa C, Dahale AB, Desai G. Evolution of bodily distress disorders. Curr Opin Psychiatry. 2020 Sep;33(5):447–50.
3. Micale MS. Approaching Hysteria: Disease and Its Interpretations. Princeton University Press;
4. M.D. SBG. Veith, Ilza. Hysteria, The History of a Disease. Chicago: University of Chicago Press, 1965. Pp. 301 + x. $7.95. Am J Clin Hypn [Internet]. 1969;11(3):201–2. Available from: https://doi.org/10.1080/00029157.1969.10402036

5. Abse DW. Hysteria and Related Mental Disorders: An Approach to Psychological Medicine. Butterworth-Heinemann;
6. North CS. The Classification of Hysteria and Related Disorders: Historical and Phenomenological Considerations. Behav Sci (Basel, Switzerland). 2015 Nov;5(4):496–517.
7. Blitzstein SM. Recognizing and treating conversion disorder. Virtual Mentor. 2008 Mar;10(3):158–60.
8. Nicholson TRJ, Stone J, Kanaan RAA. Conversion disorder: a problematic diagnosis. J Neurol Neurosurg Psychiatry. 2011 Nov;82(11):1267–73.
9. Levenson JL, Sharpe M. The classification of conversion disorder (functional neurologic symptom disorder) in ICD and DSM. Handb Clin Neurol. 2016;139:189–92.
10. Ludwig L, Pasman JA, Nicholson T, Aybek S, David AS, Tuck S, et al. Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies. The lancet Psychiatry. 2018 Apr;5(4):307–20.
11. Stone J, Carson A, Duncan R, Roberts R, Warlow C, Hibberd C, et al. Who is referred to neurology clinics?--the diagnoses made in 3781 new patients. Clin Neurol Neurosurg. 2010 Nov;112(9):747–51.
12. Carson A, Lehn A. Epidemiology. Handb Clin Neurol. 2016;139:47–60.
13. Bodde NMG, Brooks JL, Baker GA, Boon PAJM, Hendriksen JGM, Aldenkamp AP. Psychogenic non-epileptic seizures--diagnostic issues: a critical review. Clin Neurol Neurosurg. 2009 Jan;111(1):1–9.
14. Deka K, Chaudhury PK, Bora K, Kalita P. A study of clinical correlates and socio-demographic profile in conversion disorder. Indian J Psychiatry. 2007 Jul;49(3):205–7.
15. Cascella M, Thompson NS, Muzio MR, Forte CA, Cuomo A. The underestimated role of psychological and rehabilitation approaches for management of cancer pain. A brief commentary. Recenti Prog Med. 2016 Aug;107(8):418–21.
16. Bennett K, Diamond C, Hoeritzauer I, Gardiner P, McWhirter L, Carson A, et al. A practical review of functional neurological disorder (FND) for the general physician. Clin Med. 2021 Jan;21(1):28–36.
17. Christensen JS, Wild H, Kenzie ES, Wakeland W, Budding D, Lillas C. Diverse Autonomic Nervous System Stress Response Patterns in Childhood Sensory Modulation. Front Integr Neurosci. 2020;14:6.
18. Keynejad RC, Frodl T, Kanaan R, Pariante C, Reuber M, Nicholson TR. Stress and functional neurological disorders: mechanistic insights. J Neurol Neurosurg Psychiatry. 2019 Jul;90(7):813–21.
19. Kanaan RAA, Duncan R, Goldstein LH, Jankovic J, Cavanna AE. Are psychogenic non-epileptic seizures just another symptom of conversion disorder? J Neurol Neurosurg Psychiatry. 2017 May;88(5):425–9.
20. Gokarakonda SB, Kumar N. La Belle Indifférence. In Treasure Island (FL); 2021.
21. Ballmaier M, Schmidt R. Conversion disorder revisited. Funct Neurol. 2005;20(3):105–13.
22. Khaddafi MR, Amin MM. A Case Series from Rantauprapat, La Belle Indifference: A Coping Mechanism or Is There Something Organic Behind? Vol. 7, Open access Macedonian journal of medical sciences. 2019. p. 2675–8.
23. Ferrara J, Jankovic J. Psychogenic movement disorders in children. Mov Disord. 2008 Oct;23(13):1875–81.
24. Regan J, LaBarbera JD. Lateralization of conversion symptoms in children and adolescents. Am J Psychiatry. 1984 Oct;141(10):1279–80.
25. Schwingenschuh P, Pont-Sunyer C, Surtees R, Edwards MJ, Bhatia KP. Psychogenic movement disorders in children: a report of 15 cases and a review of the literature. Mov Disord. 2008 Oct;23(13):1882–8.
26. Peeling JL, Muzio MR. Conversion Disorder. In Treasure Island (FL); 2021.
27. Mehndiratta MM, Kumar M, Nayak R, Garg H, Pandey S. Hoover's sign: Clinical relevance in Neurology. J Postgrad Med. 2014;60(3):297–9.
28. Thompson PD, Colebatch JG, Brown P, Rothwell JC, Day BL, Obeso JA, et al. Voluntary stimulus-sensitive jerks and jumps mimicking myoclonus or pathological startle syndromes. Mov Disord. 1992;7(3):257–62.
29. Avbersek A, Sisodiya S. Does the primary literature provide support for clinical signs used to distinguish psychogenic nonepileptic seizures from epileptic seizures? J Neurol Neurosurg Psychiatry. 2010 Jul;81(7):719–25.
30. Hendrickson R, Popescu A, Dixit R, Ghearing G, Bagic A. Panic attack symptoms differentiate patients with epilepsy from those with psychogenic nonepileptic spells (PNES). Epilepsy Behav. 2014 Aug;37:210–4.
31. Mellers JDC. The approach to patients with "non-epileptic seizures". Postgrad Med J. 2005 Aug;81(958):498–504.
32. O'Neal MA, Baslet G. Treatment for Patients with a Functional Neurological Disorder (Conversion Disorder): An Integrated Approach. Am J Psychiatry. 2018 Apr;175(4):307–14.
33. Hoge CW, Terhakopian A, Castro CA, Messer SC, Engel CC. Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq war veterans. Am J Psychiatry. 2007 Jan;164(1):150–3.
34. Waller E, Scheidt CE. Somatoform disorders as disorders of affect regulation: a study comparing the TAS-20 with non-self-report measures of alexithymia. J Psychosom Res. 2004 Sep;57(3):239–47.
35. Carson AJ, Ringbauer B, MacKenzie L, Warlow C, Sharpe M. Neurological disease, emotional disorder, and disability: they are related: a study of 300 consecutive new referrals to a neurology outpatient department. J Neurol Neurosurg Psychiatry. 2000 Feb;68(2):202–6.
36. Roelofs K, Keijsers GPJ, Hoogduin KAL, Näring GWB, Moene FC. Childhood abuse in patients with conversion disorder. Am J Psychiatry. 2002 Nov;159(11):1908–13.
37. Singh SP, Lee AS. Conversion disorders in Nottingham: alive, but not kicking. J Psychosom Res. 1997 Oct;43(4):425–30.
38. Dosanjh M, Alty J, Martin C, Latchford G, Graham CD. What is it like to live with a functional movement disorder? An interpretative phenomenological analysis of illness experiences from symptom onset to post-diagnosis. Br J Health Psychol. 2020 Oct;
39. Robson C, Lian OS. " Blaming, shaming, humiliation": Stigmatising medical interactions among people with non-epileptic seizures. Wellcome open Res. 2017;2:55.

40. Cuomo A, Bimonte S, Forte CA, Botti G, Cascella M. Multimodal approaches and tailored therapies for pain management: the trolley analgesic model. Vol. 12, Journal of pain research. 2019. p. 711–4.
41. Tsui P, Deptula A, Yuan DY. Conversion Disorder, Functional Neurological Symptom Disorder, and Chronic Pain: Comorbidity, Assessment, and Treatment. Curr Pain Headache Rep. 2017 Jun;21(6):29.
42. Duffy JR. Functional speech disorders: clinical manifestations, diagnosis, and management. Handb Clin Neurol. 2016;139:379–88.
43. Ghanbarizadeh SR, Dinpanah H, Ghasemi R, Salahshour Y, Sardashti S, Kamali M, et al. Quetiapine versus Haloperidol in Controlling Conversion Disorder Symptoms; a Randomized Clinical Trial. Emerg (Tehran, Iran). 2018;6(1):e47.
44. Nielsen G, Stone J, Matthews A, Brown M, Sparkes C, Farmer R, et al. Physiotherapy for functional motor disorders: a consensus recommendation. J Neurol Neurosurg Psychiatry. 2015 Oct;86(10):1113–9.
45. Nielsen G, Buszewicz M, Stevenson F, Hunter R, Holt K, Dudziec M, et al. Randomised feasibility study of physiotherapy for patients with functional motor symptoms. J Neurol Neurosurg Psychiatry. 2017 Jun;88(6):484–90.
46. Gardiner P, MacGregor L, Carson A, Stone J. Occupational therapy for functional neurological disorders: a scoping review and agenda for research. CNS Spectr. 2018 Jun;23(3):205–12.
47. Fritz GK, Fritsch S, Hagino O. Somatoform disorders in children and adolescents: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry. 1997 Oct;36(10):1329–38.
48. Grattan-Smith P, Fairley M, Procopis P. Clinical features of conversion disorder. Arch Dis Child. 1988 Apr;63(4):408–14.
49. Turgay A. Treatment Outcome for Children and Adolescents with Conversion Disorder. Can J Psychiatry [Internet]. 1990;35(7):585–9. Available from: https://doi.org/10.1177/070674379003500704

Article topic: Hoarding Disorder.

Author: Rawan Osama Abu Nsair.

Editor: Hala Qaryouti.

Reviewer: Ahda Jbara, Hassan Abushukair.

Keywords: hoarding, OCD, attachment, clutter.

Overview

In 1947, New York City police received an anonymous call on a death in a mansion in Harlem, New York inhabited by two brothers, Homer, and Langley Collyer (2).

On arrival to the Collyer mansion, police found piles of clutter, including books, newspapers, and boxes reaching the ceiling in much of the mansion's area, making the house traversable through maze-like tunnels hidden through the debris. After searching, Homer, 65 years, was found dead on a chair in an upstairs room, while no trace could be found of Langley. Efforts to evacuate the house continued until 130 tons of material were removed, including fourteen grand pianos, a pipe organ, an old generator, and the chassis of a Model-T Ford. (2) [figure 1]

Eighteen days later, Langley was found buried 10 feet from where his brother was found (2), crushed under debris by one of the baits he made to satisfy his fear of intrusion (3). Since his corpse was gnawed by rats, police concluded that he had died before his paralyzed brother Homer (2), leaving him to starve to death (3).

Soon after the Collyer brothers created a junk-cluttered building by hoarding objects of no value, firefighters started using the term "Collyer mansion" to describe the dangerous debris-filled sites (4). In addition, the term "The Collyer's Syndrome" was used to describe such bizarre collecting behaviors. Nowadays, the behavior is referred to as Hoarding Disorder (HD) (5).

Hoarding Disorder is a newly added disease in The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (2013), categorized under obsessive-compulsive and related disorders, and characterized by disorganization and the persistent inability to discard possessions regardless of their actual value. (6)

Figure 1: A New York City policeman climbs over debris to enter the library in the Collyer house during a search for Langley Collyer (2).

Epidemiology

The overall prevalence of HD is estimated to be around 2%, with the elderly being at higher risk such that prevalence among individuals over 70 years reaches up to 6%. Among the elderly, hoarding severity could be slightly higher in men than in women (7). However, prevalence rates are similar across genders (8).

It is noted that HD is more common among people who live alone, and those who are not married nor in a relationship (9). A transcultural study revealed that hoarding disorder presents with similar phenomenology across the United Kingdom, Spain, Japan, and Brazil (10).

Etiology and Pathophysiology

The exact etiology of hoarding disorder is still unknown. However, the numerous studies conducted revealed correlations between hoarding disorder and several factors.

A four-factor model described a mixture of information-processing deficits, emotional attachment problems, behavioral avoidance, and beliefs about the nature of possessions (11). Hoarding disorder patients show impairment in multiple cognitive domains, such as executive functioning and attention (12). In addition, decision-making deficits that accompany the disorder increase the distress patients feel, especially when obliged to

choose whether to keep or discard an object (13). They also have an increased incidence of impaired visual memory, visual detection, and visual categorization (14) as well as lack of inhibition (15), which could be the reason behind the patients' inability to resist the urge of acquiring a new object (13). Poor memory confidence is a significant correlation between inattention and excessive saving of objects (16).

Excessive acquisition and avoidance of discarding are reinforced when patients avoid the anticipated distress of making an incorrect decision to discard a given item (13). Patients with HD have difficulties identifying and describing feelings as well as unhelpful attitudes toward the emotional experience, so they use avoidance and acquisition to regulate their emotions (17).

A recent study found that there is no significant object attachment in patients with hoarding disorder (18). However, anthropomorphism (attributing human characteristics to inanimate objects) is strongly associated with hoarding symptoms such as excessive buying and obsession to acquire free items (19). In a study done to figure out beliefs and reasons for saving, the participants validated their behavior through several reasons, e.g. fear of losing important information or wasting a potentially useful object, and emotional significance (20).

Genetics also seems to play a role in the etiology of hoarding disorder, as 50% of geriatric hoarding disorder patients reported having a mother with hoarding tendencies, and over 26% reported having had a father with such tendencies (21). A twin study indicated that heritability is moderate-to-high, with about 50% of the variability in hoarding behavior attributable to genetic factors (22).

Regarding neurobiology, these patients have significantly greater grey matter in the right frontal pole (23). In addition, greater activity is found in the right dorsolateral prefrontal cortex and the anterior cingulate cortex, which could mediate the deficits in evaluation of rewards and visual processing observed in hoarding disorder patients (24).

DSM-5 Diagnostic Criteria (25)

1. Persistent difficulty discarding or parting with possessions, regardless of their actual value.
2. The difficulty is due to both a perceived need to save the items and distress associated with discarding them.
3. The difficulty of discarding possessions results in the accumulation of possessions that congest and clutter active living areas and compromise their intended use. If living areas are uncluttered, it is only because of the interventions of third parties (family members, cleaners, authorities).

4. The hoarding causes clinically significant distress or impairment in social, occupational, or other critical areas of functioning (including maintaining a safe environment for self and others).
5. The hoarding is not attributable to another medical condition such as brain injury, cerebrovascular disease, Prader-Willi syndrome.
6. The hoarding is not better explained by the symptoms of another mental disorder (e.g., obsessions in obsessive-compulsive disorder, decreased energy in major depressive disorder, delusions in schizophrenia or another psychotic disorder, cognitive deficits in major neurocognitive disorder, restricted interests in autism spectrum disorder).

After a diagnosis is established, specify whether the disorder is:

- With excessive acquisition: If difficulty discarding possessions is accompanied by excessive acquisition of items that are not needed or for which there is no available space.

Also, specify whether the disorder is:

- With good or fair insight: The individual recognizes that hoarding-related beliefs and behaviors (about difficulty discarding items, clutter, or excessive acquisition) are problematic.
- With poor insight: The individual is mostly convinced that hoarding-related beliefs and behaviors are not problematic despite evidence to the contrary.
- With absent insight/delusional beliefs: The individual is completely convinced that hoarding-related beliefs and behaviors are not problematic despite evidence to the contrary.

Clinical Course

Hoarding disorder is a chronic progressive disorder, which usually has an onset in early adulthood (26). The average age for symptom onset is between 10 and 20 years, while the average age for the diagnosis of hoarding disorder was between 20 and 30 years (27), with daily-function impairment clear in the twenties, and definite impairment in the thirties (6). Therefore, severity increases as the age advances (27). However, some factors are associated with poorer treatment response, like male gender, early-onset, strong attachment to possessions, poor insight, comorbid depression/ anxiety disorders, cognitive impairment, and biological abnormality in the ventral prefrontal cortex (6).

On the individual's level, HD has many functional consequences. Clutter interferes with basic activities like walking throughout the house, cleaning, cooking, personal hygiene, and even sleeping. About 6% of reported cases represented a serious public health hazard, since clutter accumulation puts the patients at risk of falling, fire, and poor

sanitation (28), and affects the patient's family and neighbors. In most extreme cases it can raise legal issues, due to forced evacuation (29).

A distinct entity of hoarding disorder is "animal hoarding", in which the hoarder accumulates many animals without being able to provide the smallest standards of sanitation, nutrition, and veterinary care (25). In addition, animal hoarders are associated with poorer insight and sanitary conditions compared to object hoarders (30).

Differential Diagnoses

First, hoarding disorder should be differentiated from normal collecting behaviors which result in little clutter and impairment (31) in comparison to hoarding disorder, which causes the accumulation of enormous amounts of objects that disrupt the living space use (32). Moreover, normal collectors have a more selective and focused collecting behavior and can organize objects (32).

Hoarding behavior could be a result of many brain conditions that should be excluded before making the diagnosis, such as cerebrovascular disease, brain trauma, and central nervous system infections. Other psychiatric disorders can also cause HD, such as autism spectrum disease (ASD), dementia, schizophrenia, major depressive disorder (MDD), and obsessive-compulsive disorder (OCD) (33).

Hoarding symptoms can be a subtype of OCD or a partial symptom of obsessive-compulsive personality disorder (OCPD). Hoarding disorder patients typically don't show invasive and uncomfortable thoughts or images. They also have poorer insight in comparison to those with OCD. (6)

Attention-deficit/ hyperactivity disorder (ADHD) is a comorbidity present in more than 20% of HD patients (34). In fact, many studies revealed that both ADHD and hoarding disorder have a common biological background and considered inattention a core symptom in hoarding disorder (34). A large-scale study showed that 75% of hoarding disorder patients have a comorbid mood or anxiety disorder. The most common comorbid disorders are MDD, social anxiety disorder, and generalized anxiety disorder (29).

Treatment

Hoarding disorder is underreported, and that could be why it is unrecognized and under-treated (35). However, it is considered a treatment-resistant disease, and there are no professional guidelines for its management (29).

Psychotherapy, especially cognitive-behavioral therapy (CBT) has been proven useful when addressing the four deficits thought to be involved in the disease's etiology (mentioned above) (29). CBT involves sorting and discarding practices. For example, the therapist asks patient to bring a box of objects to the session to provide graded exposure to discarding (36). Therapy could be offered as an individual or group CBT, as group therapy may be offered as a cost-effective alternative (16). In both methods, monthly home visits can be scheduled. CBT was found to decrease hoarding symptoms by about one-third over 20–26 weekly sessions (37).

Studies on pharmacotherapy are still premature. However, some selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, (36) and serotonin and norepinephrine reuptake inhibitors (SNRIs), such as extended-release venlafaxine, (38) have been suggested as effective treatments for hoarding symptoms. Paroxetine has shown a moderate response not tolerated in high doses, while venlafaxine was shown to achieve significant improvement within 12 weeks (38).

Researchers have conducted preclinical and clinical studies investigating the benefit of atomoxetine, a non-stimulant used to treat ADHD, for treating hoarding disorder on a small sample size in which 11 out of 12 patients completed a trial of atomoxetine at flexible-dose (40-80 mg) for 12 weeks, after which their mean UCLA Hoarding Severity Scale score decreased by 41.3%, and inattention and impulsivity symptoms showed a significant mean score reduction of 18.5% from baseline (39).

Digital Hoarding

With the increasing dominance and availability of technology, digital hoarding is appearing as a new term being suggested as another subtype in the literature. It describes the accumulation of digital files to the point of loss of perspective which can result in stress and disorganization. Hoarded items can range from files to applications, music, and pictures. Disorders such as OCD and physical hoarding scores are significant risk factors. (40,41)

The first reported case was of a photographer who took nearly 1000 photos per day and found difficulty discarding them due to his attachment to them and his belief that they may be of use in the future. However, contrary to his beliefs, he never used nor reviewed the photos after taking them, resulting in an accumulation so severe that the patient had 4 external hard drives to store the original pictures and another 4 as backup (40).

With the growing availability of digital media and the feasibility of storage methods, more research should be done to explore this field.

References

1. MyHeroEdvard. American Hoarders [Internet]. Available from: https://www.deviantart.com/myheroedvard/art/American-Hoarders-209268938
2. McAllister, J. (1995). The Collyer Brothers. Grand Street, (54), 203-211..
3. Weiss KJ. Hoarding, Hermitage, and the law: Why we love the Collyer brothers. J Am Acad Psychiatry Law. 2010;38(2):251–7.
4. Ronan, K. P. (2011). Navigating the goat paths: compulsive hoarding, or Collyer Brothers syndrome, and the legal reality of clutter. Rutgers L. Rev., 64, 235..
5. Herring, S. (2011). Collyer curiosa: A brief history of hoarding. Criticism, 53(2), 159-188..
6. Nakao T, Kanba S. Pathophysiology and treatment of hoarding disorder. Psychiatry Clin Neurosci. 2019;73(7):370–5.
7. Cath DC, Nizar K, Boomsma D, Mathews CA. Age-Specific Prevalence of Hoarding and Obsessive Compulsive Disorder: A Population-Based Study. Am J Geriatr Psychiatry [Internet]. 2017;25(3):245–55. Available from: http://dx.doi.org/10.1016/j.jagp.2016.11.006
8. Postlethwaite A, Kellett S, Mataix-Cols D. Prevalence of Hoarding Disorder: A systematic review and meta-analysis. J Affect Disord [Internet]. 2019;256(April):309–16. Available from: https://doi.org/10.1016/j.jad.2019.06.004
9. Mataix-Cols D, Billotti D, Fernández De La Cruz L, Nordsletten AE. The London field trial for hoarding disorder. Psychol Med. 2013;43(4):837–47.
10. Nordsletten AE, Fernández de la Cruz L, Aluco E, Alonso P, López-Solà C, Menchón JM, et al. A transcultural study of hoarding disorder: Insights from the United Kingdom, Spain, Japan, and Brazil. Transcult Psychiatry. 2018;55(2):261–85.
11. Frost RO, Hartl TL. A cognitive-behavioral model of compulsive hoarding. Behav Res Ther. 1996;34(4):341–50.
12. Woody SR, Kellman-McFarlane K, Welsted A. Review of cognitive performance in hoarding disorder. Clin Psychol Rev [Internet]. 2014;34(4):324–36. Available from: http://dx.doi.org/10.1016/j.cpr.2014.04.002
13. Dozier ME, Ayers CR. The etiology of hoarding disorder: A review. Psychopathology. 2017;50(5):291–6.
14. Mackin RS, Vigil O, Insel P, Kivowitz A, Kupferman E, Hough CM, et al. PATTERNS of CLINICALLY SIGNIFICANT COGNITIVE IMPAIRMENT in HOARDING DISORDER. Depress Anxiety. 2016;33(3):211–8.
15. Grisham JR, Brown TA, Savage CR, Steketee G, Barlow DH. Neuropsychological impairment associated with compulsive hoarding. Behav Res Ther. 2007;45(7):1471–83.
16. Davidson EJ, Dozier ME, Pittman JOE, Mayes TL, Blanco BH, Gault JD, et al. Recent Advances in Research on Hoarding. Curr Psychiatry Rep. 2019;21(9).
17. Taylor JK, Theiler S, Nedeljkovic M, Moulding R. A qualitative analysis of emotion and emotion regulation in hoarding disorder. J Clin Psychol. 2019;75(3):520–45.
18. Yap K, Grisham JR. Object attachment and emotions in hoarding disorder. Compr Psychiatry [Internet]. 2020;100(xxxx):152179. Available from: https://doi.org/10.1016/j.comppsych.2020.152179
19. Norberg MM, Crone C, Kwok C, Grisham JR. Anxious attachment and excessive acquisition: The mediating roles of anthropomorphism and distress intolerance. J Behav Addict. 2018;7(1):171–80.
20. Dozier ME, Ayers CR: The predictive value of different reasons for saving and acquiring on hoarding disorder symptoms. J Obsessive Compuls Relat Disord 2014; 3: 220–227.
21. Ayers CR, Dozier ME, Pachana NA, Oude Voshaar RC. Predictors of hoarding severity in older adults with hoarding disorder. Int Psychogeriatrics. 2015;27(7):1147–56.
22. Iervolino AC, Ph D, Perroud N, Fullana MA, Guipponi M, Cherkas L, et al. Prevalence and Heritability of Compulsive Hoarding : A Twin Study. Am J Psychiatry. 2009;166(October):1156–61.
23. Yamada S, Nakao T, Ikari K, Kuwano M, Murayama K, Tomiyama H, et al. A unique increase in prefrontal gray matter volume in hoarding disorder compared to obsessive-compulsive disorder. PLoS One. 2018;13(7):1–13.
24. Hough CM, Luks TL, Lai K, Vigil O, Guillory S, Nongpiur A, et al. Comparison of brain activation patterns during executive function tasks in hoarding disorder and non-hoarding OCD. Psychiatry Res - Neuroimaging. 2016;255:50–9.
25. Diagnostic and Stastistical Manual of Mental Disorders Fifth Edition. American Psychiatric Association. 2013.
26. Ayers CR. Age-Specific Prevalence of Hoarding and Obsessive Compulsive Disorder: A Population-Based Study. Am J Geriatr Psychiatry [Internet]. 2017;25(3):256–7. Available from: http://dx.doi.org/10.1016/j.jagp.2016.12.001
27. Dozier, Mary E., Ben Porter, and Catherine R. Ayers. “Age of onset and progression of hoarding symptoms in older adults with hoarding disorder.” Aging & mental health 20.7 (2016): 736-742..
28. Cappelletti S, Cipolloni L, Piacentino D, Aromatario M. A lethal case of hoarding due to the combination of traumatic and confined space asphyxia. Forensic Sci Med Pathol. 2019;15(1):114–8.
29. Piacentino D, Pasquini M, Cappelletti S, Chetoni C, Sani G, Kotzalidis GD. Pharmacotherapy for Hoarding Disorder: How did the Picture Change since its Excision from OCD? Curr Neuropharmacol. 2019;17(8):808–15.
30. Ferreira EA, Paloski LH, Costa DB, Fiametti VS, De Oliveira CR, de Lima Argimon II, et al. Animal Hoarding Disorder: A new psychopathology? Psychiatry Res. 2017;258(August):221–5.
31. Nordsletten AE, Reichenberg A, Hatch SL, Fernández De La Cruz L, Pertusa A, Hotopf M, et al. Epidemiology of hoarding disorder. Br J Psychiatry. 2013;203(6):445–52.
32. Mataix-Cols D, Frost RO, Pertusa A, Clark LA, Saxena S, Leckman JF, et al. Hoarding disorder: A new diagnosis for DSM-V? Depress Anxiety. 2010;27(6):556–72.
33. Mataix-Cols D. Hoarding Disorder. N Engl J Med. 2014;370(21):2023–30.
34. Tolin DF, Villavicencio A. Inattention, but not OCD, predicts the core features of Hoarding Disorder. Behav Res Ther [Internet]. 2011;49(2):120–5. Available from: http://dx.doi.org/10.1016/j.brat.2010.12.002
35. DiMauro J, Tolin DF, Frost RO, Steketee G. Do people with hoarding disorder under-report their symptoms? J Obsessive Compuls Relat Disord [Internet]. 2013;2(2):130–6. Available from: http://dx.doi.org/10.1016/j.jocrd.2013.01.002
36. Brakoulias V, Milicevic D. Assessment and treatment of hoarding disorder. Australas Psychiatry. 2015;23(4):358–60.

37. Steketee G, Frost RO, Tolin DF, Rasmussen J, Brown TA. Waitlist-controlled trial of cognitive behavior therapy for hoarding disorder. Depress Anxiety. 2010;27(5):476–84.
38. Saxena S, Sumner J. Venlafaxine extended-release treatment of hoarding disorder. Int Clin Psychopharmacol. 2014;29(5):266–73.
39. Grassi G, Laura M, Lorenzo DCM, Elisa C, Lorenzo R, Carla G, et al. Atomoxetine for hoarding disorder: A pre-clinical and clinical investigation. J Psychiatr Res [Internet]. 2016;83:240–8. Available from: http://dx.doi.org/10.1016/j.jpsychires.2016.09.012
40. Van Bennekom MJ, Blom RM, Vulink N, Denys D. A case of digital hoarding. BMJ Case Rep. 2015;2015:1–4.
41. Thorpe S, Bolster A, Neave N. Exploring aspects of the cognitive behavioural model of physical hoarding in relation to digital hoarding behaviours. Digit Heal. 2019;5:1–8.

Topic: Psychological Child Abuse & Maltreatment.

Author: Anas Al-Waqfi.

Editor: Hala Qaryouti.

Reviewer: Ahda Jbara, Hassan Abushukair

Keywords: Child Maltreatment, Psychological Abuse, Emotional Abuse.

Introduction

Child maltreatment is an intercontinental issue of serious life-long consequences with 3 out of 4 children aged between 2–4 years regularly suffering physical punishment and/or psychological violence at the hands of parents and caregivers [1]. According to the World Health Organization (WHO), the scope of child maltreatment and abuse targets those under the legal definition of a child, under 18 years.

The four forms of abuse identified include physical abuse, sexual abuse, psychological abuse, and neglect: with psychological abuse encompassing both emotional neglect and emotional abuse. However, not any form of emotional maltreatment or poor parenting is considered dysfunctional or abusive as there is a continuum that ranges from healthy to psychological maltreatment. Therefore, the risk of harm to the child is the primary distinguisher of dysfunctional parenting from psychological maltreatment. [2]

Unfortunately, until recently, psychological child abuse and maltreatment have not gained the required attention because of the difficulty in generalizing and applying findings. This is due to lack of consistency in the definition and estimation of emotional maltreatment as well as the over-reliance on clinical, non-representative samples. [3,4]

Definitions

Psychological Abuse, also referred to as 'Emotional Child Abuse', has no single agreed-on definition till this moment, making it more challenging to identify or define than physical or sexual abuse.

In 1995, the American Professional Society of the Abuse of Children (APSAC) defined the term as "a repeated pattern of caregiver behavior or extreme incident(s) that convey to children that they are flawed, unloved, unwanted, endangered, or of value only in meeting another's needs" [8]. The multiple patterns of psychological abuse suggested by the APSAC are classified into the types shown in figure (1) below [9].

Figure 1: Patterns of psychological abuse suggested by the APSAC.

The Diagnostic and Statistical Manual of Mental disorders (DSM-5) define Psychological Child Abuse as “non-accidental verbal or non-verbal acts by a child's parent or caregiver that result or may significantly result in noteworthy psychological harm to the child”. These acts include- but are not limited to- restriction of movement; patterns of depreciating, blaming, threatening, frightening, unfairness against or ridiculing. [5]

According to the American Academy of Pediatrics (AAP), behaviors of psychological child abuse acted by the caregiver include denying emotional responsiveness as well as medical, emotional, and educational neglect [6]. Emotional maltreatment can involve acts of both commission (i.e.: spurning and terrorizing described above) and omission (ignoring need for social interactions) which can negatively influence the child’s well-being [2]. However, the caregiver must be using 1 or more of such behaviors briefly or over a longer period to be classified as abuse [7].

Epidemiology

Unfortunately, compared to other forms of maltreatment, little is known about the prevalence and outcomes of psychological abuse, mainly due to its misinterpretation and underreporting in a relatively large percentage of cases [11].

According to a US study, the yearly prevalence of single types of maltreatment, child abuse is around 10% [12]. However, a meta-analysis of studies addressing psychological abuse found that a prevalence as high as 36% was calculated when based on self-reported cases, whereas only 0.3% when based on professional reports [13]. Both emotional neglect and emotional abuse were more prevalent among females compared to males (4% vs. 2%, respectively) [1].

According to Taillieu, Brownridge, Sareen, and Afifi, 2016, the most prevalent form of emotional maltreatment is emotional neglect alone (6.2%), followed by emotional abuse alone (4.8%), and both emotional abuse and neglect (3.1%) [14]. In addition, surveys carried out in the US found that psychological and emotional maltreatment were the most regularly self-reported forms of exploitation [16]. Furthermore, several large population-based self-report studies in the United Kingdom and United States found that around 8 - 9% of women and 4% of men reported being subjected to severe psychological abuse during childhood [15].

Etiology & Risk Factors

Attachment Theory states that a firm attachment bond with at least one primary caregiver is essential for emotional development. Emotional maltreatment is believed to interfere with the development of this attachment bond [22], and the subsequent insecure attachment patterns could explain the link between childhood emotional maltreatment and mental disorders [2].

Psychological child abuse is usually associated with multiple family stressors such as a larger family size, family conflicts (e.g.: custody disputes), death of a child in the family, lack of finances for essentials, accommodation problems, adult mental health problems, or parental substance abuse [17,18]. Other stressors include employment difficulties, marital separation, pediatric exposure to violence at home, and pregnancy [11]. In addition, any history of maternal depression during a child's life has been linked to parental withdrawal and neglect [19,20].

Furthermore, children and adolescents with intellectual or cognitive disabilities may be more vulnerable to abuse [11]. Community violence, having a non-biological male caregiver, and inadequate understanding of child development are also considered important risk factors for child maltreatment [23]. In addition, a caregiver who has had low educational achievement or had been maltreated as a child can contribute to children maltreatment [24].

Allan N. Schore, author of “Affect Regulation and The Origin of The Self”, stated in his book that effects of psychological maltreatment during the first 3 years of life can be exaggerated, as rapid and extensive growth of the brain and biological systems takes place throughout this period, and it is largely affected by the child’s surrounding environment [21].

Long-term Consequences

Factors such as frequency, intensity, and duration of abuse, coping strategies practiced by the child, self-esteem, and availability of supportive relationships can alter the effects and sequelae on the psychologically abused child [25]. As per evidence available, severe emotional abuse can be as influential as physical abuse and contribute to depression and low self-esteem [3]. However, inability to control for the presence of other forms of parental aggression limit the understanding of its sequelae [26].

One study found that children emotionally abused under the age of 12 years have serious delinquency issues [10]. Childhood psychological abuse has been related to post-traumatic stress disorder, anxiety, depression, substance abuse, a decreased quality of life, as well as several axis-I and axis-II personality disorders [27–30] such as histrionic and borderline personality disorders [33], in addition to educational, socialization problems and disruptive behaviors [31,32].

Mater-University of Queensland Study of Pregnancy (MUSP) has revealed several outcomes of child maltreatment including cognitive and attention deficits, psychosis, PTSD, addiction problems, sexual issues, and physical limitations [3].

Therefore, acknowledging signs and symptoms of abuse and making proper referrals for assessment and treatment are vital skills of healthcare professionals by which further child maltreatment practices could be minimized [34].

Diagnosis

Psychological maltreatment remains a challenge to detect for healthcare professionals in general and pediatricians in particular. Pediatricians need to stay alert to consider psychological and emotional abuse in any assessment of psychological and behavioral conditions in children [34]. While pediatric providers may directly obtain signs or symptoms on emotional maltreatment by a parent or caregiver, getting history from the pediatric patient is the most beneficial tool for identification [2].

In early infancy, emotional abuse may manifest as decreased emotional expressiveness and interest in surroundings. Therefore, it is often mistaken for intellectual disability or physical illness. Consequently, children may be insecure, anxious, usually not trust-

giving, superficial in social relationships, and overly concerned with pleasing adults [35].

Pediatricians should develop methods for asking children about their relationships with their caregivers, experiences of discipline and feelings of self-worth, security, and being loved [6]. The pediatrician also needs to be aware of risk indicators for psychological maltreatment mentioned above. It is equally important to be aware of the psychological maltreatment that can be associated with exposure to intimate partner violence. Also, children who abuse animals are more likely to be the subject of abuse themselves [36].

Child abuse can be investigated through multiple factors, as recommended by the Mayo Clinic, such as: physical examination to evaluate signs and symptoms of suspected abuse or neglect, lab tests and X-rays, obtaining the child's medical and developmental history, description or monitoring the child's behavior, paying attention to the interactions between parents or caregivers and the child, having informative talks with parents or caregivers, and if possible, talking with the pediatric patient. [47]

Guidelines such as Bright Futures [37] and The Addressing Mental Health Concerns in Primary Care toolkit [38] can both help the pediatrician in children evaluation; however, they are not unique for psychological abuse. At last, physicians should acquire good understanding of the developmental roots of the adverse outcomes of emotional maltreatment and early-life trauma thus proper referrals of patients will be made to more proper treatment services [39].

Management & Prevention

As there is no complete understanding of psychological child abuse or the future life-long consequences [40]. nevertheless, the Center for Disease Control (CDC) recognizes the importance of emphasizing a safe, stable, and nurturing healthy relationships to prevent maltreatment [41].

Providers of pediatric healthcare have a unique opportunity to precisely evaluate the child’s emotional status and report reasonable suspicion to child welfare services. These are fundamentals of prevention and diagnosis therefore all healthcare workers in contact with children are considered reporters of child abuse and neglect [42] and every visit is an opportunity for investigation since psychological abuse has no apparent clinical signs. Early recognition and intervention through prenatal and early childhood home visitation by nurses carries long-term benefits such as decreased childhood internalizing problems [44], reduced antisocial behavior [46], and improved cognitive skills [44,46].

If a child report being abused, their safety is most important. Normal and healthy psychological path of thinking should be re-instituted in the child’s mindset through

several elements including encouraging the patient to tell what happened and express their feelings, reminding the child that the responsibility of being abused does not fall on him or her, reporting abuse to stakeholders, and helping provide safety. If the abuse has occurred in an institution such as school, these behaviors should be reported to the school principal and to ensure that such acts would not keep occurring. [47]

Several types of therapy have been suggested for the condition in perspective and those include (but are not limited to):

- Trauma Focused Cognitive Behavioral Therapy in which cognitive coping skills are provided and these include recognizing the relationship among thoughts, feelings, and behaviors related to everyday upsetting events and to traumatic experiences [50].
- Child-Parent Psychotherapy that is based on healing the effect of trauma in children through the parent-child relationship [51].
- Cognitive Behavioral Interventions for Trauma in Schools [52].
- Cognitive-based Cognitive behavioral therapy [53].
- Brief Psychoanalytic Psychotherapy [54].

Conclusion

Children experiencing psychological and emotional abuse usually suffer from low self-esteem, anxiety, distrustfulness, and depression. The long-term consequences of emotionally abusive behaviors may cause serious psychological health disorders that are much harder to treat or manage. As this condition commonly goes hidden and underestimated, it is therefore under-reported. Thus, strategies and certain processes should be set for the assessment of children who visit health care professionals and pediatricians for better and more comprehensive evaluation of their psychological health and well-being.

References

1. who.int/news-room/fact-sheets/detainl/child-maltreatment / Accessed 04/02/2021.
2. Jackson AM, Kissoon N, Greene C. Aspects of abuse: recognizing and responding to child maltreatment. Curr Probl Pediatr Adolesc Health Care. 2015 Mar;45(3):58-70. doi: 10.1016/j.cppeds.2015.02.001. Epub 2015 Mar 11. PMID: 25771266.
3. pediatrics.aappublications.org/content/130/2/372. / Accessed 04/02/2021.
4. Baker, A. J. L. (2009). Adult recall of psychological maltreatment: Definitional strategies and challenges. Children and Youth Services Review, 31, 703–714.http://dx.doi.org/10.1016/j.childyouth.2009.03.001.
5. The Long-Term Health Consequences of Child Physical Abuse, Emotional Abuse, and Neglect: A Systematic Review and Meta-Analysis Norman RE, Byambaa M, De R, Butchart A, Scott J, et al. (2012) The Long-Term Health Consequences of Child Physical Abuse, Emotional Abuse, and Neglect: A Systematic Review and Meta-Analysis. PLOS Medicine 9(11): e1001349. https://doi.org/10.1371/journal.pmed.1001349.
6. Roberta Hibbard, Jane Barlow, Harriet MacMillan and the Committee on Child Abuse and Neglect and AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY, Child Maltreatment and Violence Committee Pediatrics August 2012, 130 (2) 372-378; DOI: https://doi.org/10.1542/peds.2012-1552.

7. Moran, P., Bifulco, A., Ball, C., Jacobs, C. & Benaim, K. (2002). Exploring psychological abuse in childhood. I. Developing a new interview scale. Bulletin of the Menninger Clinic, 66, 213–240.
8. Tamara L. Taillieu, Douglas A. Brownridge, Jitender Sareen, Tracie O. Afifi, Childhood emotional maltreatment and mental disorders: Results from a nationally representative adult sample from the United States, Child Abuse & Neglect, Volume 59, 2016, Pages 1-12, ISSN 0145-2134, https://doi.org/10.1016/j.chiabu.2016.07.005.
9. Glaser D. Emotional abuse and neglect (psychological maltreatment): a conceptual framework. *Child Abuse & Neglect* 2002;**26**:697–714.
10. Smith CA, Thornberry TP. The relationship between childhood maltreatment and adolescent involvement in delinquency. Criminology. 1995;33(4):451–481.
11. Kimber, M., & MacMillan, H. L. (2017). Child Psychological Abuse. Pediatrics in Review, 38(10), 496–498.
12. McGee RA, Wolfe DA, Yuen SA, Wilson SK, Carnochan J: The measurement of maltreatment: a comparison of approaches. Child Abuse Negl 1995; 19:233–249
13. Stoltenborgh M, Bakermans- Kranenburg MJ, Alink LRA, van IJzendoorn MH. Child Abuse Rev. 2015;24(1):37–50.
14. Taillieu TL, Brownridge DA, Sareen J et al. Childhood emotional maltreatment and mental disorders: Results from a nationally representative adult sample from the United States. Child Abuse & Neglect 2016;59:1–12.
15. Gilbert R, Widom CS, Browne K, Fergusson D, Webb E, Janson S. Burden and consequences of child maltreatment in high-income countries. Lancet. 2009 Jan 3;373(9657):68-81. doi: 10.1016/S0140-6736(08)61706-7. Epub 2008 Dec 4. PMID: 19056114.
16. Scher CD, Forde DR, McQuaid JR, Stein MB. Prevalence and demographic correlates of childhood maltreatment in an adult community sample. Child Abuse Neglect 28: 167-180. March 2004. DOI:10.1016/j.chiabu.2003.09.012.
17. Doyle C. Emotional abuse of children: issues for intervention. Child Abuse Rev. 2002;6:330–342.
18. Department of Health, Home Office, Department for Education and Employment. Working Together to Safeguard Children: A Guide to Inter-agency Working to Safeguard and Promote the Welfare of Children. London, England: The Stationery Office; 2018. Ref: DFE-00195-2018.
19. Loh CC, Vostanis P. Perceived motherinfant relationship difficulties in postnatal depression. Infant Child Dev. 2004; 13:159–171.
20. Foster CJ, Garber J, Durlak JA. Current and past maternal depression, maternal interaction behaviors, and children's externalizing and internalizing symptoms. J Abnorm Child Psychol. 2008;36(4):527–537.
21. DOI: 10.1542/peds.2012-1552 originally published online July 30, 2012; Pediatrics 2012;130;372 PSYCHIATRY, Child Maltreatment and Violence Committee and Neglect and AMERICAN ACADEMY OF CHILD AND ADOLESCENT Roberta Hibbard, Jane Barlow, Harriet MacMillan and the Committee on Child Abuse.
22. Ainsworth MD. Infant--mother attachment. Am Psychol. 1979 Oct;34(10):932-7. doi: 10.1037//0003-066x.34.10.932. PMID: 517843.
23. Hazen AL,ConnellyCD,KelleherKJ,BarthRP,Landsverk JA. Femalecaregivers' experiences withintimatepartner violence andbehaviorproblemsinchildreninvestigatedas victims ofmaltreatment. Pediatrics 2006;117(1):99–109: [pii: 117/1/99].
24. Butchart A, Phinney Harvey A, Kahane T, Mian M, Furniss T (2006) Preventing child maltreatment: a guide to action and generating evidence. Geneva: World Health Organization and International Society for Prevention of Child Abuse and Neglect.
25. Iwaniec D, Larkin E, Higgins S. Research review: risks and resilience in cases of emotional abuse. Child Fam Soc Work. 2006; 11:73–82.
26. Miller-Perrin, C. L., Perrin, R. D., & Kocur, J. L. (2009). Parental physical and psychological aggression: Psychological symptoms in young adults. Child Abuse& Neglect, 33, 1–11. http://dx.doi.org/10.1016/j.chiabu.2008.12.001.
27. Bifulco, A., Moran, P. M., Baines, R., Bunn, A., & Stanford, K. (2002). Exploring psychological abuse in childhood: II. Association with other abuse and adultclinical depression. Bulletin of the Menninger Clinic, 6(3), 241–258.
28. Bruce, L. C., Heimberg, R. G., Blanco, C., Schneier, F. R., & Liebowitz, M. R. (2012). Childhood maltreatment and social anxiety disorder: Implications forsymptom severity and response to pharmacotherapy. Depression and Anxiety, 29, 131–138. http://dx.doi.org/10.1002/da.20909.
29. Gibb, B. E., Chelminski, I., & Zimmerman, M. (2007). Childhood emotional, physical, and sexual abuse, and diagnoses of depressive and anxiety disorders inadult psychiatric outpatients. Depression and Anxiety, 24, 256–263. http://dx.doi.org/10.1002/da.20238.
30. Afifi, T. O., Mather, A., Boman, J., Fleischer, W., Enns, M. W., MacMillan, H., et al. (2011). Childhood adversity and personality disorders: Results from anationally representative population-based study. Journal of Psychiatric Research, 45, 814–822. http://dx.doi.org/10.1016/j.jpsychires.2010.11.008.
31. Iwaniec D. An overview of emotional maltreatment and failure-to-thrive. Child Abuse Rev. 1997;6:370–388.
32. Erickson M, Egeland B, Pianta R. The effects of maltreatment on the development of young children. In: Cicchetti D, Carlson V, eds. Child Maltreatment: Theory and Research on the Causes and Consequences of Child Abuse and Neglect. New York, NY: Cambridge University Press; 1989:647–684.
33. Lobbestael, J., Arntz, A., & Bernstein, D. P. (2010). Disentangling the relationship between different types of childhood maltreatment and personality disorders. Journal of Personality Disorders, 24(3), 285–295.
34. Hornor G. Child Maltreatment: Screening and Anticipatory Guidance. Journal of Pediatric Health Care 2013;27:242–50.
35. Overview of child maltreatment (child abuse). Merck Manual Professional Version. https://www.merckmanuals.com/professional/pediatrics/child-maltreatment/overview-of-child-maltreatment. Accessed Aug. 30, 2018.

36. Lee-Kelland R, Finlay F. Children who abuse animals: when should you be concerned about child abuse? A review of the literature. Arch Dis Child. 2018 Aug;103(8):801-805. doi: 10.1136/archdischild-2018-314751. Epub 2018 Jul 17. PMID: 30018068.
37. Hagan JF, Shaw JS, Duncan P, eds. Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008:77–107.
38. American Academy of Pediatrics, Task Force on Mental Health. Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit [CD-ROM]. Elk Grove Village, IL: American Academy of Pediatrics; 2010.
39. Allen B. The use and abuse of attachment theory in clinical practice with maltreated children, part II: treatment. Trauma Violence Abuse. 2011;12(1):13–22.
40. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS Med. 2012;9(11):e1001349. doi: 10.1371/journal.pmed.1001349. Epub 2012 Nov 27. PMID: 23209385; PMCID: PMC3507962.
41. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Division of Violence Prevention. Essentials for childhood: steps to create safe, stable and nurturing relationships. http://www.cdc.gov/violenceprevention/pdf/essentials_for_childhood_framework.pdf; 2014. Accessed 14/10/14.
42. Child Welfare Information Gateway. Mandatory reporters of child abuse and neglect.2014.
43. Cohen, J. A., & Mannarino, A. P. (2017). Evidence based intervention: Trauma-focused cognitive behavioral therapy for children and families. In D. M. Teti (Ed.), Parenting and family processes in child maltreatment and intervention (91–105). Cham, Switzerland: Springer International Publishing.
44. Kitzman HJ, Olds DL, Cole RE, et al. Enduring effects of prenatal and infancy home visiting by nurses on children: follow-up of a randomized trial among children at age 12 years. Arch Pediatr Adolesc Med. 2010;164(5):412–418.
45. Olds D, Henderson CR Jr., Cole R, et al. Long-term effects of nurse home visitation on children's criminal and antisocial behavior: 15- year follow-up of a randomized controlled trial. JAMA. 1998;280(14): 1238–1244.
46. Kitzman H, Olds DL, Knudtson MD, et al. Prenatal and infancy nurse home visiting and 18-year outcomes of a randomized trial. Pediatrics. 2019; 144(6):e20183876.
47. https://www.mayoclinic.org/diseases-conditions/child-abuse/diagnosis-treatment/drc-20370867 / Accessed 04/2/2021.
48. What are the effects of emotional abuse?. https://www.medicalnewstoday.com/articles/327080. Medically reviewed by Timothy J. Legg, Ph.D., CRNP — Written by Jenna Fletcher on November 21, 2019
49. Long-term Cognitive, Psychological, and Health Outcomes Associated With Child Abuse and Neglect**.** Lane Strathearn, Michele Giannotti, Ryan Mills, Steve Kisely, Jake Najman and Amanuel Abajobir**.** Pediatrics October 2020, 146 (4) e20200438; DOI: https://doi.org/10.1542/peds.2020-0438
50. Lieberman AF, Van Horn P. Don't Hit My Mommy! Washington, DC: Zero to Three Press; 2005
51. Cohen JA, Mannarino AP, Deblinger E. *Treating Trauma and Traumatic Grief in Children and Adolescents*. New York, NY: Guilford Press; 2006.
52. Jaycox LH. Cognitive Behavioral Interventions for Trauma in Schools. Longmont, CO: Sopris West Educational Services; 2003.
53. Smith P, YuleW, Perrin S, Tranah T, Dalgleish T, Clark TM. Cognitive-behavioral therapy for PTSD in children and adolescents: a preliminary randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2007;46(8):1051-1061.
54. Trowell J, Kolvin I, Weeranamthri T, et al. Psychotherapy for sexually abused girls: psychopathological outcome findings and patterns of change. *Br J Psychiatry*. 2002;180:234-247.

Article Topic: Generalized Anxiety disorder.

Author: Ibrahim Alhawaniah.

Editor: Ibraheem Alkhawaldeh, Rami AlEmoush.

Reviewer: Ethar Hazaimeh.

Keywords: Generalized Anxiety Disorder, Psychiatry, Cognitive-Behavioural Therapy, Anxiety, Mental Disorder.

Overview

Generalized anxiety disorder **(GAD)** according to the diagnostic and statistical manual of mental disorders **(DSM-V),** is a subtype of anxiety disorder that is characterized by uncontrollable and excessive anxiety and worry for a period of at least six months that might come with physical symptoms which might hinder the individual's functional life. [1]

The physical symptoms could be only muscle tension or much worse, like diarrhea and shortness of breath. It has a wide spectrum of associated conditions. [1]

GAD 's 12-month prevalence among adults worldwide ranges between 0.4% to 3.6% [1]. A study on 811 adult patients in a university hospital in Jordan revealed a prevalence of 23.7%, which is quite higher than the range that's mentioned in the **DSM-V** [2], with females being likely to have **GAD** two times more than males, as shown in Figure (1) [3], and people aged 36-45 as much as five times more than other age groups.

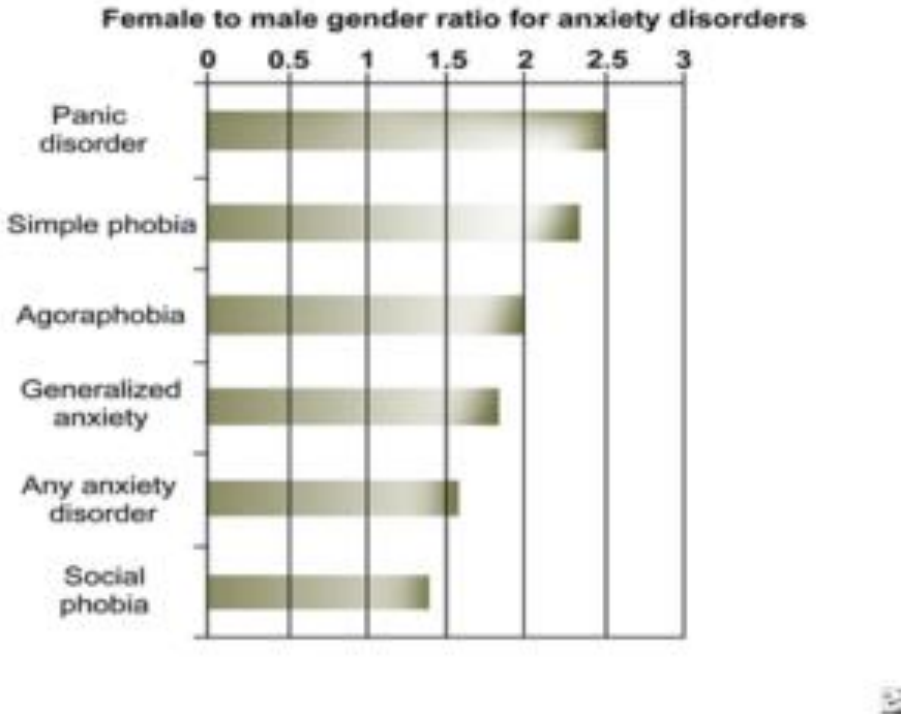


Figure (1) Female to male gender ratio.

Having a lifetime feeling of anxiety and nervousness is common in people that have GAD, making it hard to establish the exact onset of the disease. However, DSM-V mentions that it rarely occurs before adolescence and its median age of onset is 30 years. [1]

Presentation Course

The development of GAD symptoms and its course is quite the same among all patients in that it tends to be chronic, and it waxes and wanes during their lifetime, with rare incidences of full recovery. [1] Also, the earlier patients experience symptoms of **GAD,** the more likely they would have an impaired life and comorbidities.

In adolescents, **GAD** tends to inflate their concerns about their performance at school or in sports, even if nobody is evaluating them. [1] In children, **GAD** might be overdiagnosed, which is why evaluation should be made to establish whether it is **GAD** or other disorders like separation anxiety disorder or obsessive-compulsive disorder, which tend to come with symptoms that mimic **GAD's** symptoms.

Diagnosis

DSM-5 diagnostic criteria of **GAD** include [1]:

A – Excessive anxiety and worry, occurring more days than not for at least 6 months, about several events or activities (such as work or school performance).

B – The individual finds it difficult to control the worry

C – The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):

Note: Only one item is required in children.

1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D - The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E - The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).

F - The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

- A mental status examination should assess two things in **GAD** [4]. Number one includes asking about suicidal/homicidal ideation or plan, such as the following:
- Have you ever wished you were never born, thought you would be better off dead, wished to harm yourself or others, have the plan to harm yourself or others, or ever tried to kill yourself or seriously injure yourself or others?

Number two includes a formal examination of orientation/recall, like:

- Does the patient respond when you call them by name (oriented to person)?

- Is the patient oriented to place and time? When you ask what place, season, day, month, the year is it, does the patient respond appropriately?
- Does the patient have an intact short- or long-term recall? Ask the patient to spell the word "WORLD “forward and backward, count backward from 100 by 7s, and recall what he or she did to celebrate his or her birthday last year and the name of his or her first-grade teacher.

However, an easier and more practical way to diagnose GAD in clinical settings, especially in primary care is to use the GAD-7 tool, which is shown in Table (1), as it has proved its good reliability to diagnose the disorder [4].

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score ___ = Add Columns ___ + ___ + ___

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Table (1): GAD-7

Workup

When a patient is suspected to have an anxiety disorder including **GAD,** the workup that is done consists of the following [5]:

1 – Complete blood cell count

2 – Chemistry profile

3 – Thyroid function tests

4 – Urinalysis

5 – Urine drug screen

- Other studies are also done to exclude certain medical disorders, like excluding CNS disorders with an electroencephalography **(EEG),** lumbar puncture **(LP)** or brain computed tomography **(CT)** scan if indicated by history and clinical findings.
- Electrocardiography **(ECG)** is done to rule out cardiac disorders such as arrhythmias.
- Arterial blood gas analysis **(ABG)** is used to check for hyperventilation (respiratory alkalosis) and hypoxemia or metabolic acidosis.

Treatment

GAD's management includes two main ingredients which are used in synchronization. Those are **1 - Medications** and **2 - Psychotherapy**.

Psychotherapy is Cognitive-Behavioral therapy **(CBT)** which is effective in short-term management and for mild cases, especially in kids [6]. combining **(CBT)** with medicine is the ultimate best option in resistant cases [7].

In certain cases, hospitalization is indicated, these cases are mostly:

- Severe functional deterioration
- Suicide or homicide risk
- Social life impairment

As for medicine, the first line is the selective serotonin reuptake inhibitor **(SSRI)** and serotonin and norepinephrine reuptake inhibitor **(SNRI)** classes. Mainly **Escitalopram**, Duloxetine, Venlafaxine, and Paroxetine.[8]

Risk Factors

1 – Genetics: One-third of patients who have **GAD** have genetic factors.

2 – Environmental: Parental overprotection has been associated with **GAD,** but environmental factors have not been identified as a specific cause for **GAD.**

Recent Advance

A group of patients with refractory-to-treatment **GAD** was given **Ketamine** 1 mg/kg weekly for a period of 3 months subcutaneously in a university clinic trial. The patients said that they had better functionality during and after the trial, with reports of improvement even within one hour after administering the drug which lasted for a week. This sheds light on how we can improve our approach to Anxieties in general and **GAD,** as a such drugs might be used as adjunctive therapy with **SSRI, SNRI, and CBT** combination therapy to maximize efficiency. **Ketamine's** dissociative side effects were found to decrease after multiple doses, and it was found safe to be used as maintenance therapy. [9]

References

[1] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, DSM-5.
[2] M.M. Ahmad, A.I.A. Masalha, H. Fayyomi, L.O. Mari'e and F.F. Barghouti, Prevalence of generalized anxiety disorder in family practice clinics, clinical practice (2018).
[3] Medscape: Anxiety Disorders Clinical Presentation.
[4] R.L. Spitzer, K. Kroenke, J.B.W. Williams and B. Löwe, A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7, Arch Intern Med 166 (2006), pp. 1092.
[5] Medscape: Anxiety Disorders Workup.
[6] V. Hunot, R. Churchill, V. Teixeira and M. Silva de Lima, Psychological therapies for generalised anxiety disorder, Cochrane Database of Systematic Reviews (2007).
[7] J.C. Ipser, P. Carey, Y. Dhansay, N. Fakier, S. Seedat and D.J. Stein, Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders, Cochrane Database of Systematic Reviews (2006).
[8] Medscape: Anxiety Disorders treatment and management,
[9] P. Glue, S.M. Neehoff, N.J. Medlicott, A. Gray, G. Kibby and N. McNaughton, Safety and efficacy of maintenance ketamine treatment in patients with treatment-refractory generalised anxiety and social anxiety disorders, J Psychopharmacol 32 (2018), pp. 663–667.

Article topic: Schizophrenia.

Author: Rawan Osama Abu Nsair.

Editor: Rama Qatarneh.

Reviewer: Ethar Hazaimeh.

Keywords: schizophrenia, psychosis, antipsychotics, positive symptoms

Introduction

Schizophrenia is as old as the Vedas of ancient Hindus, in which the earliest known record of psychoses was recorded (ca 1400 B.C) (2). It described affected people to be nude, filthy, confused, and lacking self-control. It was thought to be brought on by devils (3).

However, the description and terminology of these cases had evolved throughout the years. The term 'démence' was first used by Phillippe Pinel in 1801 to describe the deterioration of mental health abilities in chronically ill, hospitalized patients (4). Later, in 1871, Hecker introduced the term 'hebephrenia', which is derived from 'Hebe', the Greek Goddess of youth. Hebephrenia was used to describe youthful insanity at an early age group with a deteriorating course (2).

A few years later, in 1893, the term 'dementia praecox' appeared for the first time in the fourth edition of Kraepelin's concepts of mental illness (5). He believed that 'dementia praecox' is a central nervous system disease involving profoundly serious lesions of the cerebral cortex (5).

The term that is used nowadays, 'schizophrenia', was introduced by Bleuler, in 1908 (6). He defined it as a disorder in which emotionally charged ideas or drives reach a certain degree of autonomy so that the personality falls into pieces. These fragments can then exist side by side and alternately dominate the main part of the personality and the conscious part of the patient (7). However, the definition underwent many changes with time.

Schizophrenia is a common (8) chronic (9) mental health disorder that involves disturbances in thinking (cognition), emotional responsiveness, and behavior (10). It falls under the DSM category for Schizophrenia Spectrum and Other Psychotic Disorders Class (10). It is multifactorial as both genetic and environmental factors have a proven role in its development (8).

Schizophrenia symptoms can be categorized into three groups: positive, negative, and cognitive symptoms. Positive symptoms are symptoms that are not normally present like hallucinations and delusions (8). Negative symptoms are characterized by loss or deficits, like social withdrawal and amotivation (8). Cognitive symptoms include deficits in working memory, executive functioning, and processing speed (8).

In contrast to what many people may think, schizophrenia does not involve a split personality (11). It is better described simply as a disruption of the patient's thoughts and affect (11).

Epidemiology

Schizophrenia has a low prevalence (12). Its pooled mean point prevalence is estimated to be 0.28% (12). A systematic review that was done in 2016 estimated that 21 million people worldwide are living with schizophrenia (12).

No gender differences were found in prevalence rates (12). Yet, it was noted that men have an earlier onset (13).

Although age-specific prevalence remains consistent over time and across countries, few countries like China and Netherlands showed higher prevalence estimates (12). Moreover, prevalence rates are less in most of the developing world countries (12).

Clinical features

Typically, schizophrenia appears in early adulthood (8). There is a prodromal phase that precedes the first psychotic episode by more than 10 years (14). This phase involves a decline in cognitive and social functioning since early adolescent life (15). Males experience their first psychotic episode earlier than females (10). Moreover, they usually have a more serious illness, more negative symptoms, and a poorer outcome (16).

As mentioned before, schizophrenia has positive, negative, and cognitive symptoms. Psychosis, which is a positive symptom, is an important feature in schizophrenia, although it is not unique for this disorder (17). It is manifested by hallucinations and delusions. Hallucinations can be defined as sensory perceptions in the absence of external stimuli (17). They can be auditory, visual, or tactile, but the auditory type is the predominant one (18). Delusions are false beliefs that are held with certainty which cannot be corrected (19). These positive symptoms could be worsened by stress and decrease with age (17).

Negative symptoms include a decrease in spontaneous speech, poverty of thought, anhedonia (inability to derive pleasure from usual activities), and social withdrawal (17). Mostly, these symptoms remain stable throughout the disorder's course (20).

Cognitive impairments affect the patient's memory, transitive inference, and executive functioning and these are manifested by disorganized speech and behavior (17).

Etiology and risk factors

Schizophrenia has a multifactorial cause (8). This includes interaction between genetic and environmental risk factors that affect early-life brain development (9).

Heritability is estimated to be around 80% (21). It is a polygenic disorder (8). Genome-Wide Association Studies (GWAS) have identified multiple gene loci that are involved in schizophrenia development (22). Moreover, some genetic variants that involve deletion or duplication of DNA sections have been identified to significantly increase the risk of the disorder, but these are only found in 2-3% of cases of schizophrenia (8). One of the most known examples is deletion at chromosome 22q11.2, which carries a 30-40% lifetime risk of schizophrenia development (23). Nonetheless, the concordance rate in monozygotic twins is only about 33%, and this suggests that the disorder's vulnerability is not attributed only to genetic factors (24).

Various modifiable and non-modifiable environmental risk factors have been identified. Many prenatal and perinatal events increase the risk of developing schizophrenia, e.g., maternal infections, malnutrition during pregnancy, and obstetric complications like preterm birth and pre-eclampsia (25). Being born in late winter and spring is also a risk factor, and that could be due to the higher probability of being exposed to maternal respiratory infections at this time of year (9). In addition, low maternal hemoglobin increases the risk by four times (26).

Advanced paternal age when parenting (27), urban environment (28), migration (29), exposure to discrimination (30), physical and sexual abuse (28), persistent abuse of cannabis, amphetamines, and cocaine (31) are all associated with increased risk of developing schizophrenia.

Pathogenesis

Amphetamine-induced psychosis and ketamine-induced psychosis gave rise to the dopamine hypothesis and glutamate hypothesis, respectively, in the neurobiology of schizophrenia (31). Now, evidence is established on the role of the neurotransmitters: dopamine, glutamate, and gamma-aminobutyric acid (GABA) in the development of schizophrenia (32).

The most-known theory emphasizes the role of excess presynaptic synthesis of dopamine in the striatum in the onset of the positive symptoms (33). Drugs that block dopamine receptors, especially D2 receptors have good anti-psychotic properties (34). Also, dopamine interacts with glutamate and GABA in modulating the functioning of excitatory and inhibitory interneurons in cortical circuits (35).

Hypofunction of N-methyl-D-aspartate receptors (NMDAr) (glutamate receptors located between primary and secondary glutamatergic interneurons (36)) are also strongly associated with schizophrenia symptoms (37). In addition, some reports suggest that glutamatergic hypofunction could be the cause of dopamine dysregulation in some cases (38). This hypofunction makes the GABAergic interneurons less effective, which means that there will be insufficient inhibition on the secondary glutamatergic neurons (36). As a result, these neurons will have a higher frequency in firing, and less synchronization (36). This will cause excessive firing of the dopamine neurons in the mesolimbic system (36). Also, the decreased synchronization of the neuronal activity will lead to impaired cognitive processing (39).

Moreover, glutamatergic neurotransmission has been shown to mediate the effects of acute and chronic stress (40), that epidemiological studies have reported that it has a role in the onset of psychosis (41).

Studies have also implicated neuroinflammation as an underlying mechanism in schizophrenia (42). It is noted that people exposed to childhood trauma have significantly elevated peripheral inflammatory markers in adulthood (43). Some peripheral inflammatory markers showed to increase in acute episodes and decline with effective treatment. These include interleukin-6 (IL-6), tumor necrosis factor-alpha (TNFa), soluble interleukin-2 receptor (sIL-2R), and interleukin-1 receptor antagonist (IL-1RA) (44). Moreover, 3.6% of auto-immune diseases are reported to occur in schizophrenic people (45). It is suggested that this theory could mediate the effect of some environmental factors (46).

Neuroimaging showed that schizophrenic patients have lower grey matter volume (46). Loss happens mostly in the pre-frontal and para-hippocampal regions (35). The rate of loss is reported to be associated with elevated levels of immunologic factors like TNFa (47).

However, all of these are still mechanisms, and there are interrelationships between all these pathways.

DSM-5 Diagnostic Criteria (10)

- Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
    1. Delusions
    2. Hallucinations
    3. Disorganized speech (e.g., frequent derailment or incoherence).
    4. Grossly disorganized or catatonic behavior.
    5. Negative symptoms (i.e., diminished emotional expression or avolition).
- For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
- Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
- Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
- The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
- If there is a history of autism spectrum disorder or a communication disorder of childhood-onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Specify if:

The following course specifiers are only to be used after a 1-year duration of the disorder and if they are not in contradiction to the diagnostic course criteria.

- First episode, currently in acute episode: First manifestation of the disorder meeting the defining diagnostic symptom and time criteria. An acute episode is a period in which the symptom criteria are fulfilled.

- First episode, currently in partial remission: Partial remission is a period during which an improvement after a previous episode is maintained and in which the defining criteria of the disorder are only partially fulfilled.
- First episode, currently in full remission: Full remission is a period after an earlier episode during which no disorder-specific symptoms are present.
- Multiple episodes, currently in acute episode: Multiple episodes may be determined after a minimum of two episodes (i.e., after a first episode, remission, and a minimum of one relapse).
- Multiple episodes, currently in partial remission
- Multiple episodes, currently in full remission
- Continuous: Symptoms fulfilling the diagnostic symptom criteria of the disorder are remaining for the majority of the illness course, with subthreshold symptom periods being very brief relative to the overall course.

Unspecified

Specify if:

With catatonia (refer to the criteria for catatonia associated with another mental disorder, pp. 119-120, for definition).
Coding note: Use additional code 293.89 (F06.1) catatonia associated with schizophrenia to indicate the presence of the comorbid catatonia.

Specify current severity:

Severity is rated by a quantitative assessment of the primary symptoms of psychosis, including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms. Each of these symptoms may be rated for its current severity (most severe in the last 7 days) on a 5-point scale ranging from 0 (not present) to 4 (present and severe).

Note: Diagnosis of schizophrenia can be made without using this severity specifier.

Differential diagnoses

It is important to distinguish schizophrenia from other disorders with similar clinical features to provide proper treatment.

- Some psychotic disorders such as schizophreniform disorder and brief psychotic disorder have symptoms that may overlap with schizophrenia. Yet, the duration of symptoms in schizophrenia is at least 6 months, while in schizophreniform disorder it is less than 6 months, and less than 1 month in brief psychotic disorder (10).

- Delusional disorder is a main differential as well, but unlike schizophrenia other psychotic features are absent (48).
- Mood disorders could also mimic symptoms of schizophrenia. However, in major depressive disorder and bipolar disorder, psychotic features occur exclusively during the major depressive or manic episode (10).
- Other non-psychiatric conditions should be considered as well. These include medical illnesses or conditions like hepatic encephalopathy, hypoglycemia, some electrolyte abnormalities, and sepsis (48). Nevertheless, symptoms resolve by treatment of the underlying cause (48).
- Substance abuse could also present similarly which is why the diagnosis of schizophrenia should not be made if the patient is actively using illicit drugs (48).

Management

In general, treatment aims to relieve symptoms, prevent relapse, and increase adaptive functioning (49). But, as it is unlikely for schizophrenia patients to return to their baseline level of functioning, therapy is directed to optimize the long-term outcomes (49). There are two available types of schizophrenia treatment: pharmacotherapy and non-pharmacotherapy. Pharmacotherapy should be initiated immediately if an acute psychotic episode (11). It is also vital within the first 5 years following the first episode when disease-related brain changes occur (50). Additionally, it is important to continue maintenance therapy to avoid relapse (11).

Antipsychotics are the cornerstone of schizophrenia treatment (51). There are two types of antipsychotics: typical (first generation) antipsychotics and atypical (second generation) antipsychotics. Typical antipsychotics (e.g. haloperidol) are dopamine D2 receptors antagonists and to a lesser extent serotonin 5-HT2A receptor antagonists (49). These drugs are associated with extrapyramidal adverse effects like parkinsonism, akathisia, and tardive dyskinesia (9). Atypical antipsychotics (e.g. risperidone, olanzapine, clozapine) have an antidopaminergic effect and high antiserotonergic effect (49). These drugs are preferred as first-line treatment because they have fewer extrapyramidal adverse effects (50). Still, they are associated with metabolic side effects like weight gain, diabetes mellitus type 2, hyperlipidemia, and metabolic syndrome (52). Hence, they do contribute to an increased risk of cardiovascular mortality in schizophrenic patients (53).

Clozapine has a problematic safety profile as it is known to induce agranulocytosis, orthostatic hypotension, and seizures on higher doses (49). Despite this, it remains the most effective antipsychotic in treatment-resistant schizophrenia (49). Furthermore, it has the benefit of decreasing the risk of suicide by tenfold (54).

When no improvement is established, augmentation therapy can be used. Augmentation involves using another class of agents in addition to antipsychotics, such as mood

stabilizers which could improve mood and behavior despite not having antipsychotic effects (49). Combination therapy, which involves adding another antipsychotic drug, may be used (49).

Non-pharmacological therapy is used as an adjunct to pharmacotherapy, not as an alternative (49). This includes individual, cognitive, and behavioral psychotherapy (49). It is reported that non-pharmacotherapy could help ensure adherence to medications (55). Stopping medications increases the risk of relapse, and thus, hospitalization (55). Additionally, this type of therapy may be directed to family members, raising their awareness about the importance of support and side effects of medications. It has been shown that this leads to a decline in rehospitalizations and improvement in social functioning (49).

Prognosis

The long-term outcome is heterogeneous; it ranges from complete recovery to chronic need of care (56). 75% of cases of schizophrenia have a course that is characterized by a remission phase alternating with relapses (57). However, two-thirds never recover after the first onset of psychosis (17).

In 2016, schizophrenia was ranked as the 12th most disabling disorder globally despite its low prevalence (58). It accounts for a significant health care burden (8). This could be attributed to the early onset of the disease, the low remission rates, and the high disability associated with the disease (12).

Schizophrenia is linked to high rates of comorbidities (12). These patients are at increased risk of developing coronary heart disease, stroke, and diabetes mellitus type 2 (56). They also have a three- to fourfold higher prevalence of substance abuse (17).

Schizophrenia is also associated with psychosocial impairments, that make these patients more likely to be unemployed, homeless, living in poverty, and having difficulties keeping up with household and self-care tasks (12). All of this makes them more dependent on family carers and the available mental health services (12).

In general, these patients have a lifespan that is shorter than the normal population by about 15 years (59). Mostly, deaths are related to associated physical illnesses previously mentioned (56) yet suicide does play a significant role as the lifetime risk of death by suicide is 5-10% (59).

References

1. Dissociative Identity Disorder vector illustration. Woman with other faces silhouettes. Split Personality Disorder, Borderline Disorder, Schizophrenia. Mental illness. [Internet]. Available from: https://www.shutterstock.com/image-vector/dissociative-identity-disorder-vector-illustration-woman-1354790075
2. Adityanjee, Aderibigbe YA, Theodoridis D, Vieweg WVR. Dementia praecox to schizophrenia: The first 100 years. Psychiatry Clin Neurosci. 1999;53(4):437–48.
3. Howells JG (ed.) The Concept of Schizophrenia: Historical Perspectives. American Psychiatric Press, Washington DC, 1991.
4. Gottesman II. Schizophrenia Genesis: The Origins of Madness. WH Freeman & Company, New York, 1991.
5. Kraepelin E. Dementia Praecox and Paraphrenia. (Translated by RM Barclay.) ES Livington, Edinburgh, 1919.
6. Black DW, Boffeli TJ. Simple schizophrenia: past,present and future. Am. J. Psychiatry 1989; 146: 1267– 1273.
7. Bleuler E. Dementia Praecox oder Gruppe der Schizophrenien. Deiticke, Leipzig, 1911. [Dementia Praecox or the Group of Schizophrenias. Translated by J Zinkin. International University Press, New York, 1950.].
8. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia - An Overview. JAMA Psychiatry. 2020;77(2):201–10.
9. Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, et al. Schizophrenia. Nat Rev Dis Prim. 2015;1(November).
10. Diagnostic and Stastistical Manual of Mental Disorders Fifth Edition. American Psychiatric Association. 2013.
11. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: Overview and treatment options. P T. 2014;39(9):638–45.
12. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott G, et al. Global Epidemiology and Burden of Schizophrenia : Findings from the Global Burden of Disease Study 2016. 2018;1–9.
13. Crismon L, Argo TR, Buckley PF. Schizophrenia. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 9th ed. New York, New York: McGraw-Hill; 2014:1019–1046.
14. Kahn RS, Keefe RSE. Schizophrenia is a cognitive illness: Time for a change in focus. JAMA Psychiatry. 2013;70(10):1107–12.
15. Kahn RS, Sommer IE. The neurobiology and treatment of first-episode schizophrenia. Mol Psychiatry [Internet]. 2015;20(1):84–97. Available from: http://dx.doi.org/10.1038/mp.2014.66
16. Jablensky A. (2000). Epidemiology of schizophrenia: the global burden of disease and disability. European archives of psychiatry and clinical neuroscience, 250(6), 274–285. https://doi.org/10.1007/s004060070002.
17. Coyle JT. Schizophrenia: Basic and Clinical. Adv Neurobiol. 2017;15:255-280. doi: 10.1007/978-3-319-57193-5_9. PMID: 28674984.
18. Larøi F, Sommer IE, Blom JD, Fernyhough C, Ffytche DH, Hugdahl K, et al. The characteristic features of auditory verbal hallucinations in clinical and nonclinical groups: State-of-the-art overview and future directions. Schizophr Bull. 2012;38(4):724–33.
19. Feyaerts J, Henriksen MG, Vanheule S, Myin-Germeys I, Sass LA. Delusions beyond beliefs: a critical overview of diagnostic, aetiological, and therapeutic schizophrenia research from a clinical-phenomenological perspective. Lancet Psychiatry. 2021 Mar;8(3).
20. Austin SF, Mors O, Budtz-Jørgensen E, Secher RG, Hjorthøj CR, Bertelsen M, et al. Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10year follow-up study in the OPUS cohort. Schizophr Res [Internet]. 2015;168(1–2):84–91. Available from: http://dx.doi.org/10.1016/j.schres.2015.07.021
21. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a Complex Trait. Arch Gen Psychiatry. 2003;60(12):1187.
22. Ripke S, Neale BM, Corvin A, Walters JTR, Farh KH, Holmans PA, et al. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421–7.
23. Schneider M, Debbané M, Bassett AS, Chow EWC, Fung WLA, Van Den Bree MBM, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: Results from the international consortium on brain and behavior in 22q11.2 deletion syndrome. Am J Psychiatry. 2014;171(6):627–39.
24. Hilker R, Helenius D, Fagerlund B, Skytthe A, Christensen K, Werge TM, et al. Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register. Biol Psychiatry [Internet]. 2018;83(6):492–8. Available from: http://dx.doi.org/10.1016/j.biopsych.2017.08.017
25. Bramon E, Walshe M, McDonald C, Martín B, Toulopoulou T, Wickham H, et al. Dermatoglyphics and schizophrenia: A meta-analysis and investigation of the impact of obstetric complications upon a-b ridge count. Schizophr Res. 2005;75(2–3):399–404.
26. Jaaro-Peled H, Sawa A. Neurodevelopmental Factors in Schizophrenia. Psychiatr Clin North Am [Internet]. 2020;43(2):263–74. Available from: https://doi.org/10.1016/j.psc.2020.02.010
27. Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, Feldman D, et al. Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry. 2001;58(4):361–7.
28. Stilo, S. A. & Murray, R. M. The epidemiology of schizophrenia: replacing dogma with knowledge. Dialogues Clin. Neurosci. 12, 305–315 (2010).
29. Cantor-Graae E, Selten JP. Schizophrenia and migration: A meta-analysis and review. Am J Psychiatry. 2005;162(1):12–24.
30. Boydell J, Os J Van, Mckenzie K, Allardyce J, Goel R, Mccreadie RG, et al. environment. 2001;323(December):6–9.
31. Murray RM, Paparelli A, Morrison PD, Marconi A, Di Forti M. What can we learn about schizophrenia from studying the human model, drug-induced psychosis? Am J Med Genet Part B Neuropsychiatr Genet. 2013;162(7):661–70.
32. Fusar-Poli P, Meyer-Lindenberg A. Striatal presynaptic dopamine in schizophrenia, part II: Meta-analysis of [18F/11C]-DOPA PET studies. Schizophr Bull. 2013;39(1):33–42.
33. Laruelle M, Abi-Dargham A. Dopamine as the wind of the psychotic fire: New evidence from brain imaging studies. J Psychopharmacol. 1999;13(4):358–71.

34. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: Version III - The final common pathway. Schizophr Bull. 2009;35(3):549–62.
35. Ropper AH, Marder SR, Cannon TD. SchizophreniaNEJM Review Marder. N Engl J Med. 2019;18:1753–61.
36. Schwartz TL, Sachdeva S, Stahl SM. Genetic data supporting the NMDA glutamate receptor hypothesis for schizophrenia. Curr Pharm Des [Internet]. 2012;18(12):1580–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22280435
37. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: An update for the 21st century. J Psychopharmacol. 2015;29(2):97–115.
38. McGuire P, Howes OD, Stone J, Fusar-Poli P. Functional neuroimaging in schizophrenia: diagnosis and drug discovery. Trends Pharmacol Sci. 2008;29(2):91–8.
39. Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci. 2005;6(4):312–24.
40. Popoli M, Yan Z, McEwen BS, Sanacora G. The stressed synapse: The impact of stress and glucocorticoids on glutamate transmission. Nat Rev Neurosci [Internet]. 2012;13(1):22–37. Available from: http://dx.doi.org/10.1038/nrn3138
41. Stilo SA, Murray RM. Non-Genetic Factors in Schizophrenia. 2019;
42. Carter CS, Bullmore ET, Harrison P. Is there a flame in the brain in psychosis? Biol Psychiatry [Internet]. 2014;75(4):258–9. Available from: http://dx.doi.org/10.1016/j.biopsych.2013.10.023
43. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: A meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol Psychiatry [Internet]. 2016;21(5):642–9. Available from: http://dx.doi.org/10.1038/mp.2015.67
44. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry [Internet]. 2016;21(12):1696–709. Available from: http://dx.doi.org/10.1038/mp.2016.3
45. Benros ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M, Mortensen PB. A nationwide study on the risk of autoimmune diseases in individuals with a personal or a family history of schizophrenia and related psychosis. Am J Psychiatry. 2014;171(2):218–26.
46. Radhakrishnan R, Kaser M, Guloksuz S. The Link between the Immune System, Environment, and Psychosis. Schizophr Bull. 2017;43(4):693–7.
47. Cannon TD, Chung Y, He G, Sun D, Jacobson A, Van Erp TGM, et al. Progressive reduction in cortical thickness as psychosis develops: A multisite longitudinal neuroimaging study of youth at elevated clinical risk. Biol Psychiatry [Internet]. 2015;77(2):147–57. Available from: http://dx.doi.org/10.1016/j.biopsych.2014.05.023
48. Schultz SH, North SW, Shields CG. Schizophrenia: A Review. 2007;
49. Crismon M, & Kattura R.S., & Buckley P.F. (2017). Schizophrenia. DiPiro J.T., & Talbert R.L., & Yee G.C., & Matzke G.R., & Wells B.G., & Posey L(Eds.), Pharmacotherapy: A Pathophysiologic Approach, 10e. McGraw Hill. https://accesspharmacy.mhmedical.com/co.
50. Lehman, A. F., Lieberman, J. A., Dixon, L. B., McGlashan, T. H., Miller, A. L., Perkins, D. O., Kreyenbuhl, J., American Psychiatric Association, & Steering Committee on Practice Guidelines (2004). Practice guideline for the treatment of patients with sch.
51. Kane JM, Correll CU. Past and present progress in the pharmacologic treatment of schizophrenia. J Clin Psychiatry. 2010;71(9):1115–24.
52. Pramyothin P, Khaodhiar L (2010) Metabolic syndrome with the atypical antipsychotics. Curr Opin Endocrinol Diabetes Obes 17(5):460–466.
53. Raedler TJ. Cardiovascular aspects of antipsychotics: Curr Opin Psychiatry 2010;23(6):574–581.
54. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R, Lindenmayer JP, Potkin S (2003) International suicide prevention trial study group. Clozapine treatment for suicidality in schizophren.
55. Lindenmayer JP, Liu-Seifert H, Kulkarni PM, et al. Medication nonadherence and treatment outcomes in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. J Clin Psychiatry 2009;70(7):990–996.
56. Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. Annu Rev Clin Psychol. 2014;10:425–48.
57. Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull. 2013;39(6):1296–306.
58. GBD 2016 DALYs and HALE Collaborators (2017). Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for th.
59. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. The Lancet Psychiatry [Internet]. 2017;4(4):295–301. Available from: http://dx.doi.org/10.1016/S2215-0366(17)30078-0

Article topic: Central Sleep Apnea.

Author: Ihdaa Mahmoud Bani Khalaf.

Editor: Hala Qaryouti.

Reviewer: Ethar Hazaimeh.

***Keywords: Apnea, Sleep Disorders, Pathophysiology, Psychiatry, Diagnosis, Treatment*.**

Overview

Central sleep apnea (CSA) is an intermittent repetitive cessation and/or reduction in breathing without respiratory effort, due to an abnormal ventilatory drive [1]. It is one of the four sleep-related breathing disorders, which also include obstructive sleep apnea (OSA), sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders [2].

Although almost 5 times less prevalent than OSA ([2], CSA accounts for about 5-10% of sleep medicine patients in clinics ([1]. It has been gaining massive interest in the field of sleep disorders over the last decade due to its excessive reporting in some subpopulations such as patients with heart failure, neurological disorders, or those on high-dose opiates. In addition, the disorder has a challenging nature in its early detection, diagnosis, and suitable treatment [3,4].

Pathophysiology of CSA

Central sleep apnea can be categorized into two main categories: primary (idiopathic) or secondary. The latter is related to Cheyne-Stokes respiration (CSR), medical conditions including chronic renal failure, or high-altitude periodic breathing [5]. In addition, central sleep apnea may also manifest during the initiation of treatment of OSA or may occur in association with obstructive sleep apnea-hypopnea syndrome (termed complex sleep apnea) [6]. Another CSA subtype can manifest secondary to drugs; as sodium oxybate may promote CSA, while acetazolamide and hypnotics like zolpidem may attenuate the breathing disorder [11].

CSA subtypes are represented by specific pathophysiological mechanisms that trigger certain central breathing patterns which aid in identifying the underlying disease and explaining the context of CSA occurrence. A precise knowledge of pathophysiology is necessary for accurate classification as well as for improving diagnosis and treatment strategies [7].

Another valuable distinction for identifying underlying pathology and deciding the proper ventilatory support is waking CO_2 levels [8]. Therefore, CSA can be also classified into hyperventilation (which is more common) or hypoventilation CSA.

Hypoventilation-related CSA can be seen in conditions where an absent or diminished wakefulness stimulus to breathe causes alveolar hypoventilation [9] via two mechanisms. The first is the inability to translate the central drive to breathe into adequate ventilation due to neuromuscular disorders (e.g. motor neuron disease, poliomyelitis, and neuromuscular junction disorders), and restrictive thoracic cage disorders such as scoliosis. The second mechanism is functional or anatomical lesions at the level of the respiratory centers reducing the ventilatory drive (e.g. congenital and idiopathic central alveolar hypoventilation syndromes, obesity hypoventilation syndrome, medication induced CSA in severe opioid toxicity, and structural lesions such as brain tumors, Chiari's syndrome, cerebrovascular diseases). [10]

The underlying mechanism in hyperventilation-related CSA is instability in ventilatory control, as patients have a tendency to develop unstable breathing referred to as high loop gain. This predisposes to hyperventilation and subsequent lowering of PCO_2 below the apneic threshold. When carbon dioxide drops below this threshold hypocapnia ensues, and apnea occurs until the carbon dioxide level increases above the threshold. [6,10,12])

Epidemiology and Risk Factors

There are multiple risk factors for CSA such as age, heart failure, male gender, atrial fibrillation, hypocapnia, diuretic use, prior stroke, opioid use and other less prevalent medical conditions such as neuromuscular disease. [3,9,13,14]

According to several studies, the prevalence of CSA increases with aging [13,15]. However, according to Young et al. [16] it is uncertain if age alone can be considered an independent risk factor as older people are more susceptible to developing stroke and heart failure implicated in CSA development. As a result, age may not be a true risk factor.

Regarding gender, according to Bixler and colleagues [14], post-menopausal women have an increased incidence of OSA. However, females in general have an extremely low prevalence of CSA (0.3%) compared to males (7.8%).

Regarding the above-mentioned subpopulations, CSA has a prevalence of 21-37% (for an apnea-hypopnea index (AHI) ≥ 15) in patients with stable congestive heart failure with reduced ejection fraction [3]. In patients post-stroke prevalence varies widely between 3-72% [11,17,18].

CSA is also reported in patients on opioid medications, along with OSA patients treated with continuous positive airway pressure (CPAP) so-called treatment-emergent CSA (TE-CSA) [11,19]. There are some factors that are identified as predisposing to treatment-emergent CSA (TE-CSA), such as older age, male gender, heart failure, and ischemic heart disease, in addition to the use of high PAP levels, higher residual AHI, central apnea index and arousal index [20,21].

Clinical Presentation

Symptoms of CSA are like, yet usually less severe than symptoms of patients with OSA. Patients complain of sleep fragmentation (disturbed sleep cycle due to continuous waking up), and insomnia leading to daytime hypersomnolence [1].

Diagnosis of CSA

A crucial step in CSA diagnosis is differentiation from OSA, which is proving challenging with the emergence of TE-CSA [11].

According to the third International Classification of Sleep Disorders (ICSD-3), full polysomnography (PSG) with esophageal pressure measurement showing absent ventilatory effort during the event is the gold standard for CSA diagnosis [11,18]. According to the Diagnostic and Statistical Manual of Mental Disorders- 5th edition (DSM5), the diagnosis requires positive PSG findings as well as the pathology not being better explained by another current sleep disorder [6].

The apnea-hypopnea index (AHI) is the total count of overnight respiratory events (apneas and hypopneas) divided by the total sleep time in hours [22]. It is used to classify OSA and evaluate its therapeutic success [23], and also to define TE-CSA; where an AHI >5 events per hour of sleep, more than 50% of which being due to central apneas or hypopneas is used as defining criteria for TE-CSA in adults [11].

If the esophageal pressure measurement cannot be done, surrogates such as strain gauges, respiratory inductive plethysmography (RIP), or belts with piezoelectric or polyvinylidene fluoride (PVDF) sensors can be used [11]. RIP is a device that incorporates thoracic and abdominal belts to determine spontaneous tidal breathing without employing a facemask or a mouthpiece [24].

It is worthwhile to say that there is no criterion of desaturation or of arousal required to consider an event as an apnea [25].

Treatment and Management

Treatment options for CSA include continuous positive airway pressure (CPAP), adaptive servo-ventilation (ASV), and transvenous phrenic nerve stimulation [26].

According to a randomized clinical trial (RCT) by Bradley et al., CPAP can attenuate central sleep apnea, improve nocturnal oxygen levels, lower noradrenaline levels, increase ejection fraction, and increase the distance a patient can walk in six minutes. However, CPAP does not affect survival in patients with CSA and heart failure.

Another RCT also shows supporting evidence for CPAP potentially improving both left ventricular ejection fraction and heart transplant-free survival in heart failure patients if CSA is suppressed soon after its initiation. [21, 22]

ASV is used to treat CSA, during this treatment positive airway pressure (PAP) for ventilation support is provided and adjusted as apneic episodes are detected during sleep. Nevertheless, the support provided adapts to the physiology of the patient and can deliver breaths and utilize anti-cyclic modes of ventilation to address crescendo-decrescendo breathing patterns observed in Hunter-Cheyne-Stokes respiration [26].

A novel treatment for CSA is transvenous phrenic nerve stimulation which is an implantable device that stimulates the phrenic nerve to initiate breaths and restore a physiological breathing pattern throughout sleep. This therapy stimulates the diaphragm during sleep to stabilize gas exchange and maintain normal breathing.

Recently, temporary transvenous unilateral phrenic nerve stimulation has been shown to result in a more regular breathing pattern, fewer apneic events, improved oxygen saturation, and increased end-tidal carbon dioxide, without suppressing the intrinsic drive to breathe in patients with CSA. The initial study of transvenous phrenic nerve stimulation reported a significant reduction in the number of episodes of central apnea per hour of sleep. [29,30]

Conclusion

As time passes, central sleep apnea is being more recognized due to its frequent incidence among people, especially those with cardiac disease. ASV is used to treat people with CSA and is proving to be a reliable and promising treatment modality that might improve cardiac function, improve sleep quality, and confer a survival benefit. Further physiological and clinical research is still required to investigate the central apnea syndromes.

Acknowledgment: We thank IFMSA-JO.

References

1. Muza RT. Central sleep apnoea-a clinical review. J Thorac Dis. 2015 May;7(5):930–7.
2. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015 Apr;3(4):310–8.
3. Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, et al. Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. J Card Fail. 2009 May;15(4):279–85.
4. Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. Int J Cardiol. 2006 Jan;106(1):21–8.
5. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014 Nov;146(5):1387–94.
6. Sutton WS. Neurocognitive disorders. Handbook of Geropsychiatry for the Advanced Practice Nurse: Mental Health Care for the Older Adult. 2020. 133–158 p.
7. Baillieul S, Revol B, Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Pépin J-L. Diagnosis and management of central sleep apnea syndrome. Expert Rev Respir Med. 2019 Jun;13(6):545–57.
8. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: Pathophysiology and treatment. Chest. 2007 Feb;131(2):595–607.
9. Ishikawa O, Oks M. Central Sleep Apnea. Clin Geriatr Med. 2021 Aug;37(3):469–81.
10. Martins RT, Eckert DJ. Central sleep apnea due to other medical disorders. Sleep Med Clin [Internet]. 2014;9(1):57–67. Available from: http://dx.doi.org/10.1016/j.jsmc.2013.10.002
11. Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J. 2017 Jan;49(1).
12. Hernandez AB, Patil SP. Pathophysiology of central sleep apneas. Sleep Breath. 2016 May;20(2):467–82.
13. Mehra R, Stone KL, Blackwell T, Ancoli Israel S, Dam T-TL, Stefanick ML, et al. Prevalence and correlates of sleep-disordered breathing in older men: osteoporotic fractures in men sleep study. J Am Geriatr Soc. 2007 Sep;55(9):1356–64.
14. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med. 2001 Mar;163(3 Pt 1):608–13.
15. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med. 1998 Jan;157(1):144–8.
16. Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med. 2002 Apr;162(8):893–900.
17. Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. J Clin sleep Med JCSM Off Publ Am Acad Sleep Med. 2010 Apr;6(2):131–7.
18. Siccoli MM, Valko PO, Hermann DM, Bassetti CL. Central periodic breathing during sleep in 74 patients with acute ischemic stroke - neurogenic and cardiogenic factors. J Neurol. 2008 Nov;255(11):1687–92.
19. Orr JE, Malhotra A, Sands SA. Pathogenesis of central and complex sleep apnoea. Respirology. 2017 Jan;22(1):43–52.
20. Liu D, Armitstead J, Benjafield A, Shao S, Malhotra A, Cistulli PA, et al. Trajectories of Emergent Central Sleep Apnea During CPAP Therapy. Chest. 2017 Oct;152(4):751–60.
21. Nigam G, Pathak C, Riaz M. A systematic review on prevalence and risk factors associated with treatment- emergent central sleep apnea. Ann Thorac Med. 2016;11(3):202–10.
22. Pevernagie DA, Gnidovec-Strazisar B, Grote L, Heinzer R, McNicholas WT, Penzel T, et al. On the rise and fall of the apnea-hypopnea index: A historical review and critical appraisal. J Sleep Res. 2020 Aug;29(4):e13066.
23. Bittencourt LR, Suchecki D, Tufik S, Peres C, Togeiro SM, Bagnato MC, et al. The variability of the apnoea-hypopnoea index. J Sleep Res. 2001 Sep;10(3):245–51.
24. Retory Y, Niedzialkowski P, de Picciotto C, Bonay M, Petitjean M. New Respiratory Inductive Plethysmography (RIP) Method for Evaluating Ventilatory Adaptation during Mild Physical Activities. PLoS One. 2016;11(3):e0151983.
25. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin sleep Med JCSM Off Publ Am Acad Sleep Med. 2012 Oct;8(5):597–619.
26. Mehra R. Sleep apnea and the heart. Cleve Clin J Med. 2019 Sep;86(9 Suppl 1):10–8.
27. Bradley TD, Logan AG, Kimoff RJ, Sériès F, Morrison D, Ferguson K, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med. 2005 Nov;353(19):2025–33.
28. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial. Circulation. 2007 Jun;115(25):3173–80.
29. Abraham WT, Jagielski D, Oldenburg O, Augostini R, Krueger S, Kolodziej A, et al. Phrenic nerve stimulation for the treatment of central sleep apnea. JACC Heart Fail. 2015 May;3(5):360–9.
30. Ponikowski P, Javaheri S, Michalkiewicz D, Bart BA, Czarnecka D, Jastrzebski M, et al. Transvenous phrenic nerve stimulation for the treatment of central sleep apnoea in heart failure. Eur Heart J. 2012 Apr;33(7):889–94.
31. www.webmd.com. Man sleeping in bed wearing CPAP mask [Internet]. 2021. Available from: https://www.webmd.com/sleep-disorders/sleep-apnea/sleep-apnea

Article topic: Delirium.

Author: Sulieman Mazahreh.

Editor: Fadlullah M. F. AL-Saleem.

Reviewer: Ethar Hazaimeh.

Keywords: Delirium, Acute confusion disorders, Psychiatry.

Abstract

Delirium is a common and expensive acute confused condition that is accompanied by considerable functional impairment and discomfort. It is a symptom of acute encephalopathy and is variously referred to as acute brain failure, acute brain dysfunction, or changed mental state. All patients are at risk for delirium, however, those who are more vulnerable (such as advanced age, exposure to other stresses such as infection, and specific drugs) are at a higher risk. The pathophysiologic etiology of delirium is unknown. It is critical to identify patients at risk for and those who have delirium, as well as to identify and treat variables that contribute to it as soon as possible. Because there is no one action or drug to treat delirium, it is difficult to control. As a result, risk reduction and quick treatment are dependent on a thorough plan to address the relevant variables. When multimodal methods are employed, delirium can be avoided or reduced, improving patient outcomes.

History of Delirium

Delirium is one of the earliest described kinds of psychoses, however many medical professionals still see it as an unknown and unrecognized condition. [1] Hippocrates (5th century BC), the father of traditional medicine, initially identified phrenitis and paraphrenitis, which are today recognized as a somatic kind of delirium and referred to as variably expressed acute behavioral disorders that occur during physiological inflammation. [2]

Introduction

Delirium is a frequent and costly acute confusing disorder that causes significant functional impairment and suffering. It is a sign of acute encephalopathy and is also known as acute brain failure, acute brain dysfunction, or altered mental state.

It is difficult to regulate delirium since there is no one activity or treatment to cure it.

Etiology and pathogenesis

Despite its great frequency and morbidity, little is known about delirium. Advanced age, prior cognitive impairment drugs particularly those with significant anticholinergic potential, sleep deprivation, hypoxia and anoxia, metabolic abnormalities, and a history of alcohol or drug misuse are all known risk factors for delirium.[3] Several ideas have been offered throughout the years in an attempt to explain the mechanisms that contribute to the development of delirium.[4] Each suggested theory has concentrated on a certain mechanism or pathologic process, as well as observational and experience evidence or empirical data. However, no one unitary pathophysiologic mechanism has been found yet. [5]

Figure 1: Theories on the onset of delirium. Diagrams illustrating the interrelationships of current views on the pathophysiology of delirium and how they may be related to one another.

Clinical presentation

Delirium is characterized by a wide spectrum of cognitive and noncognitive neuropsychiatric symptoms in the areas of motor activity, sleep-wake cycle, emotional expression, perception, and thinking. This wide phenomenological spectrum reflects the pervasive disturbance of brain function and can resemble a variety of different neuropsychiatric illnesses. Regardless of its etiology, delirium has a uniform manifestation that shows the failure of a single common neuronal circuit. [6] Understanding specific symptom frequencies and patterns can give crucial information about the neurological foundations of this entity. [7]

Table 1

Frequency of phenomenological manifestations in delirium

Core diagnostic features

Attentional deficits (97–100%)

Thought process abnormalities (54–79%)

Other core symptoms

Disorientation (76–96%)

Memory deficits (88–96%)

Sleep-wake cycle disturbances (92–97%)

Motoric alterations (24–94%)

Language disturbances (57–67%)

Non-core symptoms

Perceptual disturbances (50–63%)

Delusions (21–31%)

Affective changes (43–86%)

Clinical subtypes

Motor behavior disturbances are always present and obvious in delirium. There are over 30 studies that demonstrate that motorically defined clinical subgroups of delirium differ in terms of the presence of nonmotor symptoms, etiology, pathophysiology, detection rates, treatment experience, episode duration, and prognosis. However, data have been contradictory with improved prognosis in hypoactive individuals, hyperactive presentations, or patients with normal motor function. [8]

Lipowski distinguished between 'hyperactive' and 'hypoactive' psychomotor presentations, subsequently adding a third 'mixed' category in which parts of both occur within short time frames.[9] Liptzin and Levkoff developed criteria based on activity and related psychomotor activities.[10] O'Keeffe used questions from the Brief Psychiatric Rating Scale to define delirium subgroups based on activity within the first 48 hours. Other ways include using symptom items from the Memorial Delirium Assessment Scale (MDAS), the Delirium Rating Scale (DRS) and its most recent version (DRS-R-98), as well as visual analog scales and 'clinical impression'. [11]

Workup and Diagnosis

The following are the characteristic elements of delirium as outlined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV): [12]

1. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with diminished ability to focus, sustain, or shift attention.
2. A change in cognition (e.g., memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better explained by a pre-existing, established, or evolving dementia.
3. Disturbance occurs over a short length of time (typically hours to days) and tends to fluctuate throughout the day.
4. Depending on the cause.

In the examination of delirium, clinicians meet two diagnostic problems. The first step is to recognize that the illness exists, and the second is to evaluate the patient for any medical issues that may have provoked the event.

Despite developments in medical technology, the history and physical examination remain the cornerstones in the diagnosis of delirium. Further testing may be necessary after a comprehensive review; however, overreliance on laboratory tests and diagnostic imaging might reduce physician-patient contact, making the nuances of delirium harder to evaluate. [13]

If delirium is suspected, the first step should be to elicit the elements that define the disease. Clinicians who use the DSM-IV criteria at the bedside have a better chance of making a proper diagnosis. The patient's state of awareness should be the focus of the initial examination. Patients should be checked for their degree of orientation and questioned on regular items to rule out any memory problems. Conversations can frequently indicate a chaotic cognitive process or be devoid of any content. If the doctor is unaware of the patient's baseline mental health, family or carers can frequently convey information that may help in the patient's evaluation. [14]

Laboratory, Imaging, and Other Studies to Consider in Delirium Diagnosis [15]

Basic laboratory evaluation, including:

- Full blood count (CBC): infection and severe anemia
- Serum electrolytes: Electrolyte imbalances, particularly hypernatremia and hyponatremia
- Creatinine and blood urea nitrogen levels: dehydration and occult renal failure (rare)
- Glucose: hypoglycemia, hyperglycemia, and hyperosmolar condition

- Liver function tests (aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase): occult choledocholithiasis, hepatic injury

- Workup for infectious diseases:

- Chest radiography: Pneumonia if fever or physical signs are present.
- Urinalysis and culture: Consider urinary tract infection when fever or other genitourinary symptoms are present.
- Lumbar puncture: If delirium is chronic, unexpected, or inexplicable, or occurs in younger individuals, there is a high suspicion of meningitis or subarachnoid hemorrhage based on history and physical examination.

- Myocardial infarction and arrhythmia on electrocardiogram

- Hypercarbia in chronic obstructive pulmonary disease: Venous blood gases

- Drug concentrations: Some medicines might cause delirium even when serum levels are "normal."

- Toxicology screening: If consumption is suspected, younger people are more likely to be affected.

- CT and MRI brain imaging: Based on the history and physical examination, there is a high likelihood of stroke or bleeding, or delirium is chronic, unexpected, or inexplicable, or happens in younger individuals.

- Electroencephalography: If an occult seizure is detected, it frequently shows diffuse slow-wave activity, although it is rarely useful in evaluating and treating reversible causes.

Management

The care of delirium patients must include many broad goals; some of which include ensuring the patient's and staff's safety, identifying, and treating the underlying causes, and improving the patient's level of function.

Cognitive impairment, behavioral dyscontrol, and other delirium-related behavioral alterations can jeopardize the patient or medical personnel. The psychiatric consultant should constantly assess the risk of suicide, self-harm, and violence, and then create a plan to reduce these risks. Self-destructive or suicidal behavior can be caused by underlying cognitive dysfunction (along with sensory and perceptual impairment, hallucinations, or delusions). Furthermore, a patient may be impulsive and attempt to get out of bed, roam, and fall (which might result in considerable damage or death) as

well as remove IV lines, tubes, or catheters. Removal of potentially harmful things from the room and surrounding area, placement of sitters to offer more monitoring, use of physical restraints, and commencement of pharmacologic therapy are all frequently needed.

Risk Factors

It is critical to identify triggering risk factors for delirium in order to apply prevention treatments to individuals who are most at risk. Several variables appear to contribute to the acute syndrome, and over 100 of them have been investigated for a relationship with an increased risk of developing delirium in the ICU. [17] These hazards may be divided into two categories: those that potentially predispose the patient to delirium (modifiable and nonmodifiable) and those that are connected to the care received in the ICU or the surroundings. [18]

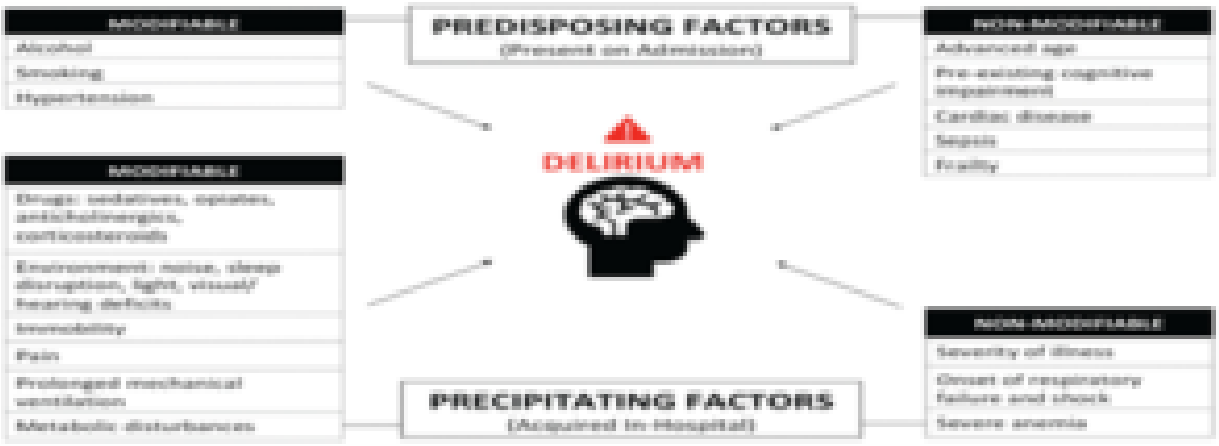


Figure 2 Factors that predispose to and precipitate ICU delirium Delirium is caused by both baseline or predisposing, risk factors (on the top) and acquired, or precipitating, risk factors (on the bottom) (bottom). These may be changeable (on the left) or nonmodifiable (on the right) (right). ICU stands for intensive care unit.

Conclusion

Although delirium remains an acute-care concern, its significance for primary care, outpatient specialty, post - acute care, and long-term care physicians cannot be overstated. With the world's population continuing to age, dementia and delirium will remain widespread health issues. Prompt detection of delirium and distinction from dementia will be critical in deciding the proper therapy in the outpatient environment. Knowing when to refer patients for emergency or inpatient treatment is part of this differentiation. Similarly, learning to recognize protracted or subacute delirium in patients who have recently been hospitalized would be useful for outpatient physicians. As delirium research advances, physicians will be able to better avoid triggering

variables such offending drugs while delivering more focused therapies to clear this critical geriatric condition.

References

[1] T. Rabinowitz, Delirium: an important (but often unrecognized) clinical syndrome, Curr. Psychiatry Rep. 4 (2002) 202–208. https://doi.org/10.1007/s11920-002-0030-9.

[2] P. Alexander, P. Wilson, A Treatise on Febrile Diseases, n.d.

[3] J.R. Maldonado, Delirium in the acute care setting: characteristics, diagnosis and treatment, Crit. Care Clin. 24 (2008) 657–722, vii. https://doi.org/10.1016/j.ccc.2008.05.008.

[4] J.R. Maldonado, Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment, Crit. Care Clin. 24 (2008) 789–856, ix. https://doi.org/10.1016/j.ccc.2008.06.004.

[5] J.R. Maldonado, Neuropathogenesis of delirium: review of current etiologic theories and common pathways, Am. J. Geriatr. Psychiatry. 21 (2013) 1190–1222. https://doi.org/10.1016/j.jagp.2013.09.005.

[6] P.T. Trzepacz, Update on the neuropathogenesis of delirium, Dement. Geriatr. Cogn. Disord. 10 (1999) 330–334. https://doi.org/10.1159/000017164.

[7] P.T. Trzepacz, The neuropathogenesis of delirium, Psychosomatics. 35 (1994) 374–391. https://doi.org/10.1016/s0033-3182(94)71759-x.

[8] N. Gupta, J. de Jonghe, J. Schieveld, M. Leonard, D. Meagher, Delirium phenomenology: what can we learn from the symptoms of delirium?, J. Psychosom. Res. 65 (2008) 215–222. https://doi.org/10.1016/j.jpsychores.2008.05.020.

[9] Z.J. Lipowski, Transient cognitive disorders (delirium, acute confusional states) in the elderly, Am. J. Psychiatry. 140 (1983) 1426–1436. https://doi.org/10.1176/ajp.140.11.1426.

[10] B. Liptzin, S.E. Levkoff, An empirical study of delirium subtypes, Br. J. Psychiatry. 161 (1992) 843–845. https://doi.org/10.1192/bjp.161.6.843.

[11] S.T. O'Keeffe, Clinical subtypes of delirium in the elderly, Dement. Geriatr. Cogn. Disord. 10 (1999) 380–385. https://doi.org/10.1159/000017174.

[12] S.B. Guze, Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), Am. J. Psychiatry. 152 (1995) 1228–1228. https://doi.org/10.1176/ajp.152.8.1228.

[13] K. Hayashi, M. Motoishi, S. Sawai, K. Horimoto, J. Hanaoka, Postoperative delirium after lung resection for primary lung cancer: Risk factors, risk scoring system, and prognosis, PLoS One. 14 (2019) e0223917. https://doi.org/10.1371/journal.pone.0223917.

[14] S.K. Inouye, C.H. van Dyck, C.A. Alessi, S. Balkin, A.P. Siegal, R.I. Horwitz, Clarifying confusion: the confusion assessment method. A new method for detection of delirium, Ann. Intern. Med. 113 (1990) 941–948. https://doi.org/10.7326/0003-4819-113-12-941.

[15] M.L.P. Mattison, Delirium, Ann. Intern. Med. 173 (2020) ITC49–ITC64. https://doi.org/10.7326/AITC202010060.

[16] T.A. Stern, C.M. Celano, A.F. Gross, J.C. Huffman, O. Freudenreich, N. Kontos, S.H. Nejad, J. Repper-Delisi, B.T. Thompson, The assessment and management of agitation and delirium in the general hospital, Prim. Care Companion J. Clin. Psychiatry. 12 (2010) PCC.09r00938. https://doi.org/10.4088/PCC.09r00938yel.

[17] E.E. Vasilevskis, J.H. Han, C.G. Hughes, E.W. Ely, Epidemiology and risk factors for delirium across hospital settings, Best Pract. Res. Clin. Anaesthesiol. 26 (2012) 277–287. https://doi.org/10.1016/j.bpa.2012.07.003.

[18] J.C. Korevaar, B.C. van Munster, S.E. de Rooij, Risk factors for delirium in acutely admitted elderly patients: a prospective cohort study, BMC Geriatr. 5 (2005) 6. https://doi.org/10.1186/1471-2318-5-6.

Article topic: Bulimia Nervosa.

Author: Sara Awwad.

Editor: Ihdaa Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

keywords: Bulimia Nervosa, Bulimarexia, Bingeing.

Introduction

Eating disorders (EDs) are psychiatric conditions that seriously harm a person's physical and mental health. [2] The manifestation of these concerns differs by gender; for example, problems with body image in men may emphasize muscularity, while, in women, these problems may emphasize weight loss more.[3] Over 30 million people are affected by eating disorders, which are also significantly associated with morbidity and mortality. [4] The word "bulimia" which means "ox hunger" in Greek, was created to emphasize the characteristic of "gross overeating". [5] Bulimia Nervosa (BN), which is also called Bulimarexia or Bingeing, belongs to EDs, it is a mental disease characterized by emotional disturbances that are addressed by consuming large amounts of food and then vomiting to avoid weight gain.[6] Such behavioral patterns compromise neurobiological functions and have a negative influence on both physical and mental health. [5] Although it affects both sexes, Bulimia Nervosa often manifests in adolescence or early adulthood and is far more common in girls and young women. It affects individuals, regardless of sexual orientation, but non-heterosexual *(non-heterosexual is an umbrella term, describing homosexual, bisexual, asexual, and other people who do not identify as heterosexual)* males have been demonstrated to have a higher prevalence.[7]

Epidemiology

There are some methodological issues with epidemiological studies on eating disorders. In the community, eating disorders are quite rare, and getting help is frequently avoided or postponed. The lifetime prevalence rates of Bulimia Nervosa are up to 3% of females and more than 1% of males suffer from this disorder during their lifetime. Over time, there has been a decrease in the overall incidence rate of bulimia nervosa. Moreover, it may carry five or more times increased mortality risk. [7]

Correlates and comorbidities

Several correlates exist for patients with Bulimarexia. These correlations include things like childhood obesity, sexual abuse, low self-esteem, parental substance use and obesity, parental expectations, and previous dieting. Other examples, such as a history of psychiatric disorders and substance abuse, are more likely to be ascertained in an eating disorder encounter. Between 69.4% and 94.5% of Bulimarexia patients meet the criteria for at least one added DSM-IV disorder. Anxiety disorders range from 40.0% to 80.6%; mood disorders range from 49.9% to 70.7%, major depressive disorders forming 31.0% to 50.1%; impulse-control disorders range from 9.54% to 63.8%.[8]

Pathophysiology

There is a great deal of confusion surrounding the definition of eating disorders, including whether they should be considered difficulties with eating or body image or neurotic, psychotic, or psychosomatic disorders. [10] Research on the fundamental causes of eating disorders is ongoing. Understanding these illnesses is more challenging by interactions between genetic and environmental factors at a critical stage of development. [2]

Etiology

Bulimia Nervosa is a psychogenic disturbance in eating behavior characterized by episodes of uncontrollable eating binges that are frequently followed by self-induced vomiting, fasting, or the abuse of laxatives to prevent ensuing weight gain.[11] Among the elements reported to influence the growth of bulimia are social influences which include the thin-ideal body image espoused for women as the shrinking ideal body image for women, the increasing number of dieting articles and advertisements in women's magazines, the centrality of appearance in the female gender role, and the importance of appearance for women's societal success. [9]

Eating disorders seem highly heritable, with an estimate between 0.55 and 0.62 for BN. The hereditary risk for eating disorders (EDs) appears to vary by gender. Particularly, sex steroids might be crucial (as moderators or mediators) in the expression of ED behaviors. The genetic risk for developing an ED is 50% higher in men than it is in women before puberty. After puberty, the male risk remains steady, but the female risk rises to 50%. This sharp rise in risk for females (which is steady until puberty) suggests that genetic risk has been activated, in connection with the start of puberty, and emphasizes the potential role of estrogen in risk activation. [10]

In a sample of monozygotic twins with normal body mass index, those with higher estrogen levels had more ED symptoms. The serotonin system and brain-derived neurotropic factor genes, both of which are linked to ED symptoms, are controlled by estrogen. According to one study, men who have a female twin are more likely to get an ED than those who have a male twin. As a result, genetic data emphasize the significance of puberty in the emergence of EDs in females and implicate sex hormones, particularly estrogen, as key players in this process. [10]

DSM-5 Diagnostic criteria for bulimia nervosa [1]

1. Frequent binge eating incidents. Two of the following characteristics describe an episode of binge eating: [13]
2. Eating, in a discrete duration of time (e.g., within any 2-h period), the quantity of food that is larger than what most individuals would eat in a similar period under similar circumstances [13]
3. Lack of control overeating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating). [13]
4. Repeatedly using unhealthy coping mechanisms to avoid gaining weight, such as self-induced vomiting, abusing laxatives, diuretics, or other drugs, fasting, or engaging in excessive exercise.
5. In general, throughout the course of three months, binge eating and inappropriate compensatory behaviors both occur at least once per week.
6. Body type and weight significantly influence how one feels about oneself. Food addiction not observed in YFAS
7. The disruption does not just happen during anorexia nervosa episodes. [11]

Complications

Skin

Russell signs It is pathognomonic for self-induced vomiting and results from repeatedly inserting the hand into the mouth to cause vomiting while being traumatized by the teeth. Since many of these patients may vomit on their own or with the help of objects, the Russell sign is rarely observed in them. [6]

Teeth and mouth

Abnormalities of the teeth and mouth, specific c for purging via vomiting, including dental erosions and damage to the oral mucosa and pharynx. Dental erosions are irreversible and are the most common oral manifestation due to chronic regurgitation. It is also thought that trauma to the oral mucosa, particularly the pharynx and soft palate, arises from the patient putting something foreign in their mouth to induce vomiting or the caustic effect of the vomitus on the mucosal lining. [6]

Head, ears, nose, and throat

The danger of subconjunctival hemorrhages increases with violated vomiting, and this can also result in recurrent epistaxis. Because the pharyngeal tissue meets stomach acid regularly in those who frequently vomit, pharyngitis is usually observed. The development of hoarseness, coughing, and dysphagia is also possible. [6]

Parotid gland

More than 50% of patients who self-induce vomiting to purge may get parotid gland hypertrophy or sialadenosis.[6]

Cardiovascular

Electrolyte changes brought on by vomiting and diuretics or laxatives are among the cardiac problems that are specifically associated with purging. People who engage in various forms of purging are increasingly more likely to experience conduction problems, including severe arrhythmias and QT prolongation, because of the electrolyte imbalances that result, particularly hypokalemia and acid-base disorders. Ipecac, which includes the cardiotoxic alkaloid emetine, can cause many conduction disturbances and irreparable cardiomyopathy when consumed in excess.[6]

Pulmonary

Vomiting increases intrathoracic and intra-alveolar pressures, which leads to pneumomediastinum. Pneumomediastinum may also come across nontraumatic alveolar rupture in the setting of malnutrition and therefore nonspecific in differentiating patients who purge from those who restrict.[6]

Gastrointestinal

- Esophageal complications excessive vomiting increases the risk of gastroesophageal reflux disease and other esophageal problems, such as Barrett's esophagus and esophageal adenocarcinoma, by exposing the esophagus to gastric acid and damaging the lower esophageal sphincter. Uncommon complications are esophageal rupture, known as Boerhaave syndrome, and Mallory-Weiss tears. [7]
- Colonic inertia. people engaging in excessive and chronic stimulant laxative abuse may be at risk for a “cathartic colon,” a condition whereby the colon becomes an inert tube incapable of moving stool forward. [7]
- Melanosis Coli, black discoloration of the colon of no known clinical significance.[6]

Endocrine

Patients with type 1 diabetes mellitus, previously known as diabulimia but now known as eating-disorder Diabetes Mellitus type 1, may manipulate their blood glucose levels as a means of purging calories. The risk factors for these patients include severe hyperglycemia, ketoacidosis, and early microvascular sequelae such as retinopathy and neuropathy.[6]

Effect of covid 19 among patients with EDs

The lockdown and the stay-at-home regulations made this population more isolated and lonelier for people who live alone. A systematic review aimed to determine how the coronavirus lockdowns affected the severity of ED symptoms. The results were that concerns about one's looks, and body image were more prevalent in women and young individuals, and they had a higher chance of their eating disorder symptoms getting worse during the COVID-19 lockdown.[12]

Management

The first steps in treating a patient with BN are medical stabilization and, if necessary, correction of any electrolyte imbalances (The most hazardous BN consequence is the emergence of an electrolyte imbalance, which can result in cardiac arrhythmia, seizures, and death) [5]. Hospitalization may be necessary for medical instability (including severe bradycardia, orthostatic hypotension, and seizures), dehydration, hypokalemia, arrhythmia, excessive bingeing and purging, suicidality, or failure of outpatient treatment.[4]

Treatment

Adults' treatment Cognitive-Behavioral Therapy

The first-line treatment for adults with BN is cognitive-behavioral therapy (CBT). Dieting eventually results in binge eating, which then encourages the practice of inappropriate compensatory behaviors (such as self-induced vomiting, laxative and/or diuretic abuse, and excessive exercise), reaffirms body image problems, and motivates attempts to quit dieting. The cognitive-behavioral model of BN, therefore, postulates that concerns about one's weight and form and eating disorder behaviors are mutually reinforcing and sustain a vicious cycle that maintains BN. CBT-BN uses an approach to introduce behavioral techniques and cognitive strategies to target symptoms delineated in the cognitive behavioral model of BN. The procedure is carried out in 20 sessions

over roughly 6 hours a month. CBT-BN first focuses on behavioral therapy because the doctor aids the patient in controlling their eating Behavior patterns and self-evaluation.[13]

Treatment for children and adolescent

Family-based Treatment (FBT)

The goal of family-based treatment for BN (FBT-BN) in adolescents is to restore normal adolescent development while also normalizing adolescent eating patterns and empowering parents. The fundamental tenants of (FBT BN) include agnosticism with respect to the cause of BN. Parents are also believed to have the knowledge and resources necessary to aid in their child's recovery from BN. Three phases of the FBT-BN are presented over the course of 20 sessions or six months. Parents are entrusted with interrupting their adolescent's eating disorder behaviors in the first phase of FBTBN by giving them regular meals and snacks and keeping an eye on them afterward to prevent inappropriate compensatory actions. In the second phase, the adolescent gradually regains developmentally proper authority over meals and snacks when the eating disorder behaviors have been resolved. After achieving developmentally adequate autonomy in feeding themselves, the adolescent enters Phase 3, which focuses on addressing typical teenage development concerns and aiding the adolescent in creating an identity outside of BN. The teenager is weighed at the start of each session of FBT-BN.[13]

Pharmacotherapy

Psychotherapy is considered the treatment of choice for BN. If psychotherapy is unavailable or unsuccessful, pharmacotherapy may be considered as a stand-alone treatment for BN. Research suggests that a combination of CBT and medication was superior to medication alone in promoting reductions in BN symptoms. Until now no psychotropic medications have been developed to treat BN specifically. Rather, medications developed for other conditions, antidepressants and antiepileptics are used .[13]

Prognosis

According to a 10-year follow-up study including 50 bulimia nervosa patients from a placebo-controlled trial of mianserin treatment, 52% of those who received the placebo had totally recovered, and just 9% still had all their bulimia nervosa symptoms. In a bigger study, 222 participants from an antidepressant and organized, intense group treatment experiment were examined. It was discovered that after a mean follow-up of 11.5 years, 11% of the participants still fit the criteria for bulimia nervosa, while 70% were in full or partial remission. Shorter sickness duration, earlier age of onset, greater

social class, and a family history of alcohol misuse have all been linked to a good prognosis. A history of substance abuse, premorbid and paternal obesity, and, in some studies, a personality problem has all been linked to poor prognosis. Early progress (a reduction in the purging of >70% by session) was the best indicator of outcome in an evaluation of the response to cognitive behavioral therapy (CBT). But a further systematic review of the outcome literature discovered no indication that early intervention is associated with a better prognosis. Only four pretreatment predictors of a poor outcome for the treatment of bulimia nervosa were consistently identified in a systematic review evaluating the cost-effectiveness of treatments and prognostic indicators: characteristics of borderline personality disorder, concurrent substance abuse, a lack of motivation for change, and a history of obesity.[14]

Conclusion

According to Treasure et al., "eating disorders are incapacitating, fatal, and expensive mental diseases that significantly worsen physical health and disrupt psychosocial functioning." This makes finding effective treatments even more crucial. A unique perspective on the burden of illness is to consider the costs to the person and society. Treatment expenses, a direct financial impact, and lost income for both patients and caregivers are all part of the disease costs associated with ED [15]. BN's main symptoms are attempts to shed weight and a fear of being obese. Although patients with BN typically weigh within a normal range, some fall in the higher or lower normal limits.[16] Effective psychological therapies exist, particularly cognitive behavior therapy (CBT).[15]

Reference

1. Treasure, J., Duarte, T. A. & Schmidt, U. Eating disorders. *Lancet (London, England)* **395**, 899–911 (2020).
2. Kutz, A. M., Marsh, A. G., Gunderson, C. G., Maguen, S. & Masheb, R. M. Eating Disorder Screening: A Systematic Review and Meta-analysis of Diagnostic Test Characteristics of the SCOFF. *J. Gen. Intern. Med.* **35**, 885–893 (2020).
3. Castillo, M. & Weiselberg, E. Bulimia Nervosa/Purging Disorder. *Curr. Probl. Pediatr. Adolesc. Health Care* **47**, 85–94 (2017).
4. Mele, G., Alfano, V., Cotugno, A. & Longarzo, M. A broad-spectrum review on multimodal neuroimaging in bulimia nervosa and binge eating disorder. *Appetite* **151**, (2020).
5. Nitsch, A., Dlugosz, H., Gibson, D. & Mehler, P. S. Medical complications of bulimia nervosa CME MOC. *Clin. J. Med.* **88**, (2021).
6. Van Eeden, A. E., Van Hoeken, D. & Hoek, H. W. C URRENT OPINION Incidence, prevalence and mortality of anorexia nervosa and bulimia nervosa. doi:10.1097/YCO.0000000000000739.
7. Trent, S. A., Moreira, M. E., Colwell, C. B. & Mehler, P. S. ED management of patients with eating disorders. *Am. J. Emerg. Med.* **31**, 859–865 (2013).
8. Stice, E. Review of the evidence for a sociocultural model of bulimia nervosa and an exploration of the mechanisms of action. *Clin. Psychol. Rev.* **14**, 633–661 (1994).
9. Timko, C. A., DeFilipp, L. & Dakanalis, A. Sex Differences in Adolescent Anorexia and Bulimia Nervosa: Beyond the Signs and Symptoms. *Curr. Psychiatry Reports 2019 211* **21**, 1–8 (2019).
10. Hauck, C., Cook, B. & Ellrott, T. Food addiction, eating addiction and eating disorders. *Proc. Nutr. Soc.* **79**, 103–112 (2020).
11. Gao, Y., Nasser Bagheri, · & Furuya-Kanamori, L. Has the COVID-19 pandemic lockdown worsened eating disorders symptoms among patients with eating disorders? A systematic review. **1**, 3.
12. Hagan, K. E. & Walsh, B. T. State of the Art: The Therapeutic Approaches to Bulimia Nervosa. *Clin. Ther.* **43**, 40–49 (2021).
13. Bulimia nervosa. (2010).

14. van Hoeken, D. & Hoek, H. W. Review of the burden of eating disorders: mortality, disability, costs, quality of life, and family burden. *Curr. Opin. Psychiatry* **33**, 521–527 (2020).
15. Herpertz-Dahlmann, B. Adolescent Eating Disorders: Update on Definitions, Symptomatology, Epidemiology, and Comorbidity. *Child Adolesc. Psychiatr. Clin. N. Am.* **24**, 177–196 (2015).

Topic: Binge Eating disorder (BED).

Author: Sohail Batarseh.

Editor: Ihdaa Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: Binge eating disorder, Obesity, Eating dysregulation, Treatment, COVID-19.

Introduction

Eating disorders are fatal and incapacitating mental illnesses that severely damage physical health and interfere with psychosocial functioning.[1] Moreover, attitudes toward food, weight, and body image significantly influence the development and maintenance of eating disorders such as Binge eating disorders.[1]

Binge Eating disorder (BED) was first listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), as an eating disorder provisional diagnosis under the heading of Eating Disorder Not Otherwise Specified.[1] It is now classified as a stand-alone diagnosis in the proposed Draft Revisions Disorders and Criteria for DSM-5[2] (**Diagnostic and Statistical Manual)**.

Diagnostic systems recognized the basic feeding and eating disorders, and it covered six primary food and eating disorders: *Anorexia nervosa, bulimia nervosa, binge eating disorder, avoidant-restrictive food intake disorder, pica, and rumination disorder* [3].

Binge eating disorder BED is characterized by recurrent binge eating episodes in the absence of proper compensatory behavior such as fasting, purging, or strenuous activity.[3] It is closely related to obesity because it involves calorie overconsumption .[4] BED is far worse than overeating since it is linked to more tremendous subjective suffering over eating behavior, it commonly lowers the quality of life and is connected to psycho-pathological traits mainly stress, negative effects, depression, or anxiety, and can be comorbid with diseases such as metabolic syndrome, which mostly includes type 2 diabetes, hyperparathyroidism, and hypertension.[5] There is still much to learn about the etiology of BED, besides there are a lot of categories of risk factors for eating disorders: social, psychological, biological (including genetic and more). [2]

Epidemiology and Etiology

A study on the risk factors for the emergence of ED points to the significant importance of biological components. Although neither gene nor genome-wide research has discovered really verified genes for eating disorders, the role of genetic variables on the emergence of an ED is suggested.[6]

Data on the prevalence of Bulimia Nervosa and Binge Eating differ depending on the country, in the US a survey estimated the prevalence to be 0.6% for AN (Anorexia nervosa), 1.0% for BN, and 2.8% for BED.[7] When we look at AN(Anorexia nervosa) and BN, which occur in a 1:9 male-to-female ratio, we notice the male-to-female ratio is more balanced in BED about 4:6.[8] The interaction of biological variations between men and women and the unequal impact of sociocultural variables on the sexes have been hypothesized to be the cause of the sex differences in EDs (eating disorders).[4]

Among other biological variations, scientists believe that estrogen's organizational effects during puberty encourage the formation of BEDs in genetically susceptible females.[9] Recent research investigated differences between 208 men and 1117 women using data from 11 randomized controlled psycho-social BED therapy treatments these studies used Baseline and outcome symptoms to assess via the interview and questionnaire versions of the Eating Disorder Examination (EDE), women and men reported similar levels of dietary restraint and binge-eating episode frequencies at baseline .[5]

In comparison to women, males expressed much fewer worries about their physical appearance, weight, and eating habits. Men and women did not differ after treatment in terms of the: overall EDE score, the number of binge-eating events in the previous 28 days, the remission of binge eating, or early study dropout.[10]

Although the frequency of eating disorders has grown by 25% worldwide, only around 20% of those patients seek treatment.[11]

Psychopathological features associated with BED

FA (food addiction) refers to compulsive overeating that resembles addiction and is marked by cravings and difficulty avoiding high-calorie meals.[12]

Although FA (food addiction) could seem to be comparable to BED (binge eating disorder), it is crucial to remember that FA (food addiction) is still a contentious notion

that has not yet been acknowledged as a diagnostic entity, while BED is a recognized and diagnosable mental condition.[6]

Between 30.0 and 80.0% of people with BED have comorbid mood and anxiety problems at any given moment[13]and sometimes there are certain associated diseases like bipolar illness[14] The majority of BED patients also have impairments in their psychological health, which might include issues with autonomy, environmental mastery, and self-acceptance[15] and overvaluation of body shape and weight, which is closely linked to mental distress, eating-related psychopathology, and an even worse prognosis for the disease.[16]

Neurobiology

The exposure to enticing food signals affected several groups, including obese and non-obese people as well as those with bulimia nervosa, by an increase in activity in the insula and the orbitofrontal cortex (OFC).[17] Not surprisingly, these areas of the brain correspond to the major and secondary taste cortices. In recent research, while perceiving appetizing food signals, people with BED in particular exhibit higher prefrontal activity in comparison to other disordered eating groups and healthy control participants.[18]

These early results lend to the theory that BED patients are more sensitive to food rewards. Additionally, using a classification analysis based on neural responses as people view appetizing foods shows that activity in many rewards processing regions, including the orbitofrontal cortex (OFC) and striatum, identifies people with BED in comparison to non-BED obese or BN (bulimia nervosa) people with a fair degree of accuracy. [19]

In the last 100 years, researchers made the first discoveries of how the ovarian cycle affects food intake in intact female rats and how the removal of the ovaries causes an accumulation of fat tissue in the previous century, the menstrual cycle has been linked to fluctuations in women's appetite and satiety.[20]

Ovarian hormones work as gene transcription factors in several neurobiological systems that are known to be connected to disordered eating behavior, suggesting that they may have a genetic impact on the central nervous system.[21]

Even though most of the research on BED neurobiology has been conducted in females, the effects of ovarian hormones on eating behavior and weight management have not been scientifically shown.[7]

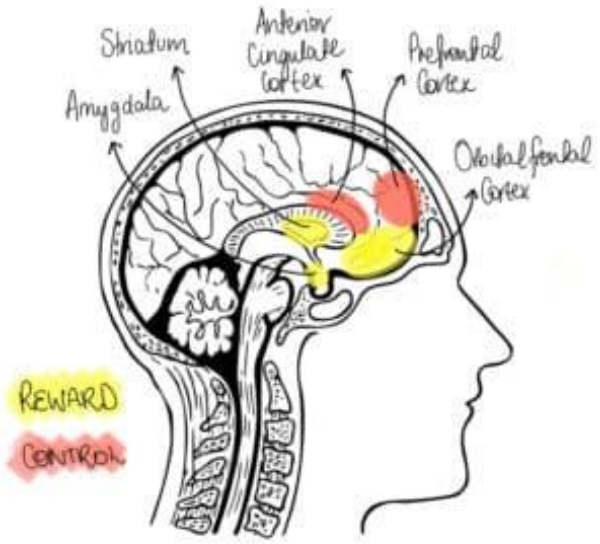


Figure 1. this figure is increased activity in the emotional center of the brain – the amygdala and increased activation of the reward network striatum and orbital frontal cortex does not; self-control and planning network frontal cortex and anterior cingulate cortex remain underactive. 22.

Treatment

There is a lot of pharmaceuticals, physiological and recent advanced treatment. Findings show that BED diagnosis is clinically useful in producing unique results across various therapy.[2]

Psychological Treatment

Cognitive-behavioral therapy

Cognitive behavioral therapy (CBT) is a type of psychological care that is useful for a variety of issues, such as depression, anxiety disorders, …. etc.[8]

More than 50% of patients who get Cognitive-behavioral therapy have complete recovery from binge eating, as well as significant improvements in the related depression, psychosocial functioning, and particular eating disorder psychopathologies such as overvaluing body form and weight.[9]

IPT (Interpersonal Psychotherapy)

Has been changed for the treatment of both bulimia nervosa and BED. IPT (interpersonal Psychotherapy) was initially created as a brief, manual-based psychotherapy for depression.[9] The focus is mostly on aiding patients in identifying and

resolving interpersonal issues that are currently plaguing them and supporting their eating disorders. The therapy is noninterpretive and non-directive.[9]

Guided self-help

Self-help therapies based on CBT principles are the subject of an expanding corpus of research. A self-help book plus a small number of brief therapy sessions delivered by medical professionals with varied levels of CBT experience and skill make up guided self-help (CBTgsh).[9]

Pharmacologic Therapy

Research has focused on antidepressant drugs for a long time, and many more antidepressants are now accessible, yet binge eating has taken on a new form, determined by the need to reduce weight-study of medications in pharmacotherapy that have direct or indirect effects on appetite has taken place-, for example, fenfluramine, formerly prescribed for weight reduction but no longer available due to heart valve problems.[23]

The US Food and Drug Administration has authorized the lipase inhibitor orlistat as an anti-obesity drug, the combination of orlistat and CBTgsh led to a substantially greater post-treatment rate of binge eating remission when compared to placebo plus CBTgsh, but not at a 3-month follow-up when both the drug and CBTgsh were stopped.[24] and after a lot of trials for several drugs, Several trials used lisdexamfetamine have been the most current attempt at treating BED with medication.[25]

VR (virtual reality) cue exposure treatment is one of the most widely used contemporary clinical applications in EDs (**eating disorders**Disorders) Cue Exposure Therapy (CET). In general, VR-CET reduces anxiety reactions to food-related stimuli and cravings which is a strong and uncontrolled want for a specific meal, which lowers the likelihood of overeating in patients with BN or BED.[26] by stimulating the feeling of the patient using VR so he or she will have BED episodes and we will try to control them even using medication or psychological therapy.[10]

The impact of the COVID-19 pandemic on eating disorders, especially BED

COVID-19 has an unbelievably adverse impact on eating disorders as one of the main impacts was feeling lonely. Staying at home caused emotions of loneliness, worry, and melancholy, which worsened ED symptoms. According to several types of research, social media and traditional media messages frequently focused on the fear of gaining weight in general; people with EDs found stress and triggers in topics like diet

discussion, exercise, and good eating throughout the pandemic.[27] However, People who experienced the pandemic reported that lockdown procedures protected them from past stresses or triggers, gave them time to take care of themselves and think, and in some cases, increased their social support.[28]

Conclusion

Eating disorders affect people of various ages and socioeconomic groups, which have evolved during the past 60 years in the setting of significant environmental changes. These eating disorders take on a range of forms with overlapping and different clinical and etiological characteristics. A meta-analysis of 36 studies mentioned that up to About 26% of people with eating disorders attempt suicide.[11] Making EDs potentially lethal. Additionally, they may result in significant health problems as well as significant psychological suffering. As the eating disease consumes time and energy, leads to self-absorption, and lowers self-esteem, important relationships suffer.

Treatment should begin as soon as possible; in order to concentrate on the acute misery, the patient is experiencing. Also, work to empower the patient and family to overcome the eating problem.[12]

References

1. Diagnostic and statistical manual of mental disorders. 4th ed. Washington (DC). *Am Psychiatr Assoc Diagnostic*.
2. Wonderlich SA, Gordon KH, Mitchell JE et al. The validity and clinical utility of binge eating disorder.
3. Treasure J, Duarte TA, Schmidt U. Eating disorders. *Lancet*. 2020;395(10227):899-911. doi:10.1016/S0140-6736(20)30059-3
4. . Razzoli M, PearsonC, Crow S BA. Stress, overeating, and obesity: Insights from human studies and preclinical models. Neurosci Biobehav ReNo Title.
5. JE M. Medical comorbidity and medical complications associated with binge-eatingdisorderNo Title.
6. Hinney, A., Volckmar AL. Genetics of eating disorders. Curr Psychiatry Rep 15.
7. McElroy, S.L., Crow, S., Blom, T.J. et al. Prevalence and correlates of DSM-5 eating disorders in patients with bipolar disorder.
8. Hudson JI, Hiripi E, Pope HG, Kessler RC. The Prevalence and Correlates of Eating Disorders in the National Comorbidity Survey Replication. *Biol Psychiatry*. 2007;61(3):348-358. doi:10.1016/j.biopsych.2006.03.040
9. Culbert KM, Racine SE KK. The influence of gender and puberty on the heritability of disordered eating symptoms.
10. Shingleton RM, Thompson-Brenner H, Thompson DR et al. Gender differences in clinical trials of binge eating disorder: an analysis of aggregated data. J Consult.
11. Mitchison D, Mond J, Bussey K et a. DSM-5 full syndrome, other specified, and unspecified eating disorders in Australian adolescents: prevalence and clinical significance.
12. Schulte EM GA. Development of the modified Yale food addiction scale version 2.0.
13. Grilo CM, White MA, Barnes RD MR. Psychiatric disorder co-morbidity and correlates in an ethnic diverse ample of obese patients with binge eating disorder in primary care settings.
14. Cossrow N, Pawaskar M, Witt EA, Ming EE, Victor TW, Herman BK et al. Estimating the prevalence of binge eating disorder in a community sample from the United States: comparing DSM-IV-TR and DSM-5 criteria.
15. Tomba E, Offidani E, Tecuta L, Schumann R BD. Psychological well-being in out-patients with eating disorders.
16. CM. G. Why no cognitive body image features such as overvaluation of shape/weight in the binge eating disorder diagnosis?
17. Porubská, Veit, Preissl, Fritsche, & Birbaumer, 2006; Schienle, Schafer, Hermann & V. Regional grey matter volume abnormalities in bulimia nervosa and binge-eating disorder.
18. Geliebter, A., Ladell, T., Logan, M., Schneider, T., Sharafi, M., & Hirsch J. Responsivity to food stimuli in obese and lean binge eaters using functional MRI. Appetite.

19. Weygandt, M., Schaefer, A., Schienle, A., & Haynes JD. Diagnosing different binge-eating disorders based on reward-related brain activation patterns. Human Brain.
20. Pohle-Krauza RJ, Carey KH, Pelkman CL. Dietary restraint and menstrual cycle phase modulated l-phenylalanine-induced satiety. *Physiol Behav*. 2008;93(4-5):851-861. doi:10.1016/j.physbeh.2007.11.051
21. Ostlund H, Keller E HY. Estrogen receptor gene expression in relation to neuropsychiatric disorders.
22. Why can't I stop binge eating? Food on the brain. https://bodymatters.com.au/why-cant-i-stop-binge-eating-food-on-the-brain/
23. Crow SJ. Pharmacologic Treatment of Eating Disorders. *Psychiatr Clin North Am*. 2019;42(2):253-262. doi:10.1016/j.psc.2019.01.007
24. Grilo CM, Masheb RM SS. Cognitive behavioral therapy guided self-help and orlistat for the treatment of binge eating disorder: a randomized, double-blind, placebo-controlled trial.
25. McElroy SL, Hudson J, Ferreira-Cornwell MC et al. Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: results of two pivotal phase 3 randomized controlled trials.
26. Gutiérrez-Maldonado, J., Wiederhold, B. K., & Riva G. Future directions: How virtual reality can further improve the assessment and treatment of eating disorders and obesity.
27. Branley-Bell, D., & Talbot C V. "It is the only constant in what feels like a completely upside down and scary world": Living with an eating disorder during COVID-19 and the importance of perceived control for recovery and relapse.
28. Branley-Bell, D., & Talbot C V. Exploring the impact of the COVID-19 pandemic and UKlockdown on individuals with experience of eating disorders.

Article topic: Factitious Disorder.

Author: Rawan Osama Abu-Nsair.

Editors: Ihdaa Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: factitious disorder, fabricate, Munchausen.

Introduction

Hieronymus Karl Friedrich von Munchausen is a German officer who fought in the Russo-Turkish War. [2] After retirement, he worked as a paid entertainer and was a well-known wartime fabulist in Hanover. [2] Lunar travel, riding a cannonball, and being eaten by a giant fish, are all some of his tales that inspired the German Writer Rudolf Erich Raspe to write a social satire based on von Munchausen's tales. [3]

Years after, in 1951, Richard Asher was the first to link von Munchausen's falsehoods with the factitious behavior of some patients, calling it "Munchausen's Syndrome". [4]

This eponym was replaced by the new nomenclature: "Factitious Disorder (FD)". After that, it appeared first in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-3) in 1980. [5] In detail, it is now defined as a psychiatric disorder in which sufferers intentionally fabricate illness, injury, impairment, or psychological signs and symptoms to gain hospital admission and undergo medical procedures without any clear gain. [6]

FD has two subtypes. The first is "Factitious disorder Imposed on Self"; in which the patient fabricates illness or injury on himself. [6] The second is "Factitious disorder Imposed on Another;" which was previously known as "Factitious Disorder by Proxy". [6] In this subtype, the patient presents another person as ill or impaired. [6]

Figure (1); factitious disorder (1).

Epidemiology

The exact prevalence of Factitious Disorder in hospital settings is currently unknown. [7] This could be since these patients are usually efficient at hiding their behavior, as well as the involvement of multiple physicians in treating, and the lack of trained healthcare providers in making the diagnosis. [8] In addition, the abundance of online medical knowledge may enable patients to present with complex medical problems. [9]

FD accounts for 0.8%-1% of psychiatric referrals. [10] A recent systematic review of 455 cases of FD [9] found that 33.8% of patients were males, consistent with many other earlier studies that reported a female predominance. [11] Furthermore, the mean age of presentation is 34.2 years. [9] Interestingly, 57% of patients have a healthcare-related occupation, with the single most common occupation being nursing. [9]

Etiology and pathogenesis

According to DSM-5, FD patients tend to intentionally produce symptoms only to assume the sick role. [6] It is believed that this motivation is related to psychological deficits rooted in early childhood trauma including physical and mental abuse. [12] There are many suggested theories about the psychology that lies behind FD, but none are approved. [9]

In the meantime, the literature suggests that mothers who have childhood histories of loss, abuse, privation, bereavement, a longstanding history of relational dangers, and

disrupted attachment are at a higher risk to fabricate or induce illness in their children. [13]

Pathological liars showed a strongly activated prefrontal cortex during lying, a 22% increase in its white matter, and a 14% reduction in the grey matter when compared to normal people. [14] However, it is still controversial whether changes in this area lead to the factitious behavior or the act of lying resulted in these organic changes. [15]

DSM-5 Diagnostic Criteria [6]

Factitious Disorder Imposed on Self

1. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception.
2. The individual presents himself or herself to others as ill, impaired, or injured.
3. The deceptive behavior is evident even in the absence of obvious external rewards.
4. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Specify:

Single episode

Recurrent episodes (two or more events of falsification of illness and/or induction of injury)

Factitious Disorder Imposed on Another

(Previously Factitious Disorder by Proxy)

1. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, in another, associated with identified deception.
2. The individual presents another individual (victim) to others as ill, impaired, or injured.
3. The deceptive behavior is clear even in the absence of obvious external rewards.
4. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Note: The perpetrator, not the victim, receives this diagnosis.

Specify:

Single episode

Recurrent episodes (two or more events of falsification of illness and/or induction of injury).

Clinical presentation

Most patients are presented to general hospitals in their mid-30s. [16] In any case, FD patients are attracted more to presentations that are associated with fast-track admission. [9] Moreover, a recent study found that 58.7% of patients induce injury or illness on themselves, 22.2% falsely report a medical problem, and 19.1% try only to simulate a medical problem. [9]

The variety of presentations depends on the patient's imagination and medical knowledge. [17] However, this is limited by the nature of the fabricated medical problem. [9] For example, most are presented with dermatological or endocrinological problems, respectively. [9] This could be also attributed to the increased awareness of physicians in these specialties in FD and the commonly fabricated symptoms. [9]

Overall, those patients usually have a medical history full of multiple investigations and treatments. [18] Also, they tend to show a lack of concern for the medical problem. [19] Moreover, their behavior is characterized by disobedience to hospital rules and excessive arguing with medical care providers. [20] Interestingly, when hospitalized they receive few or no visits at all. [20] When confronted, they tend to aggressively deny or leave without a formal discharge. [20] However, the diagnosis is mostly made by a passing physician or nurse who recognizes the patient. [21]

Differential diagnosis

To begin with, motivation plays an essential role in differentiating FD from other similar disorders. For example, external incentives like avoiding military duty, work, or obtaining financial compensation, are associated with Malingering. [22] In contrast, FD patients have no clear external rewards, and the motivation is always obscure. [23] A recent case report suggested that there could be an overlap between the two diagnoses, as some degree of gain in the form of free accommodation and food was present. [24] In somatic symptom disorder, although there are excessive medical concerns and visits, there is no evidence of deception. [6] This is also true with Conversion disorder (functional neurological symptoms disorder), which is characterized by neurological symptoms that are inconsistent with neurological pathophysiology. [6]

As aforementioned, early-life trauma which could predispose to FD, [12] is also associated with Personality disorders, especially borderline personality disorder. [25] Moreover, this suggests a strong co-morbidity between the two disorders. [25] Also, a recent study found that Depression is the most common co-morbid psychiatric

disorder. [9] In addition, other common comorbid disorders include anxiety, substance abuse, conversion disorder, and eating disorders. [9]

Management

Initially, management of these patients includes acute management and long-term management like engaging the patient in psychotherapy. [26] Additionally, it is necessary to avoid direct confrontation in the acute or inpatient setting as this could be counter therapeutic. [22] This led to the emergence of "Supportive confrontation", in which the confrontation process involves at least two of the caregivers, highlighting the patient's need for help, and reassuring them that care will continue. [27] In spite of this, some could interrupt confrontations, or even escalate their self-destruction behavior, and seek care elsewhere. [26] Only 17.2% of the confronted patients acknowledged their fictitious behavior. [11]

In long-term management, there are many suggested treatments, including psychotherapy, behavioral therapy, medication treatment, and multidisciplinary approaches. [28] Unfortunately, FD treatment is not based on controlled and randomized trials. [28] Also, a systematic review reported no difference in effectiveness between any of the suggested treatments of FD. [28]

Prognosis and effect on life

In general, FD is a chronic disease, although it can be limited to one or more brief episodes [29] and recovery is rare. [30]

This disorder carries significant morbidity and mortality, and legal issues could arise in some cases. [31] Besides, the multiple unnecessary investigations, medical procedures, and hospitalizations form a huge economic burden and strain the medical care system. [21] A six-year follow-up of one patient revealed four hospitalizations with a total cost of 47,487.14 $. [21]

A recent systematic review reported that 14.1% of patients have current suicidal ideation or earlier suicidal attempts. [9] Judicial issues could arise also in FD imposed on another, as it may be consistent with abuse, especially if the victim is a child, a vulnerable adult, or an elder. [32]

Munchausen by Internet

This term appeared first in 2000, to describe cases of virtual FD, in which patients show factitious behaviors but on online platforms. [33] They may use chat rooms or online

support groups to falsely be a serious illness that could negatively affect real patients. (34)

The continuous invasion of social media in our lives could make it an increasing issue. (33) Literature about this pattern is not enough. More research should be done to evaluate the prevalence and the potential harm.

References

1. XU NICOLE. Illustration about Munchausen Syndrome for Nautilus Mag [Internet]. 8 Dec. 2016. Available from: https://nicole-xu.tumblr.com/post/154210943894/illustration-about-munchausen-syndrome-for
2. Cule J, Burns C, Musajo-somma A, Tricot J, Blair J, Weir S. Official journal of the International Society Revue officielle de la Societe Internationale June 2002. 2002;(June).
3. Fisher JA. Investigating the barons: Narrative and nomenclature in Munchausen syndrome. Perspect Biol Med. 2006;49(2):250–62.
4. Asher R. "Munchausen's Syndrome." The Lancet. 1951;257(6650):339–41.
5. Diagnostic and Statistical Manual of Mental Disorders Third Edition. American Psychiatric Association. 1980.
6. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition. American Psychiatric Association. 2013.
7. Kahn A, Boroff ES, Martin KA, Northfelt DW, Heigh RI. Factitious disorder in Crohn's disease: Recurrent pancytopenia caused by surreptitious ingestion of 6-mercaptopurine. Case Rep Gastroenterol. 2015;9:137–41.
8. Eaton JS Jr. Playing sick? untangling the web of Munchausen syndrome, Munchausen by proxy, malingering, and factitious disorder. Am J Psychiatry. 2006;163(2):334-335.
9. Yates GP, Feldman MD. Factitious disorder: A systematic review of 455 cases in the professional literature. Gen Hosp Psychiatry [Internet]. 2016;41:20–8. Available from: http://dx.doi.org/10.1016/j.genhosppsych.2016.05.002
10. Jafferany M, Khalid Z, McDonald KA, et al. psychological aspects of factitious disorder. Prim Care Companion CNS Disord. 2018;20(1):17nr02229.
11. Krahn LE, Li H, O'Connor MK. Patients who strive to be ill: Factitious disorder with physical symptoms. Am J Psychiatry. 2003;160(6):1163–8.
12. Tasman,A.,Mohr, W.K., 2011.FundamentalsofPsychiatry. JohnWiley&Sons, Oxford.
13. Kozlowska K. Abnormal illness behaviours: A developmental perspective. Lancet [Internet]. 2014;383(9926):1368–9. Available from: http://dx.doi.org/10.1016/S0140-6736(13)62640-9
14. Yang Y, Raine A, Lencz T, Bihrle S, Lacasse L, Colletti P. Prefrontal white matter in pathological liars. Br J Psychiatry. 2005;187(OCT.):320–5.
15. Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullén F. Extensive piano practicing has regionally specific effects on white matter development. Nat Neurosci. 2005;8(9):1148–50.
16. Bass C, Halligan P. Factitious disorders and malingering: Challenges for clinical assessment and management. Lancet [Internet]. 2014;383(9926):1422–32. Available from: http://dx.doi.org/10.1016/S0140-6736(13)62186-8
17. Haddad, S. A., Winer, K. K., Gupta, A., Chakrabarti, S., Noel, P., & Klein, H. G. (2002). A puzzling case of anemia. Transfusion, 42(12), 1610–1613. https://doi.org/10.1046/j.1537-2995.2002.00269.x.
18. Birman M V., Lee DH. Factitious disorders of the upper extremity. J Am Acad Orthop Surg. 2012;20(2):78–85.
19. Burke F. D. (2008). Factitious disorders of the upper limb. The Journal of hand surgery, European volume, 33(2), 103–109. https://doi.org/10.1177/1753193408087230.
20. Cheng T. O. (1999). Munchausen syndrome. Journal of internal medicine, 245(5), 544–545.
21. Hoertel N, Lavaud P, Le Strat Y, Gorwood P. Estimated cost of a factitious disorder with 6-year follow-up. Psychiatry Res [Internet]. 2012;200(2–3):1077–8. Available from: http://dx.doi.org/10.1016/j.psychres.2012.05.004
22. Galli S, Tatu L, Bogousslavsky J, Aybek S. Conversion, Factitious Disorder and Malingering: A Distinct Pattern or a Continuum? Front Neurol Neurosci. 2017;42:72–80.
23. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
24. Coebergh JA, Amlani A, Edwards M, Mah YH, Agrawal N. A brain origin for factitious disorder (Munchausen's) with malingering? A single case with an old frontal lobe lesion. Neurocase [Internet]. 2021;27(1):8–11. Available from: https://doi.org/10.1080/13554794.2020.1858110
25. O'Shea B. Factitious disorders: The Baron's legacy. Int J Psychiatry Clin Pract. 2003;7(1):33–9.
26. McCullumsmith C, Ford C. Simulated illness: the factious disorders and malingering. Psychiatr Clin North Am 2011; 34: 621–41.
27. Reich P, Gottfried LA. Factitious disorders in a teaching hospital. Ann Intern Med 1983; 99: 240–47.
28. Eastwood S, Bisson JI. Management of factitious disorders: A systematic review. Psychother Psychosom. 2008;77(4):209–18.

29. Sousa Filho D de, Kanomata EY, Feldman RJ, Maluf Neto A. Munchausen syndrome and Munchausen syndrome by proxy: a narrative review. Einstein (Sao Paulo). 2017;15(4):516–21.
30. Bass, C., & Taylor, M. (2013). Recovery from chronic factitious disorder (Munchausen's syndrome): a personal account. Personality and mental health, 7(1), 80–83.
31. Eisendrath SJ, McNiel DE. Factitious physical disorders, litigation, and mortality. Psychosomatics. 2004;45(4):350–3.
32. Dumitrascu CI, Gallardo KE, Caplan JP. Malingering Imposed on Another: A Diagnosis That is Missing in Action? Psychosomatics [Internet]. 2015;56(6):609–14. Available from: http://dx.doi.org/10.1016/j.psym.2015.07.006
33. Feldman MD. Munchausen by Internet: Detecting Factitious Illness and Crisis on the Internet. South Med J. 2000;93(7):669–72.
34. Geile J, Aasly J, Madea B, Schrader H. Incidence of the diagnosis of factitious disorders – Nationwide comparison study between Germany and Norway. Forensic Sci Med Pathol. 2020;16(3):450–6.

Article Title: Depersonalization/Derealization Disorder.

Author: Leen Sawalha.

Editor: Ihdaa Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: Depersonalization, derealization, dissociation, detachment.

Overview

Picture being trapped in a dreamlike trance forever – an eternal curse. This is what those suffering from depersonalization/derealization disorder experience. It is a psychiatric illness in which the person feels as if they are detached from their body (in depersonalization) and as if their surrounding environment is fake (in derealization). [1]

Epidemiology and Risk Factors

Depersonalization/derealization disorder is quite uncommon; it affects 0.76% - 1.9% of the population. The prevalence in those with other specified mental disorders ranges from 1.8% - 53.8%, and 4.4% - 41.9% in those with unspecified/mixed disorders. [1] It does not have a gender predilection. [2]

It usually happens in those with chemical and psychological risk factors. Traumatic events such as dealing with childhood emotional or sexual abuse could unshackle the gates open for the disorder, making it present as a defense mechanism of sorts. It can be imagined as a dam, holding back the riptide. It acts to provide sanctuary to the person, shielding them from the overwhelming emotions that come with such distressing situations. [3]

Risk factors include:[4]

- Life stressors and trauma
- Neglect in childhood
- Abuse in childhood
- Use of illicit drugs
- Psychiatric condition or growing up with a parent with a psychiatric condition

Pathophysiology

There are many neurotransmitters affiliated with the disorder. NMDA glutamatergic pathways, endogenous opioids, and serotonergic pathways all show an involvement. [3]

The NMDA antagonist ketamine can induce a dissociative episode, even in those without the disorder. [5] K opioid agonists produce the same effect; [6] so do cannabinoids. A prominent theory suggests that cannabinoids block specific areas on NMDA receptors (different from the part blocked via non-competitive antagonists), and this is what causes dissociative symptoms. [3] Serotonin receptor agonists, such as LSD (lysergide) and DMT (dimethyltryptamine), have also been implicated in the production of dissociative states. [2]

A novel study states that there is a strong inverse correlation between the amount of 24-hour urine noradrenaline and the degree of depersonalization, suggesting that the lack of noradrenaline could also aid a hand in its pathophysiology. [7]

Lastly, the hypothalamic-pituitary axis may have a role in its pathogenesis; however, studies show inconsistent and conflicting evidence. [3]

Clinical Presentation

'I no longer exist; I am living in a movie; I am looking at myself from the outside' – these are all common phrases uttered by the patients. This can be a petrifying experience causing immense agony, making them feel as though they are losing their mind; however, these seemingly alarming declarations are masked by their flat effect, making it puzzling for physicians to correctly identify the cause. [4] They are more prone to attempt suicide, however, since they usually have other mental illnesses (such as major depressive disorder), the exact cause of increased suicidal ideations is unclear whether it is due to comorbid mental illnesses or as a direct result of the disorder. [2]

Five specific symptoms were found to be consistent in patients with the disorder:[8]

- Feeling detached from one's body
- Perceptual distortions
- Numbing of emotions
- Disrupted experiences of time and related imagery
- Feeling as though surroundings are fake

Figure 1: A representation of how those suffering from this disorder feel as if they are watching themselves from the outside. [15]

Diagnosis of depersonalization

The use of questionnaires aids in the identification of depersonalization/derealization disorder. One of the most popular scales is the Dissociative Experiences Scale.[9] It is important to note that this scale is not used for diagnosis, rather, it provides extra data concerning the treatment and episodes of the dissociative disorder. [9] It screens for 3 items: amnesia, depersonalization, and absorption. [10] A more specific scale used for distinguishing depersonalization/derealization disorder from other diseases is the Cambridge Depersonalization Scale. [10] This scale is reliable and valid; it has even been able to distinguish Temporal lobe epilepsy (TLE) and anxiety (both of which present with depersonalization) from the disorder itself. A score of 70 suggests the disorder to be depersonalization/derealization disorder. [10]

DSM 5 Criteria

To diagnose depersonalization/derealization disorder, the following DSM-5 criteria must be met:[11]

- Recurring/persisting either depersonalization, derealization, or both.
- During an episode, reality testing remains unchanged
- Social/occupational distress due to the symptoms
- Not due to another medical illness, other psychiatric illness, or drug use

Treatment

In a pilot study by Nuller et al, Naloxone was administered to 14 patients. 7 of the 14 patients had a significant decrease in the depersonalization symptoms, while the symptoms of another 3 completely disappeared. [12]

Unfortunately, no medication has shown any efficacy. Fluoxetine has been tried; however, it was of no avail. [3]

Behavioral therapy can also be used. Blue described a case of a 50-year-old woman suffering from the disease. She was given an astonishing number of 16 different drugs, all of which failed miserably in treating her. She only responded to behavioral therapy. This indicates its potential efficacy - even over pharmacotherapy. [13]

In those with a history of depersonalization due to adverse events, the use of therapy targeting the causative trauma can help the individual better process it, leading to better coping with the dissociation. [3]

Prognosis

Depersonalization disorder has a chronic course in 2/3rd of patients, starting in adolescents. It impairs the individual's ability to function day to day in social settings and work. Any future traumatic event, or even an elevation in stress levels, can amplify symptoms, stripping away the individual's ability to function. [14]

Conclusion

To say we are close to understanding this complex disorder would be a great leap in optimism; it is under-researched, thus, is usually confused with other disorders. With more studies, we could hopefully be able to rid this world of this debilitating, but silent, nightmare.

References

[1] J. Yang, L. S. M. Millman, A. S. David, and E. C. M. Hunter, "The Prevalence of Depersonalization-Derealization Disorder: A Systematic Review.," *J. trauma dissociation Off. J. Int. Soc. Study Dissociation*, pp. 1–34, Jun. 2022, doi: 10.1080/15299732.2022.2079796.
[2] D. Simeon, M. Knutelska, D. Nelson, and O. Guralnik, "Feeling unreal: a depersonalization disorder update of 117 cases," *J. Clin. Psychiatry*, vol. 64, no. 9, pp. 990–997, Sep. 2003, doi: 10.4088/JCP.V64N0903.
[3] D. Simeon, "Depersonalisation disorder: a contemporary overview," *CNS Drugs*, vol. 18, no. 6, pp. 343–354, 2004, doi: 10.2165/00023210-200418060-00002.
[4] "Depersonalization/derealization disorder: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis - UpToDate." https://www.uptodate.com/contents/depersonalization-derealization-disorder-epidemiology-pathogenesis-clinical-manifestations-course-and-diagnosis#H10289535 (accessed Sep. 30, 2022).

[5] H. Valerie Curran and C. Morgan, “Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later,” *Addiction*, vol. 95, no. 4, pp. 575–590, 2000, doi: 10.1046/J.1360-0443.2000.9545759.X.
[6] S. L. Walsh, B. Geter-Douglas, E. C. Strain, and G. E. Bigelow, “Enadoline and butorphanol: evaluation of kappa-agonists on cocaine pharmacodynamics and cocaine self-administration in humans,” *J. Pharmacol. Exp. Ther.*, vol. 299, no. 1, pp. 147–158, 2001, Accessed: Sep. 30, 2022. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/11561074/.
[7] D. Simeon, O. Guralnik, M. Knutelska, R. Yehuda, and J. Schmeidler, “Basal norepinephrine in depersonalization disorder,” *Psychiatry Res.*, vol. 121, no. 1, pp. 93–97, Nov. 2003, doi: 10.1016/S0165-1781(03)00205-1.
[8] D. Simeon, D. S. Kozin, K. Segal, B. Lerch, R. Dujour, and T. Giesbrecht, “De-constructing depersonalization: Further evidence for symptom clusters,” *Psychiatry Res.*, vol. 157, no. 1–3, pp. 303–306, Jan. 2008, doi: 10.1016/J.PSYCHRES.2007.07.007.
[9] E. Mazzotti *et al.*, “Is the Dissociative Experiences Scale able to identify detachment and compartmentalization symptoms? Factor structure of the Dissociative Experiences Scale in a large sample of psychiatric and nonpsychiatric subjects.,” *Neuropsychiatr. Dis. Treat.*, vol. 12, pp. 1295–1302, 2016, doi: 10.2147/NDT.S105110.
[10] M. Sierra and G. E. Berrios, “The Cambridge Depersonalisation Scale: a new instrument for the measurement of depersonalisation,” *Psychiatry Res.*, vol. 93, no. 2, pp. 153–164, Mar. 2000, doi: 10.1016/S0165-1781(00)00100-1.
[11] American Psychiatric Association, “American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition,” *Arlington*, p. 991, 2013, Accessed: Sep. 30, 2022. [Online]. Available: http://encore.llu.edu/iii/encore/record/C__Rb1280248__SDSM-V__P0,2__Orightresult__X3;jsessionid=ABB7428ECBC4BA66625EDD0E0C5AAFA5?lang=eng&suite=cobalt.
[12] Y. L. Nuller, M. G. Morozova, O. N. Kushnir, and N. Hamper, “Effect of naloxone therapy on depersonalization: a pilot study.,” *J. Psychopharmacol.*, vol. 15, no. 2, pp. 93–95, Jun. 2001, doi: 10.1177/026988110101500205.
[13] F. R. Blue, “Use of directive therapy in the treatment of depersonalization neurosis,” *Psychol. Rep.*, vol. 45, no. 3, pp. 904–906, 1979, doi: 10.2466/PR0.1979.45.3.904.
[14] L. W. Roberts, J. G. Hoop, and T. W. Heinrich, “Clinical psychiatry essentials,” p. 607, 2010.
[15] “No Title,” [Online]. Available: https://medium.com/@kyleflemington/life-with-mental-illness-a-depersonalization-story-1b8dd006daaa.

Article topic: Pica Disorder.

Author: Rama khaled hussban.

Editor: Ihdaa Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: pica, pagophagia, iron deficiency, lead poisoning.

Introduction

The term “Pica” has come from “pica-pica” the Latin word for the magpie bird; because of gathering and eating a variety of objects for curiosity.[1] And the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines a pica as eating nonnutritive, nonfood substances over a period of at least one month.[2]

Pica refers to the persistent, compulsive craving to ingest inedible substances. And for diagnosis, this behavior must last for at least one month, also not be in keeping with the child's developmental stage, and not be socially normative or culturally acceptable.[3]

Pica is common in children between 18 months to six years, women during pregnancy, and intellectually impaired persons.[1] However, pica usually occurs as an isolated disorder, some states occur with schizophrenia, autistic spectrum disorder, attention-deficit hyperactivity disorder, depression, OCD, and trichotillomania.[3,4,5]

Epidemiology

It is difficult to evaluate the exact prevalence of pica because of different studied populations, cultural practices, regional differences, under-reporting, etc.[1] Although pica is more occurrence than is expected either because the condition may be overlooked by physicians or under-reported by patients or parents.[1]

Pica is a little more common in boys than girls. It is also more common in blacks than whites. The percentage of prevalence decreases with age. And it is more common among children in lower socioeconomic classes, immigrants, and refugees.[6] The incidence is increased in children whose siblings or mothers have pica before. Children with sickle cell anemia are at greater risk for developing pica than those without sickle cell anemia.[1, 7]

A German prevalence study of 804 children observed that 12.3% of children have been associated with pica behavior at some point in their lives.[1] A meta-analysis of studies on the prevalence of pica during pregnancy showed that 27.8% of pregnant women reported experiencing pica. The study also declared that the sample was heterogeneous throughout the world, with a higher prevalence in Africa compared to other continents. And even the prevalence rate of pica could be as high as 77% in African children.[2 A] high prevalence of pica is reported in patients with mental retardation, almost 10%; it correlates with the severity of mental retardation.[1]

Etiology

There is not a direct cause for pica, but there are many risk factors such as child neglect, stress, maternal deprivation, low socioeconomic status, etc.[1,8]

There is some evidence that pica is an attention-seeking device; the high incidence of working mothers and families with young children may suggest this behavior.[1] Moreover, relief of anxiety and emotional stress in the child by oral gratification is often a psychological response to an absent or poorly functioning mother.[9]

lesions in the hypothalamus and anterior cingulate gyrus may lead to hyperphagia. Thus, abnormalities in the eating center of the hypothalamus may result in pica in some individuals. And the mentally disabled child remains at a more infantile developmental level for longer than the normal child.[10]

Iron deficiency anemia has an implicated hand. Many population-based studies have observed low serum iron/ferritin and other micronutrients among patients with pica.[11,12] However, a study conducted with substances consumed by patients with pica has not shown an increase in the bioavailability of iron among these substances.[13] This suggests that the idea that these cravings arise from a need for serum iron is an inadequate pathophysiological explanation for this phenomenon.[13]

Pet-keeping motivates pica as children may eat pet food by imitation.[1] Occasionally, pica may be associated with medications such as risperidone, olanzapine, and tramadol.[14] In animal studies, cisplatin can induce pica behavior in specific strains in mice.[15]

In pagophagia (ingestion of ice), a Japanese study hypothesized that when a patient with anemia chews ice, it rises perfusion and improves brain function. They contributed to the activation of the dive reflex which would lead to peripheral vasoconstriction and an increase in central perfusion.[16] Another explanation can be sympathetic activation which would also increase blood flow to the brain.[16]

DSM 5 Diagnostic Criteria [32]

- Persistent eating of nonnutritive, nonfood substances over a period of at least 1 month**.**
- The eating of nonnutritive, nonfood substances is inappropriate for the developmental level of the individual**.**
- The eating behavior is not part of a culturally supported or socially normative practice.
- If the eating behavior occurs in the context of another mental disorder (e.g., intellectual disability [intellectual developmental disorder], autism spectrum disorder, schizophrenia) or medical condition (including pregnancy), it is sufficiently severe to warrant more clinical attention.

Clinical manifestations

The materials ingested because of pica depend on availability in the environment and conscious selection factors.[1]

Various substances may be craved, including clay (geophagia), raw starch (amylophagia), dirt (co-niophagia or chthonophagia), hair (trichophagia), ice (pagophagia), raw, raw potatoes (gemelophagia), fibrous plant roots (phytobezoar), paint chips (plumbophagia), sand, pebbles/stones (lithophagia), sharp objects (acuphagia), glass (hyalophagia), soap (sapophagia), feces (coprophagia), burned matches (cautopyreiophagia), uncooked rice (ryzophagia), paper (xylophagia), vomitus (emetophagia), wooden materials, sponge, polyurethane foam, grass, leaves, paper, chalk, baby talcum powder, crayons, pencil erasers, cigarette butts, ashes, charcoal, coins, buttons, cloth, eggshells, and insects. [1,3,17]

Coprophagia and emetophagia usually occur in individuals with neuropsychiatric disorders. [18] Geophagia and amylophagia are the most common types of picas.[17]

Clinical signs are usually secondary to complications related to the substance ingested, as the physical examination is often normal in children with pica.[19] Bezoar formation results in mechanical bowel problems, intestinal obstruction, and perforation.[19] Lead poisoning appears with neurological signs such as(lethargy, seizure, headache, encephalopathy, cranial nerve palsy, and papilledema) as well as gastrointestinal signs such as(constipation, abdominal pain, colic vomiting, anorexia, and diarrhea).[19] Toxocara and Ascaris parasitic infectious agents in clay lead to signs including cough, fever, myocarditis and encephalitis, visual disturbance, and hepatomegaly.[19]

Evaluation

Laboratory evaluation should be based on suspected ingestion.[1] A peripheral smear, complete blood count, and differential white cell count may be needed to decide if there is iron deficiency anemia (hypochromic, microcytic anemia), parasitic infestation (eosinophilia), or lead poisoning (punctate basophilia).[1]

Lead (in pica for paint and chalk) and zinc levels should be checked whether proper.[20] A basic metabolic panel should be obtained, especially in clay ingestion which may cause metabolic disturbances such as hypokalemia. [21]

If parasitism is suspected, fecal samples should be examined for ova and parasites. [1] If increased lead absorption is suspected, X-ray examination of long bones may show bands of increased density at the metaphyses known as “lead lines".[1] A plain abdominal film should be considered in children with abdominal symptoms. [1]

Complications

The complications of pica can be classified by the type of substance ingested.[1]

Pagophagia leads to iron deficiency (especially during pregnancy), tooth decay, and sensitivity while amylophagia can cause high blood sugar and obesity due to its high carbohydrate content.[22,1] Also, excessive starch consumption has been associated with iron deficiency anemia.[23]

The ingested material induces a secondary iron deficiency anemia either by binding the iron to the clay particles or by acting as an ion exchange resin.[1]

Geophagia can lead to hypokalemia with myopathy, iron and zinc deficiency, intestinal obstruction or perforation, dental injuries, and parasitic infestations.[24] Clay also is a source of many infectious agents such as parasites. In addition, geophagy is also a significant cause of lead poisoning.[1]

As a result, both lead poisoning and iron deficiency can lead to impaired neurocognitive development.[25]

Pica with baking soda may lead to electrolyte abnormalities such as zinc deficiency, hypokalemia, hyperkalemia, hyperphosphatemia, and metabolic alkalosis. And Electrolyte disturbance is more common in patients with chronic renal disease.[1]

Pica during pregnancy can have dangerous consequences on the growing fetus, it can cause intrauterine toxicity which may kill the fetus. Maternal geophagy has been associated with childhood motor function delay too.[26]

Sometimes, fatalities can result from intestinal obstruction, bowel perforation, infections (bacterial, parasitic), poisoning (lead, mercury, arsenic, phosphorous), and electrolyte imbalances (hypokalemia, hyperkalemia).[27]

Management

Using strategies to decrease exposure to the craved substance, such as reducing access or providing an appropriate substitute with a similar texture.[28] If there was a deficiency in iron, zinc, and another nutrient, provide supplementation.[29] Differential reinforcement is a common strategy to get patients to respond differently to pica by redirecting the unwanted behavior to other activities.[30]

Behavioral therapy can reduce the severity of pica by 80% in mentally disabled individuals.[31] Anticipatory guidance, for teaching children the dangers of pica in communities where pica is common, may have a good role in preventing pica.[1]

Relieving family economic and housing difficulties, and attention to the individual's emotional needs and stresses are especially important for treatment.[1] An understanding and supportive attitude for the mother may enable her to provide better care for the child.[1]

Conclusion

Pica is a critical issue to highlight. It has associated with iron deficiency and lead poisoning. So, the medical field should share awareness about diagnosis, risk factors, and complications.

References

1. Leung AKC, Hon KL. Pica: A Common Condition that is Commonly Missed - An Update Review. Curr Pediatr Rev 2019; 15: 164–169.
2. Ardeshirian KA, Howarth DA. Esperance pica study. 2017.
3. McNaughten B, Bourke T, Thompson A. Fifteen-minute consultation: The child with pica. Arch Dis Child Educ Pract Ed 2017; 102: 226–229.
4. Ree IMC, Smits-Wintjens VEHJ, van der Bom JG, van Klink JMM, Oepkes D, Lopriore E. Neonatal management and outcome in alloimmune hemolytic disease. Expert Review of Hematology 10 2017 607–616.
5. Bharti A, Mishra A, Sinha V, Anwar Z, Kumar V, Mitra S. Paper eating: An unusual obsessive-compulsive disorder dimension. Ind Psychiatry J 2015; 24: 189.
6. Khan Y, Tisman G. Pica in iron deficiency: A case series. J Med Case Rep 2010; 4.
7. Aloni MN, Lecerf P, Lê PQ *et al.* Is pica under-reported in children with sickle cell disease? A pilot study in a Belgian cohort. Hematology (United Kingdom) 2015; 20: 429–432.
8. Singhi S, Singhi P, Adwani GB. Role of Psychosocial Stress in the Cause of Pica. .
9. Poon CY. Childhood Immunization n Part II. .
10. Rangwala SD, Tobin MK, Birk DM, Butts JT, Nikas DC, Hahn YS. Pica in a Child with Anterior Cingulate Gyrus Oligodendroglioma: Case Report. Pediatr Neurosurg 2017; 52: 279–283.
11. Nchito M, Wenzel Geissler P, Mubila L, Friis H, Olsen A. Effects of iron and multimicronutrient supplementation on geophagy: A two-by-two factorial study among Zambian schoolchildren in Lusaka. Trans R Soc Trop Med Hyg 2004; 98: 218–227.

12. Geisslerl ? W, Shulma&3 CE, Prince%l RJ *et al*. Geophagy, iron status and anaernia among pregnant women on the coast of Kenya. 1998.
13. Hooda PS, Henry CJK, Seyoum TA, Armstrong LDM, Fowler MB. The potential impact of soil ingestion on human mineral nutrition. Science of the Total Environment 2004; 333: 75–87.
14. Psychiatry Clin Neurosci - 2018 - Chawla - Tramadol-associated pica. .
15. Yamamoto K, Yamatodani A. Strain differences in the development of cisplatin-induced pica behavior in mice. J Pharmacol Toxicol Methods 2018; 91: 66–71.
16. Hunt MG, Belfer S, Atuahene B. Pagophagia improves neuropsychological processing speed in iron-deficiency anemia. Med Hypotheses 2014; 83: 473–476.
17. Golden CD, Rasolofoniaina BJR, Benjamin R, Young SL. Pica and Amylophagy Are Common among Malagasy Men, Women and Children. PLoS One 2012; 7.
18. Sharma TR, Aly M, Kavuru B. Coprophagia and pica in individuals with mild to moderate dementia and mixed (iron deficiency and macrocytic) anemia. Journal of the American Geriatrics Society 59 2011 2375–2377.
19. McNaughten B, Bourke T, Thompson A. Fifteen-minute consultation: The child with pica. Arch Dis Child Educ Pract Ed 2017; 102: 226–229.
20. Poy MS, Weisstaub A, Iglesias C, Fernández S, Portela ML, López LB. Diagnóstico de pica durante el embarazo y deficiencia de micronutrients en mujeres argentinas. Nutr Hosp 2012; 27: 922–928.
21. Ukaonu C, Hill DA, Christensen F. Hypokalemic myopathy in pregnancy caused by clay ingestion. Obstetrics and Gynecology 2003; 102: 1169–1171.
22. Advani S, Chachra S, Dhawan P, Kochhar G. Eating everything except food (PICA): A rare case report and review. J Int Soc Prev Community Dent 2014; 4: 1.
23. Maksoud C, Dhadham GC, Kothari S, Elfarra H. Abstracts S253 698 Amylophagia in Iron Defi ciency Anemia: Uncommon and Commonly Missed. 2010.
24. From Botswana 593. .
25. Hon KL, Fung CK, Leung AKC. Childhood lead poisoning: An overview. Hong Kong Medical Journal 23 2017 616–621.
26. Mireku MO, Davidson LL, Zoumenou R, Massougbodji A, Cot M, Bodeau-Livinec F. Consequences of prenatal geophagy for maternal prenatal health, risk of childhood geophagy and child psychomotor development. Tropical Medicine and International Health 2018; 23: 841–849.
27. Loots DP, du Toit-Prinsloo L. A fatal outcome of pica. Forensic Sci Med Pathol 2016; 12: 108–112.
28. Matson JL, Hattier MA, Belva B, Matson ML. Pica in persons with developmental disabilities: Approaches to treatment. Res Dev Disabil 2013; 34: 2564–2571.
29. Roy A, Fuentes-Afflick E, Fernald LCH, Young SL. Pica is prevalent and strongly associated with iron deficiency among Hispanic pregnant women living in the United States. Appetite 2018; 120: 163–170.
30. Call NA, Simmons CA, Mevers JEL, Alvarez JP. Clinical Outcomes of Behavioral Treatments for Pica in Children with Developmental Disabilities. J Autism Dev Disord 2015; 45: 2105–2114.
31. Hagopian LP, Rooker GW, Rolider NU. Identifying empirically supported treatments for pica in individuals with intellectual disabilities. Research in Developmental Disabilities 32 2011 2114–2120.
32. Sutton WS. Neurocognitive disorders. Handbook of Geropsychiatry for the Advanced Practice Nurse: Mental Health Care for the Older Adult. 2020. 133–158 p.

Article topic: Narcolepsy.

Author: Manar Al-Titi.

Editors: Lubna Al-Rawabdeh, Samah Al-Ajjawe.

Reviewer: Ethar Hazaimeh.

Keywords*: Multiple Sleep Latency Test (MSLT), Polysomnography (PSG), Sleep Onset REM Periods (SOREMPs).*

Introduction

Narcolepsy is a chronic neurological disorder characterized by excessive and overwhelming drowsiness, cataplexy (episodes of muscle weakness at times of intense emotion), hypnagogic hallucinations (vivid dreams at the onset of sleep), and sleep paralysis (temporary inability to move the body as a unit). before falling asleep or upon waking). This is one of the most common reasons for preventing daytime sleepiness after obstructive sleep apnea. [1,2]

Narcolepsy occurs in two forms in both children and adults, depending on whether cataplexy is present [3]. Type 1 narcolepsy, formerly known as narcolepsy with cataplexy, includes cataplexy as one of the first symptoms and is associated with low levels of orexin (also called hypocretin) in the cerebrospinal fluid (CSF). Narcolepsy type 2, or narcolepsy without cataplexy, has all the features of narcolepsy type 1 except cataplexy and low CSF orexin levels.

Epidemiology

Type 1 narcolepsy (narcolepsy with cataplexy) is estimated to have a prevalence of 27 to 50 per 100,000 people and an incidence of 0.75 per 100,000 person-years [4-5]. It is equally common in men and women [6-7]. Narcolepsy usually begins in the teens and early 20s but occasionally occurs as early as the age of five or after 40 years of age. The prevalence of type 2 narcolepsy (narcolepsy without cataplexy) is undetermined because it is understudied and more difficult to diagnose, but it has been estimated at 21 to 36 per 100,000 people.

Etiologies

Loss of orexin (hypocretin) signaling, genetic factors, and, more rarely, brain lesions can cause narcolepsy.

Orexin/Hypocretin: Narcolepsy results from the loss of the neuropeptides orexin-A and orexin-B (also known as hypocretin-1 and hypocretin-2) [8,9]. These neurotransmitters are products of the pre-pro-orexin gene and are produced by neurons in the lateral hypothalamus [10,11]. Orexins A and B have excitatory effects when bound to OX1 and OX2 receptors on postsynaptic neurons.

Orexins are released during wakefulness and increase the activity of many brain regions involved in promoting wakefulness, including the locus coeruleus, raphe nuclei, and tubercle mammillary nucleus [12]. By increasing the activity of these wakefulness-promoting monoaminergic neurons, orexins stabilize wakefulness, prevent inappropriate transitions to rapid eye movement (REM) or non-REM sleep, and inhibit REM sleep. The loss of orexins also allows REM-related phenomena (eg, cataplexy, hypnagogic hallucinations, and sleep paralysis) to invade the waking state.

Animal models first identified the importance of orexins in narcolepsy. Dogs with OX2 receptor mutations were found to show drowsiness and cataplexy similar to human narcolepsy [13]. Mice lacking orexin peptides or orexin-producing neurons also had severe narcolepsy [14]. Remarkably similar behavior was observed in mice lacking both orexin receptors.

People with narcolepsy are usually classified as having either type 1 narcolepsy (narcolepsy with cataplexy) or type 2 narcolepsy (narcolepsy without cataplexy). It was later shown that people with type 1 narcolepsy are also deficient in orexin. individuals with type 1 narcolepsy had an approximately 91% decrease in the number of hypothalamic orexin-producing neurons with little or no detectable orexin-A in their cerebrospinal fluid [15-17]. The neuronal loss appears to be selective because adjacent neurons containing the melanin-concentrating hormone are conserved.

In the brains of patients with type 1 narcolepsy, an increase in the number of histamine-producing neurons and a decrease in the number of corticotropin-releasing hormone-producing neurons have been observed [18-19]. These are compensatory responses to the loss of excitatory stimuli from orexin neurons, and their physiological significance remains unclear.

The cause of narcolepsy type two is unknown, and these sufferers have normal cerebrospinal fluid (CSF) orexin-A levels. It has been hypothesized that this disorder may result from much less widespread loss of the orexin neurons [20], impaired orexin receptor signaling, or a separate mechanism. About 24 percent of sufferers who have narcolepsy type 2 have low CSF orexin-A levels, and about 1/2 of these people can also later strengthen cataplexy, suggesting the progression of the disorder [21].

Genetic factors — Narcolepsy happens sporadically, but genetic factors play an important role. The DQB1*0602 haplotype (a subtype of DQ1) is present in 94 percent of sufferers with cataplexy and in 95 percent of those with orexin deficiency [22]. Some

additional human leukocyte antigen (HLA) haplotypes may further expand the hazard of narcolepsy, whilst others show up protecting. [23]. Though these and other genetic factors may predispose some humans to boost narcolepsy, environmental factors are extra important, as only about 25 percent of affected monozygotic twins are concordant for narcolepsy [24].

Autoimmune speculation — Researchers hypothesize that the orexin neurons are selectively killed by an autoimmune process, since narcolepsy is strongly associated with a certain HLA haplotype, DQB1*0602 [25]. The onset of narcolepsy appears best in the spring, suggesting that it may also be brought on with the aid of a wintry weather infection [26]. One viable set is streptococcal pharyngitis because anti-streptolysin O (ASO) and anti-DNase B titers are time to time elevated, especially in the first year after the onset of narcolepsy [27].

A T cell-mediated process is feasible due to the fact narcolepsy is linked to a polymorphism in the T cell receptor alpha gene [28]. Supporting this idea, quite a few research have shown that patients with narcolepsy regularly have T cells that target a couple of epitopes of the pre-pro-orexin protein [29]. A humoral mechanism may additionally also contribute, as antibodies against tribbles homolog 2, a protein expressed in neurons, is expanded in some patients quickly after the onset of narcolepsy. The number of astrocytes might also be expanded in the orexin neuron region, which is regular with an inflammatory or neurodegenerative process.
Individuals in countless countries in Europe developed narcolepsy type 1 quickly after receiving Pandemrix, an AS03-adjuvanted 2009 H1N1 influenza vaccine. Pandemrix used to be used in some European countries during the 2009-2010 H1N1 influenza pandemic, but it used to be no longer used in the United States. One proposed mechanism is cross-reactivity between the human orexin two receptor and influenza nucleoprotein A, a protein found in higher concentrations in Pandemrix compared with different H1N1 vaccines.
It appears probable that the orexin neurons are killed by using an autoimmune mechanism, however, the method must be accurate. Neuroimaging studies have discovered no consistent abnormalities [30], and CSF of sufferers shut to narcolepsy onset lacks improved protein or oligoclonal bands [31-32].

Secondary narcolepsy — In rare cases, posterior hypothalamus and midbrain lesions can cause narcolepsy. Tumors, vascular malformations, strokes, and inflammatory approaches such as neurosarcoidosis have all been suggested to cause secondary narcolepsy, due to direct damage to the orexin neurons or their projections [33]. Narcolepsy can additionally appear with genetic syndromes such as Prader-Willi syndrome or Niemann-Pick disease type C, and sleepiness and cataplexy-like activities are seen in some patients with Prader-Willi syndrome [34].

DSM-5 Diagnostic Criteria

A. Recurrent durations of an irrepressible need to sleep, lapsing into sleep or napping going on within the same day. These need to have been going on at least three times per week over the previous 3 months.

B. The presence of at least one of the following:

1. Episodes of cataplexy, described as either (a) or (b), going on at least a few times per month:

a. In humans with long-standing disease, quick (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained attention are precipitated through laughter or joking.

b. In children or in persons within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or global hypotonia, besides any obvious emotional triggers.

2. Hypocretin deficiency as measured by cerebrospinal fluid (CSF) hypocretin-1 immunoreactivity values (less than or equal to one-third of the values determined in healthy subjects tested with the same assay, or less than or equal to one). hundred percent hundred). ten pg/ml). Low CSF hypocretin-1 levels should not be observed in the context of acute brain injury, inflammation, or infection.

3. Nocturnal sleep polysomnography displaying fast eye movement (REM) sleep latency less than or equal to 15 minutes, or a multiple sleep latency check to display an implied sleep latency less than or equal to 8 minutes and two or extra sleep-onset REM periods.

Specify whether:

G47.411 Narcolepsy with cataplexy or hypocretin deficiency (type 1): Criterion B1 (episodes of cataplexy) or Criterion B2 (low CSF hypocretin-1 levels) is met.

G47.419 Narcolepsy besides cataplexy and either except hypocretin deficiency or hypocretin unmeasured (type 2): Criterion B3 (positive polysomnography/multiple sleep latency test) is met, however, Criterion B1 is now not met (i.e., no cataplexy is present) and Criterion B2 is now not met (i.e., CSF hypocretin-1 stages are not low or have now not been measured).

G47.421 Narcolepsy with cataplexy or hypocretin deficiency due to a clinical condition.

G47.429 Narcolepsy without cataplexy and besides hypocretin deficiency due to a medical situation Coding note: For the subtype narcolepsy with cataplexy or hypocretin deficiency due to a clinical circumstance and the subtype narcolepsy besides cataplexy and barring hypocretin deficiency due to a scientific condition, code first the underlying clinical situation (e.g., G71.11 myotonic dystrophy; G47.429 narcolepsy barring cataplexy and besides hypocretin deficiency due to myotonic dystrophy).

Specify present-day severity:

Mild: Need for naps solely once or twice per day. Sleep disturbances, if present, are mild. Cataplexy, if present, is rare (occurs less than once a week).

Moderate: Need for more than one nap daily. Sleep may additionally be moderately disturbed. Cataplexy, when present, occurs daily or every few days.

Severe: Regular sleepiness and, often, fantastically disturbed nocturnal sleep (which may additionally include immoderate body motion and vivid dreams). Cataplexy, when present, is drug-resistant, with a couple of attacks daily.

Diagnosis

All sufferers with chronic daylight hours sleepiness must have a thorough history, sleep history, physical exam, and neurologic examination searching for proof of cataplexy, hypnagogic or hypnopompic hallucinations, or sleep paralysis. Questions that are useful in detecting viable narcolepsy consist of the following:

- Are you sleepy most of the day?
- Do you feel rested on waking in the morning?
- Are your naps refreshing?
- Do you ever see, feel, or hear things that you know aren't there as you are falling asleep?
- Are you ever unable to move when you first awake or as you are falling asleep?
- Do you have muscle weakness when you laugh or tell a joke?
- Over the last two weeks, how often have you fallen asleep when you did not intend to?

Question	Implication
Are you sleepy most of the day?	Sleepiness is present but could be caused by a variety of conditions
Do you feel rested upon waking in the morning? Are your naps refreshing?	Sleepiness is probably not caused by poor quality sleep (eg, sleep apnea, etc)

Do you have vivid dreams during daytime naps?	Possible REM sleep during naps
Do you ever have muscle weakness when you tell a joke or laugh?	Cataplexy
Do you ever see, hear, or feel things that you know are not there as you are falling asleep?	Hypnagogic hallucinations
Are you ever unable to move when you first awake or just before falling asleep?	Sleep paralysis
Over the last two weeks, how often have you fallen asleep when you did not intend to?	Functional impact of daytime sleepiness; complements the Epworth Sleepiness Score

If the answer to any of these questions is yes, then narcolepsy should be considered, and each should have a polysomnogram and more than one sleep latency test performed.

Sleep research — The purpose of the polysomnogram is to exclude alternative and coexisting causes of persistent daytime sleepiness, which might also warrant specific therapy [35]. The motive behind more than one sleep latency takes a look at multiple sleep latency test (MSLT) is to measure the mean sleep latency and pick out sleep onset speedy eye motion periods (SOREMPs). Stimulants and other psychoactive medications ought to be stopped one week earlier than testing, and antidepressants have to be stopped at least three weeks earlier than trying out (four weeks for fluoxetine) to keep away from speedy eye motion (REM) sleep rebound effects. The patient should additionally have actigraphy or an entire sleep log for one to two weeks prior to the MSLT to document adequate quantities and timing of sleep.

Polysomnography (PSG) evaluates sleep architecture, sleep quality, and different physiological parameters. Patients who have narcolepsy commonly reveal spontaneous awakenings, mildly decreased sleep efficiency, and increased light non-REM sleep. Patients with narcolepsy kind 1 and occasionally those with narcolepsy type two may show REM sleep within 15 minutes of the onset of sleep [36]. In contrast, wholesome individuals enter REM sleep 80 to hundred minutes after the onset of sleep. Polysomnographic characteristics of alternative issues are described separately.

The MSLT starts in the morning, 1.5 to 3 hours after the PSG. The patient is placed in sleep-inducing surroundings (ie, dark, quiet room) and prompted to try to sleep. Monitoring includes electroencephalography (EEG), electrooculography, intellectual or submental electromyography, and electrocardiography (ECG). Each nap session continues for 15 minutes after sleep onset to realize REM sleep. The sleep latency is documented for every nap session. If the patient no longer falls asleep, the nap session is terminated after 20 minutes, and the sleep latency is documented as being 20 minutes.

This is repeated at two-hour intervals till the patient has had four or 5 possibilities to nap [37].

On average, wholesome subjects fall asleep in about 10 to 15 minutes, while human beings with narcolepsy fall asleep in much less than 8 minutes, offering objective proof of their sleep propensity [38]. The naps of sufferers with narcolepsy often include REM sleep, and the presence of two or greater naps having REM sleep (known as SOREMPs) is a crucial characteristic of narcolepsy [39-40].

The MSLT has several barriers in the diagnostic evaluation of narcolepsy that must be considered:

- An MSLT is valid only if the PSG confirmed at least six hours of sleep at some stage in the preceding night. Greater quantities of sleep may additionally be wished to be considered adequate in youth and adults with longer sleep times.
- The MSLT has terrible test-retest reliability and can be falsely poor or nice 20 to 30 percent of the time, especially in narcolepsy sufferers who lack cataplexy. For poor studies, the test needs to be repeated if the records are strongly suggestive of narcolepsy.
- The MSLT may additionally be less sensitive for the prognosis of narcolepsy in older adults because sleep latency increases and SOREMPs grow to be less universal with age.
- More than two SOREMPs are not specific for analysis of narcolepsy. SOREMPs are common in shift workers and can show up with other disorders that extend REM sleep pressure, such as inadequate sleep, untreated sleep apnea, or circadian phase delay. In fact, 5-10% of the typical population may even have two or more SOREMPs and up to 20% have a recommended sleep onset latency of ≤ 8 minutes. SOREMPs that immediately follow stage N1 sleep may be extra unique for narcolepsy than those that follow stage N2 or N3 sleep [41].
- REM sleep-suppressing medicines (eg, antidepressants, stimulants) can forestall the appearance of SOREMPs, and withdrawal from these capsules can produce SOREMPs, for up to several weeks after discontinuation.

Other laboratory assessments — Measurement of orexin-A (hypocretin-1) in cerebrospinal fluid (CSF) is useful in sure medical conditions [42]. Examples include when the multiple sleep latency check is hard to interpret due to both bad midnight sleep (eg, insomnia, sleep apnea, circadian rhythm sleep disorders); the incapacity to discontinue antidepressants or other sleep-modulating medications prior to testing; when the affected person is a young child (the MSLT has no longer been standardized in younger young people and, thus, is difficult to interpret or when the patient has ordinary cataplexy (90 percent of sufferers with real cataplexy have low orexin levels). A commercially reachable assay for CSF orexin-A is handy in the United States via Mayo Clinic Laboratories.

HLA checking out is now not hobbies for diagnosing narcolepsy. Most humans with narcolepsy are DQB1*0602 positive, however, this discovery is now not specific because this haplotype additionally occurs in 12 to 40 percent of healthful Americans, and more than 98 percent of DQB1*0602 superb folks do not have narcolepsy. Still, some clinicians discover HLA trying out beneficial in people with cataplexy, as over 89 percent of patients with narcolepsy with cataplexy elevate DQB1*0602 [43]. Conversely, in patients with extraordinary cataplexy, lack of DQB1*0602 affords help in opposition to a prognosis of narcolepsy with cataplexy.

Differential Diagnosis

When narcolepsy is suspected, various surrogate conditions must be considered, especially when cataplexy is no longer present. The correct differential analysis depends on which symptom or sign gave rise to suspicion of narcolepsy:

- **Chronic daytime sleepiness**: Many conditions can cause daytime sleepiness by interfering with sleep duration or quality. These include inadequate sleep, obstructive sleep apnea, central sleep apnea, periodic limb movements, sleep and waking rhythm disorders (eg, rotating shift work), mood disorders, and hypersomnia. It is common for more than one of these circumstances to exist.

Sleep recording and actigraphy are useful when the circadian disease is suspected or to provide evidence of chronic sleep deprivation. In patients with delayed sleep phase disorder, a two-time sleep latency test (MSLT) can show multiple numbers of sleep-onset REM periods (SOREMPs) even after five hours of sleep the night before, when normal sleep duration extends to the end of the night. late tomorrow. Similarly, uncorrected sleep deprivation may result in an expanded variety of SOREMPs in -MSLT that are now not unique to a diagnosis of narcolepsy.

- **Cataplexy**: sudden muscle weakness that occurs while a person is awake. Intense Thoughts Trigger Cataplexy [44] The cause of cataplexy is still under investigation, most people with cataplexy have a loss of certain brain cells that produce the hormone orexin (also called hypocretin). Orexin plays an essential role in the sleep-wake cycle.

Much of what we know about the relationship between cataplexy and orexin (hypocretin) comes from research on narcolepsy type 1. This research suggests that several factors may also play a role in orexin loss in people with narcolepsy type 1.

- **Hypnagogic hallucinations and sleep paralysis**: These symptoms are common in narcolepsy but can also occur as isolated phenomena, often triggered by inadequate sleep, obstructive sleep apnea, circadian rhythm sleep disorders, and anxiety. They can also occur as a rebound phenomenon in patients who stop

taking substances that suppress REM sleep (e.g. alcohol, amphetamines, antidepressants) [45,46]. About 21 percent of healthy people may experience infrequent hypnagogic hallucinations or sleep paralysis (eg, 2 or 3 times a year), but many people with narcolepsy experience these symptoms more frequently (eg, 3 or 4 times a month). In contrast to the hallucinations of schizophrenia and other psychotic disorders, patients with narcolepsy often distinguish hypnagogic hallucinations as dream phenomena.

Treatment

Narcolepsy has no cure, but medication and lifestyle adjustments can help manage symptoms.

Drugs for narcolepsy include:

- sodium oxybate (Xyrem) and oxybate salts (Xywav). These drugs work well to relieve cataplexy. They help improve nighttime sleep, which is often poor in narcolepsy.
- Serotonin-norepinephrine reuptake inhibitors (SNRIs) or selective serotonin reuptake inhibitors (SSRIs).
- Tricyclic antidepressants. These ancient antidepressants can treat cataplexy. But they can cause side effects like dry mouth and dizziness.

Researchers are studying possible unique treatments for narcolepsy. Drugs under study include those that target hypocretin chemistry. Researchers are also studying immunotherapy. More research is needed before these pills are available.

References

1. Scammell TE. Narcolepsy. N Engl J Med 2015; 373:2654.
2. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. Lancet 2007; 369:499.
3. American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed, American Academy of Sleep Medicine, 2014.
4. Longstreth WT Jr, Koepsell TD, Ton TG, et al. The epidemiology of narcolepsy. Sleep 2007; 30:13.
5. Partinen M, Saarenpää-Heikkilä O, Ilveskoski I, et al. Increased incidence and clinical picture of childhood narcolepsy following the 2009:// H1N1 pandemic vaccination campaign in Finland. PLoS One 2012; 7:e33723.
6. Ohayon MM, Priest RG, Zulley J, et al. Prevalence of narcolepsy symptomatology and diagnosis in the European general population. Neurology 2002; 58:1826.
7. Silber MH, Krahn LE, Olson EJ, Pankratz VS. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. Sleep 2002; 25:197.
8. Silber MH, Krahn LE, Olson EJ, Pankratz VS. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. Sleep 2002; 25:197.
9. Shin YK, Yoon IY, Han EK, et al. Prevalence of narcolepsy-cataplexy in Korean adolescents. Acta Neurol Scand 2008; 117:273.
10. Sakurai T, Amemiya A, Ishii M, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 1998; 92:573.
11. de Lecea L, Kilduff TS, Peyron C, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci U S A 1998; 95:322.

12. Hagan JJ, Leslie RA, Patel S, et al. Orexin A activates locus coeruleus cell firing and increases arousal in the rat. Proc Natl Acad Sci U S A 1999; 96:10911.
13. Lin L, Faraco J, Li R, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 1999; 98:365.
14. Chemelli RM, Willie JT, Sinton CM, et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 1999; 98:437.
15. Peyron C, Faraco J, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 2000; 6:991.
16. Olafsdóttir BR, Rye DB, Scammell TE, et al. Polymorphisms in hypocretin/orexin pathway genes and narcolepsy. Neurology 2001; 57:1896.
17. Hungs M, Lin L, Okun M, Mignot E. Polymorphisms in the vicinity of the hypocretin/orexin are not associated with human narcolepsy. Neurology 2001; 57:1893.
18. Valko PO, Gavrilov YV, Yamamoto M, et al. Increase of histaminergic tuberomammillary neurons in narcolepsy. Ann Neurol 2013; 74:794.
19. John J, Thannickal TC, McGregor R, et al. Greatly increased numbers of histamine cells in human narcolepsy with cataplexy. Ann Neurol 2013; 74:786.
20. Thannickal TC, Nienhuis R, Siegel JM. Localized loss of hypocretin (orexin) cells in narcolepsy without cataplexy. Sleep 2009; 32:993.
21. Andlauer O, Moore H 4th, Hong SC, et al. Predictors of hypocretin (orexin) deficiency in narcolepsy without cataplexy. Sleep 2012; 35:1247.
22. Hor H, Kutalik Z, Dauvilliers Y, et al. Genome-wide association study identifies new HLA class II haplotypes strongly protective against narcolepsy. Nat Genet 2010; 42:786.
23. Mignot E, Lin L, Rogers W, et al. Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. Am J Hum Genet 2001; 68:686.
24. Mignot E. Genetic and familial aspects of narcolepsy. Neurology 1998; 50:S16.
25. Mahlios J, De la Herrán-Arita AK, Mignot E. The autoimmune basis of narcolepsy. Curr Opin Neurobiol 2013; 23:767.
26. Han F, Lin L, Warby SC, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. Ann Neurol 2011; 70:410.
27. Aran A, Lin L, Nevsimalova S, et al. Elevated anti-streptococcal antibodies in patients with recent narcolepsy onset. Sleep 2009; 32:979.
28. Hallmayer J, Faraco J, Lin L, et al. Narcolepsy is strongly associated with the T-cell receptor alpha locus. Nat Genet 2009; 41:708.
29. Latorre D, Kallweit U, Armentani E, et al. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. Nature 2018; 562:63.
30. Draganski B, Geisler P, Hajak G, et al. Hypothalamic gray matter changes in narcoleptic patients. Nat Med 2002; 8:1186.
31. Fredrikson S, Carlander B, Billiard M, Link H. CSF immune variables in patients with narcolepsy. Acta Neurol Scand 1990; 81:253.
32. Overeem S, Geleijns K, Garssen MP, et al. Screening for anti-ganglioside antibodies in hypocretin-deficient human narcolepsy. Neurosci Lett 2003; 341:13.
33. Mayo-- MC, Deng JC, Albores J, et al. Hypocretin Deficiency Associated with Narcolepsy Type 1 and Central Hypoventilation Syndrome in Neurosarcoidosis of the Hypothalamus. J Clin Sleep Med 2015l; 11:1063.
34. Vossler DG, Wyler AR, Wilkus RJ, et al. Cataplexy and monoamine oxidase deficiency in Norrie disease. Neurology 1996; 46:1258.
35. Harsh J, Peszka J, Hartwig G, Mitler M. Night-time sleep and daytime sleepiness in narcolepsy. J Sleep Res 2000; 9:309.
36. Andlauer O, Moore H, Jouhier L, et al. Nocturnal rapid eye movement sleep latency for identifying patients with narcolepsy/hypocretin deficiency. JAMA Neurol 2013; 70:891.
37. Carskadon MA, Dement WC, Mitler MM, et al. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986; 9:519.
38. Roehrs T, Roth T. Multiple Sleep Latency Test: technical aspects and normal values. J Clin Neurophysiol 1992; 9:63.
39. Mitler MM, Van den Hoed J, Carskadon MA, et al. REM sleep episodes during the Multple Sleep Latency Test in narcoleptic patients. Electroencephalogr Clin Neurophysiol 1979; 46:479.
40. Richardson GS, Carskadon MA, Flagg W, et al. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. Electroencephalogr Clin Neurophysiol 1978; 45:621.
41. Drakatos P, Suri A, Higgins SE, et al. Sleep stage sequence analysis of sleep onset REM periods in the hypersomnias. J Neurol Neurosurg Psychiatry 2013; 84:223.
42. Dauvilliers, Y., Arnulf, I., & Mignot, E. (2007). Narcolepsy with cataplexy. Lancet, 369(9560), 499–511.
43. Overeem S, Scammell TE, Lammers GJ. Hypocretin/orexin and sleep: implications for the pathophysiology and diagnosis of narcolepsy. Curr Opin Neurol 2002; 15:739.
44. Capittini C, De Silvestri A, Terzaghi M, et al. Correlation between HLA-DQB1*06:02 and narcolepsy with and without cataplexy: approving a safe and sensitive genetic test in four major ethnic groups. A systematic meta-analysis. Sleep Med 2018; 52:150.
45+46. Szklo-Coxe M, Young T, Finn L, Mignot E. Depression: relationships to sleep paralysis and other sleep disturbances in a community sample. J Sleep Res 2007; 16:297.
47. Ohayon MM. Prevalence of hallucinations and their pathological associations in the general population. Psychiatry Res 2000; 97:153.

Article topic: Neuroleptic Induced Parkinsonism.

Author: Mahmoud Abu Tafesh.

Editor: Ihda Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: drug-induced, tremor, antipsychotic, dopamine receptors, secondary parkinsonism.

INTRODUCTION

Drug-induced parkinsonism is the second most common reason of parkinsonism after Parkinson's disease and their distinction has important implications in terms of management, treatment, and prognosis. (2) However, distinguishing between these conditions can be challenging from the clinical aspect, especially in the initial stages. (2)

Drug-induced parkinsonism (DIP) was initially described as a complication of antipsychotic drugs. Still, it was later recognized as a possible side effect of several other compounds including antiemetics, cholinomimetics, antidepressants, anti-vertigo medications, calcium channel antagonists, antiarrhythmics, and antiepileptic drugs. (3) However, the most common cause of DIP is Neuroleptic Induced Parkinsonism. (4)

Epidemiology

The true prevalence of drug-induced parkinsonism is not confirmed as the case is often under-recognized and epidemiological studies tend to include all categories of parkinsonism or drug-induced movement disorders, rather than drug-induced parkinsonism alone. (5)

The elderly are more prone to developing drug-induced parkinsonism with neuroleptics. (6) In a case-controlled study to evaluate the use of neuroleptic drugs in the 90 days before starting antiparkinson treatment, older people were about 5 times more prone to be commenced on antiparkinson medications while taking neuroleptics compared to non-users. (6) There are 7 Authors who concluded that drug-induced parkinsonism is often misdiagnosed as Parkinson's Disease (PD) in the elderly. Drug-induced parkinsonism develops in almost 100% of patients with HIV infection treated with neuroleptics. (7)

Pathology

The history of Drug-Induced Parkinsonism (DIP) parallels antipsychotics. (8) Parkinsonism as a side effect of chlorpromazine was first reported 3 years after its release. (8) It was soon recognized that all typical antipsychotics had the potential to cause Extra Pyramidal Symptoms (EPS), including parkinsonism, acute dystonia, and akathisia. (8) Typical antipsychotics are chlorpromazine, promazine, haloperidol, perphenazine, fluphenazine, and pimozide. (8) About 80% of patients taking typical antipsychotic drugs show more than one kind of EPS. (8) Dopamine receptors are heavily distributed in the brain, and typical antipsychotics may act on dopamine receptors in the striatum. Therefore, all patients taking antipsychotics have the risk of developing parkinsonism and other EPS. (8) Parkinsonism usually appears days to weeks after starting to take antipsychotics, but in rare cases, the onset delay may be several months or more. (8) Scientists thought that the risk of EPS is low for atypical antipsychotics. (8) Atypical antipsychotics include clozapine, risperidone, olanzapine, aripiprazole, and quetiapine. (8) Scientists originally thought that their low frequency of associated EPS was because of them being more strongly antagonistic toward serotonin-2A receptors than toward dopamine receptors. (8) Scientists have considered this serotonin-dopamine hypothesis a useful model for developing atypical antipsychotics that shows superior antipsychotic efficacy with a lower incidence of EPS compared to typical antipsychotics. (8) The recent "fast-off" theory suggested that their fast dissociation from D2 receptors after they have blocked them can explain their lower risk of EPS. (8)

The reversal of parkinsonism after stopping offending drugs does not indicate the disappearance of underlying pathology. (4) Neuroleptics can unmask preclinical Parkinson's Disease (PD) in patients with insufficient Substantia Nigra (SN) damage for the disease to manifest clinically. (4) Though the mechanism of sustained parkinsonian features after stopping neuroleptics remains to be established, it is uncommon that dopamine receptor block leads to retrograde SN neuronal degeneration. Also, l-dopa does not appear to be toxic to SN. (4)

Clinical presentation and complications

The clinical features of Drug-induced parkinsonism (DIP) are variable but in summary, they include variable tremors, depression, and dementia that may present before the onset of parkinsonism. (9) And the onset of these symptoms is more often in the elderly. (9) The differential diagnosis between DIP and other types of parkinsonism is not always easy and may not be possible based only on the clinical symptoms. (9) idiopathic Parkinson’s Disease (IPD) is characterized by asymmetric involvement of body limbs. Asymmetry is less characteristic of DIP although it may occur. (9) In contrast with vascular parkinsonism, which heavily involves the legs and produces frequent

impairment of gait, DIP produces a less severe gait disorder and a more pronounced 'masked' facial expression. (9)

Parkinsonism has also been related to a series of abused substances. (10) Scientists have associated Alcohol with withdrawal from Parkinsonism. (10) Cocaine is known to cause parkinsonism due to direct vascular damage and is a major risk factor for antipsychotic-induced extrapyramidal side effects. (10)

There is a study that reports that physicians should be aware of DIP as a potential neurological complication after bone marrow transplant (BMT) to avoid further taking of drugs that could aggravate symptoms. (11) The natural course of Neuroleptic induced parkinsonism (NIP) remains unknown, including whether NIP is a risk factor for the later development of tardive dyskinesia. (12)

Diagnosis

Neuroleptic drugs cause basal ganglia side effects which are frequently ignored, misdiagnosed, or mistreated by the patient or physician. (13) Such side effects must be expected, and proper management instituted so that patient compliance with the drug regimen is increased, and the therapeutic relationship is controlled. (13) Side effects can be detected in frequent and complete examinations of the head and neck, limbs, chest, and back. (13) The various medications for drug-induced parkinsonism are reviewed, with an emphasis on the indications for section and the effects of each drug. (13)

The examination of a patient who may have side effects from neuroleptics must be thorough and frequently repeated. (13) That enables the correct treatment to be initiated and the patient's progress to be monitored. (13) Because only one extremity or one muscle group may be affected by drug-induced parkinsonism, the physician must examine each part of the body. (13)

For the head and neck, when side effects are present, the face is characterized by masked facies and rigidity of muscles both at rest and during active movements, such as talking or smiling. (13) But extremities, each limb, and joint should be examined separately. (13) However, in the trunk and other areas, dystonias or muscle contractures can occur in the back, eyes, or one of the extremities. (13)

DSM-5 criteria for Neuroleptic induced Parkinsonism

The DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria for neuroleptic-induced parkinsonism are as follows (14):

A. Development of at least two of the following parkinsonian symptoms: resting tremor, cogwheel rigidity, bradykinesia, and postural instability.

B. Symptoms must develop within four weeks of starting or increasing the dose of a neuroleptic medication or within four weeks of reducing or stopping an effective antiparkinsonian medication.

C. The symptoms must not meet the criteria for dementia with Lewy bodies, Parkinson's disease, or another specific Parkinsonian disorder.

D. Symptoms must cause distress and/or functional impairment.

It is important to note that neuroleptic-induced parkinsonism is a common side effect of many antipsychotic medications, and it is important to monitor individuals for the development of these symptoms when prescribing such medications.

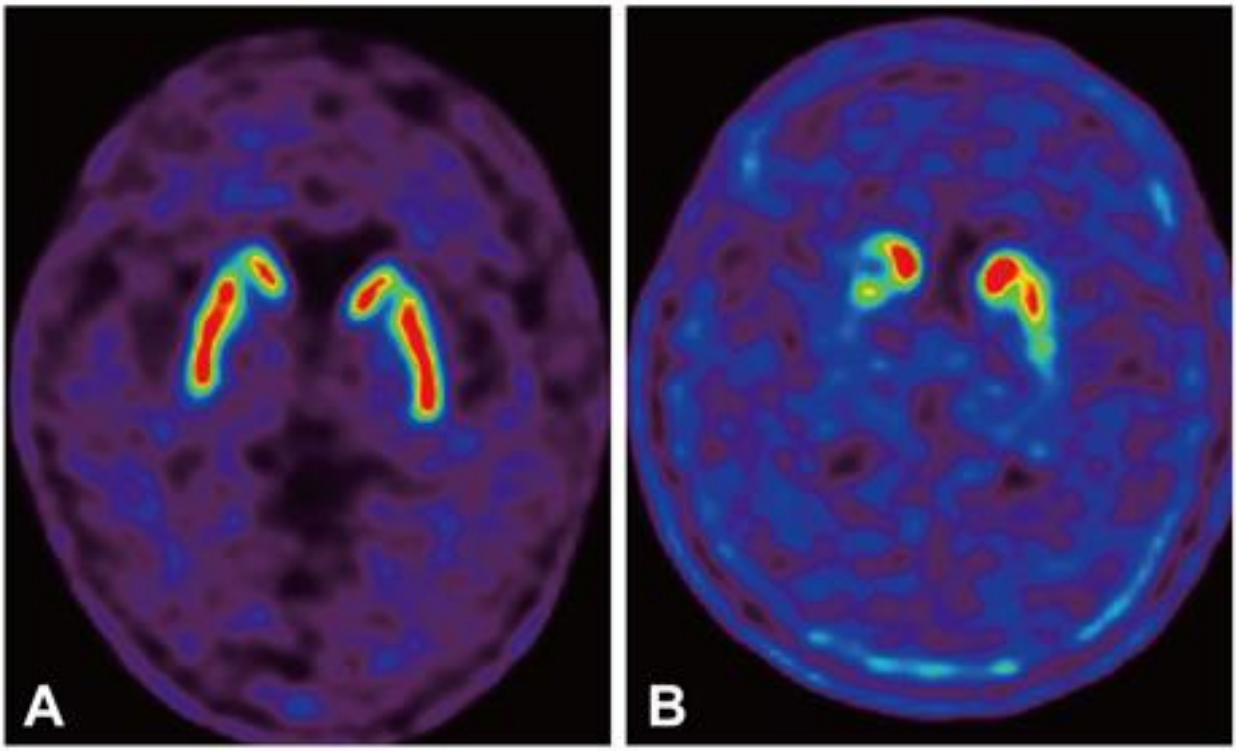


Figure 1: I-FP-CIT PET imaging in two DIP patients. DAT uptake was normal and symmetric in the bilateral striatum in a pure DIP patient (A). In contrast, it decreased severely in the right striatum in a patient who was diagnosed with PD unmasked by DRBAs (B). DAT: dopamine transporter, DIP: drug-induced parkinsonism, DRBA: dopamine receptor blocking agents, PD: Parkinson's disease. (8) [/caption]

Treatment and management

There are three major components in the management of side effects caused by neuroleptic-induced parkinsonism. (13) Which are education and reassurance, a decrease in the dosage of the neuroleptic drug, and the administration of an antiparkinsonian drug. (13)

Patients should be forewarned that side effects may occur and that their appearance is a sign that tells us that the medication is working. (13) Patients should be encouraged to report side effects early. (13) They can be reassured that most side effects remit spontaneously within a few days or weeks, and that medication is available for more serious side effects. (13)

Decreasing the dosage of the neuroleptic drug is often the best approach if the psychosis (on anxiety or impulsivity) that warranted its use is under control. (13) The physician and the patient must weigh the advantages of a decrease in the side effects with the disadvantage of recurrences of symptoms. (13) If the neuroleptic cannot be decreased, then it may be prudent to prescribe medication for the side effects. (13)

It is commonly assumed that all antiparkinsonian agents are equally effective, but there may be significant differences between the drug groups in their effectiveness and side effects. (13) The earliest drugs used for basal ganglia side effects included atropine, belladonna, scopolamine, stramonium, and hyoscine. (13) Even among these older drugs, a differential effect was noticed, with scopolamine and hyoscine more effective for tremors, and atropine and stramonium better for rigidity and dystonias. (13) However, these drugs caused prominent anticholinergic side effects, and today synthetic preparations are more commonly used. (15) Although many of the agents useful in treating Parkinson's disease have been useful for drug-induced parkinsonism, L-dopa has not been very effective because of the dopamine blockade of the neuroleptics. (15)

Class of Antiparkinsonian Drug	Antiparkinsonian Drug	Levodopa Equivalent Dose, mg/100 mg levodopa[a]
Amantadine	Amantadine	100
Anticholinergic agents	Trihexyphenidyl	NA
	Biperiden	NA
	Tropatepine	NA
Catechol-*O*-methyl transferase inhibitors	Entacapone	NA
	Tolcapone	NA
Levodopa	Levodopa + carbidopa/benserazide	100; 75[b]; 133[c]
Piribedil	Piribedil	100
Selegiline	Selegiline	10
Type 1 dopamine agonists[d]	Pramipexole (salt)	1
	Ropinirole	5
	Pergolide	1
Type 2 dopamine agonists[e]	Apomorphine	10
	Bromocriptine	10
	Lisuride	1

Table 1: Antiparkinsonian Drugs Available in France in 2007. (16)

Risk factors

The age and size of hyperechogenic Substantia Nigra (SN), measured by transcranial ultrasound (TCS), seem to be associated with the occurrence and severity of NIP in neuroleptic-treated psychiatric patients. (17)

In contrast, smoking has a certain protecting effect. (18) It is accepted that the prevalence of smoking is increased in psychiatric patients as compared to healthy controls. Studies have reported prevalence rates to vary from 68% (19) to 94%. (18) in schizophrenic patients, while depressed patients showed an elevated lifetime prevalence of smoking with 74% compared to 53% in healthy controls. (20) Concerning the protecting effect, tobacco smoke acts as a brain MAO-B inhibitor. (21) and reduces crucial role by inducing microsomal enzymes, thus, increasing hepatic metabolism. (23) This did not result in higher neuroleptic doses for smokers as other authors reported but was associated with a greater number of prescribed neuroleptic drugs. (17)

Prognosis

Scientists found it difficult to predict the prognosis in patients with DIP. (18) Scientists evaluated whether the combined use of F-N-(3-fluoro propyl)-2 beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane (FP-CIT) positron emission tomography (PET) and cardiac meta-iodobenzylguanidine (MIBG) scintigraphy can be used to help differentiate the prognosis in patients with DIP. (18) Among 20 patients enrolled, only 16 showed normal Dopamine transporter (DAT)uptake and normal myocardial sympathetic innervation. After the withdrawal of the suspected drugs, the patients experienced a clinical remission of parkinsonian motor symptoms in 3 months and did not face any new movement symptoms after at least 2 years of follow-up. (24)

Absence of NIP in psychotic patients receiving adjunctive ECT

A hypothesis is proposed that bilateral electroconvulsive therapy (ECT) protects against neuroleptic-induced parkinsonism and thereby may reduce the risk for the later development of tardive dyskinesia. (25)

References

1. Paras hospitals. PARKINSONISM [Internet]. Available from: https://www.parashospitals.com/blogs/parkinsonism-overview
2. Brigo F, Erro R, Marangi A, Bhatia K, Tinazzi M. Differentiating drug-induced parkinsonism from Parkinson's disease: an update on non-motor symptoms and investigations. Parkinsonism Relat Disord. 2014 Aug;20(8):808–14.
3. Munhoz RP, Bertucci Filho D, Teive HAG. Not all drug-induced parkinsonism is the same: the effect of drug class on motor phenotype. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2017 Feb;38(2):319–24.

4. Shuaib UA, Rajput AH, Robinson CA, Rajput A. Neuroleptic-induced Parkinsonism: Clinicopathological study. Mov Disord. 2016 Mar;31(3):360–5.
5. Thanvi B, Treadwell S. Drug induced parkinsonism: a common cause of parkinsonism in older people. Postgrad Med J. 2009 Jun;85(1004):322–6.
6. Avorn J, Bohn RL, Mogun H, Gurwitz JH, Monane M, Everitt D, et al. Neuroleptic drug exposure and treatment of parkinsonism in the elderly: a case-control study. Am J Med. 1995 Jul;99(1):48–54.
7. Lera G, Zirulnik J. Pilot study with clozapine in patients with HIV-associated psychosis and drug-induced parkinsonism. Mov Disord. 1999 Jan;14(1):128–31.
8. Shin H-W, Chung SJ. Drug-induced parkinsonism. J Clin Neurol. 2012 Mar;8(1):15–21.
9. López-Sendón J, Mena MA, de Yébenes JG. Drug-induced parkinsonism. Expert Opin Drug Saf. 2013 Jul;12(4):487–96.
10. Brust JCM. Substance abuse and movement disorders. Mov Disord. 2010 Oct;25(13):2010–20.
11. Pavletic ZS, Bishop MR, Markopoulou K, Wszolek ZK. Drug-induced parkinsonism after allogeneic bone marrow transplantation. Bone Marrow Transplant. 1996 Jun;17(6):1185–7.
12. Friedman JH. Viewpoint: challenges in our understanding of neuroleptic induced parkinsonism. Parkinsonism Relat Disord. 2014 Dec;20(12):1325–8.
13. Hoffman BF. The diagnosis and treatment of neuroleptic-induced Parkinsonism. Hosp Community Psychiatry. 1981 Feb;32(2):110–4.
14. Association AP. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS [Internet]. 991 p. Available from: file:///C:/Users/Dell/Downloads/Telegram Desktop/American_Psychiatric_Association_Diagnostic_and_Statistical_Manual.pdf
15. MCGEER PL, BOULDING JE, GIBSON WC, FOULKES RG. Drug-induced extrapyramidal reactions. Treatment with diphenhydramine hydrochloride and dihydroxyphenylalanine. JAMA. 1961 Sep;177:665–70.
16. Tzourio C. Antiparkinsonian Drugs Available in France in 2007 [Internet]. 2007. Available from: https://www.researchgate.net/figure/Antiparkinsonian-Drugs-Available-in-France-in-2007_tbl1_51159695
17. Jabs BE, Bartsch AJ, Pfuhlmann B. Susceptibility to neuroleptic-induced parkinsonism--age and increased substantia nigra echogenicity as putative risk factors. Eur Psychiatry. 2003 Jun;18(4):177–81.
18. Hamera E, Schneider JK, Deviney S. Alcohol, cannabis, nicotine, and caffeine use and symptom distress in schizophrenia. J Nerv Ment Dis. 1995 Sep;183(9):559–65.
19. Ziedonis DM, Kosten TR, Glazer WM, Frances RJ. Nicotine dependence and schizophrenia. Hosp Community Psychiatry. 1994 Mar;45(3):204–6.
20. Glassman AH, Helzer JE, Covey LS, Cottler LB, Stetner F, Tipp JE, et al. Smoking, smoking cessation, and major depression. JAMA. 1990 Sep;264(12):1546–9.
21. Aceto MD, Martin BR. Central actions of nicotine. Med Res Rev. 1982;2(1):43–62.
22. Rajput AH, Rozdilsky B, Hornykiewicz O, Shannak K, Lee T, Seeman P. Reversible drug-induced parkinsonism. Clinicopathologic study of two cases. Arch Neurol. 1982 Oct;39(10):644–6.
23. Ereshefsky L, Saklad SR, Watanabe MD, Davis CM, Jann MW. Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. J Clin Psychopharmacol. 1991 Oct;11(5):296–301.
24. Kim J-S, Oh Y-S, Kim Y-I, Yang D-W, Chung Y-A, You I-R, et al. Combined use of 123I-metaiodobenzylguanidine (MIBG) scintigraphy and dopamine transporter (DAT) positron emission tomography (PET) predicts prognosis in drug-induced Parkinsonism (DIP): a 2-year follow-up study. Arch Gerontol Geriatr. 2013;56(1):124–8.
25. Mukherjee S, Debsikdar V. Absence of neuroleptic-induced parkinsonism in psychotic patients receiving adjunctive electroconvulsive therapy. Convuls Ther. 1994 Mar;10(1):53–8.

Article Title: Rumination Disorder.

Author: Lujain Al Badareen.

Editor: Ihda Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: rumination syndrome, eating disorder, Gastric regurgitation, Functional gastrointestinal disorder.

Overview

The term rumination, which refers to both humans and animals, is derived from the Latin ruminor, meaning "to take out of the throat" or "to chew out"[1] it is a normal process in animals known as ruminants, such as cows and goats. [2] Rumination syndrome is a purposeful gastrointestinal sickness characterized by the aid of using repetitive handy regurgitation of lately ingested meals into the mouth, accompanied by the aid of using a brand-new episode of chewing and then swallowing or expelling the bolus, which typically does not taste acidic or bitter because it occurs a few minutes after eating. [3]

Rumination syndrome could have an impact on every child and adult and is classified via Rome IV as functional gastrointestinal disorder criteria and as an eating disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). [4] It can result in significant impairments, including medical complications (eg, tooth damage, weight loss, electrolyte imbalance) and psychosocial complications (eg, avoidance of work or social meals). [5,6]

The diagnosis includes important and common features such as the episode tends to recur until the belching material becomes acidic, and the taste of the regurgitated material is usually pleasant to the patient. [2] Doctors frequently misdiagnose it as refractory gastroesophageal reflux disease or recurrent vomiting, often resulting in a prolonged diagnostic delay. [7]

Epidemiology

The exact prevalence and incidence of rumination disorder are uncertain as different diagnostic criteria are used to diagnose depending on the clinical setting, [8] as well as patients take years to be accurately diagnosed and tend to see many physicians leading to sparse inaccurate data. [2] Even though it is considered a rare disorder, its true

prevalence is most likely underestimated, given the lack of recognition of said pathology by both clinicians and patients. [3]

Using the Rome II criteria, the authors of the Canadian study reported a prevalence of 0.8% (95% confidence interval 0.3%-1.3%) in the general population using the questionnaires. [9] The global prevalence of functional gastrointestinal pathologies, according to the Rome IV criteria, was established in a recently published multicenter study, describing a prevalence of rumination syndrome of 2.8% (3.1% women, 2.5% men) through an online survey and a prevalence of 1.1% (1.4% women, 0.8% men) through personal interviews. [10] The prevalence of rumination syndrome is higher in patients with fibromyalgia or eating disorders and might reach 7-8%. [11]

In a study on a pediatric population from 4 provinces of Sri Lanka, 2,160 children and adolescents, between the ages of 10 and 16 years, were surveyed, using the Rome III criteria, prevalence obtained by questionnaire was 5.1% and was similar in boys and girls (5.1% and 5%, respectively). [3] Rumination syndrome is suspected of playing a more significant role in the treatment-refractory gastrointestinal reflux disease, nausea, and vomiting. [12]

Etiology

The etiology of rumination disorder is multifactorial; However, the proper motives are rarely known. [8] Several risk factors have been associated with the condition, which include all the following:[13]

1. Emotional neglect (infants). [8]
2. Emotional stresses. [14]
3. Presence of mental health diagnoses such as obsessive-compulsive disorder, anxiety, depression, adjustment disorder, post-traumatic stress disorder, and attention deficit-hyperactivity disorder (ADHD). [15]
4. Developmental delay. [8]
5. Fibromyalgia. [11]
6. Rectal evacuation disorder. [7]

Pathophysiology

The pathophysiology of rumination syndrome is not fully understood and involves several overlapping mechanisms, [8] the primary mechanism and key event include an often-unperceived increase in the stimulation of all abdominothoracic muscles during eating or the postprandial period, increasing the intra-abdominal pressure and negative intrathoracic pressure. [8]

Gastroduodenal manometry and more recently the high-resolution esophageal impedance manometry technique have demonstrated this retrograde gastric flow content that reaches the buccal cavity in patients presenting with rumination is produced due to the simultaneous combination of elevated intra-abdominal pressure and negative intrathoracic pressure, resulting in an esophagogastric gradient in the direction of the oral cavity. [3]

In high-resolution postprandial esophageal impedance manometry, gastric pressure follows the ruminative phenomenon, which in most cases is typically greater than 30 mmHg of proximal reflux episodes, ([16] which is associated with upper and lower esophageal sphincter relaxation at the time of gastric pressurization. [3] Those observations reveal that the increase of intra-abdominal pressure, alone, cannot explain the rumination phenomenon and that upper and lower esophageal sphincter relaxation plays a leading role in that process. [17,18]

In the comparison of rumination patients with controls, using the gastric barostat test, the patients with rumination syndrome presented with more nausea and abdominal bloating sensation than the controls. [3] At 4 and 8 mmHg of gastric distension pressure, the lower esophageal sphincter tone was more reduced in those patients than in the controls, suggesting greater gastric sensitivity as well as lower esophageal sphincter relaxation during the gastric distension maneuver. [3] Nonetheless, accommodation and gastric emptying were within normal ranges in most patients with rumination syndrome. [19]

Electromyographic studies of the abdominal muscles have shown that gastric insufficiency is due to the maneuver of sudden contraction of the intercostal muscles, together with the contraction of the anterior abdominal muscles. [20] The simultaneous activation of all abdominothoracic muscles in those patients can be appreciated as a characteristic "R" or retrograde wave on electromyography. [8]

In a group of 5 patients with rumination syndrome, diagnosed by the Rome III criteria, and monitored with high-resolution esophageal impedance manometry and videofluoroscopic recording to evaluate the barrier of the gastroesophageal junction in rumination episodes, the ascension of the gastroesophageal junction was observed from the abdominal cavity to the thoracic cavity, generating a “pseudo-hernia” with gastric content and air. [3] However, the importance of that observation is still being disputed, especially because it has also been described in healthy persons during physical activity. [21] Prevalence of sliding hiatal hernia was seen in 50% of the cohort of both a rumination syndrome group and a gastroesophageal reflux disease group. [16]

According to patterns observed in high-resolution esophageal impedance manometry, there are 3 rumination variants have been described:[16] Primary rumination: characterized by an increase in intra-abdominal pressure that precedes retrograde flow

from the stomach into the esophagus. [3] Secondary rumination: similar to the primary but the increase in abdominal pressure follows an event of gastroesophageal reflux. [3]

Rumination associated with supra gastric belching: produced by a mechanism similar to that of a supra gastric belch, in which the aboral movement of the diaphragm creates subatmospheric pressure in the esophageal body and the upper esophageal sphincter relaxes, the air then enters the esophageal body, which can be seen as increasing in impedance toward the oral cavity, after which the air is rapidly (in less than a second) expelled from the esophageal body and is manifested as a return to baseline impedance. [3]

The increase in intra-abdominal pressure is caused by the expulsion of air and precedes the reverse flow of gastric contents. [3] The maintenance of rumination syndrome is often associated with psychosocial diseases. [8] Several smaller studies suggest that many patients with rumination syndrome have a higher burden of underlying somatic disorders, depression, or even anxiety. [2,22] Rumination might be maintained because it provides (pain) relief or aid in weight control. [23] A pathophysiologically distinguished subtype of rumination syndrome is infantile rumination, which is related to emotional neglect. [24,25]

Diagnosis

Histopathology

Duodenal biopsies were analyzed by Halland et al. [26] from 22 patients diagnosed with rumination and compared with 10 controls. Histological analysis showed that patients with rumination syndrome had mild eosinophilia, and an increased number of intraepithelial lymphocytes compared to controls. [8]

The authors guess that the muscle mechanisms leading to rumination could be in the context of low-grade inflammation, but further research is needed to confirm what the hypothesis said. [27]

Evaluation

According to the ROME-IV criteria for rumination, the diagnosis can be made based on clinical findings without invasive testing. [8] In contrast, the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria require that repeated regurgitation should not be due to a medical condition which most often requires some form of testing for exclusion. [8]

Moreover, as many patients commonly wait years to be accurately diagnosed, some patients are disappointed about the diagnosis of the functional gastrointestinal disorder and objective tests help patients better understand the diagnosis of rumination. [28,29]

The recommended evaluation of patients suspected of having rumination disorder includes:[8]

- Assessment of potential underlying eating disorders. [8]
- Endoscopy and-or CT enterography to exclude mechanical obstruction. [8]
- High-resolution esophageal manometry (HRIM) with impedance testing (children and adults). [8]
- Electromyography [EMG] of the abdominothoracic muscles:[8] will show a characteristic spiking of activity during episodes of rumination. [30]
- Gastric emptying studies and pH studies are not necessary for diagnosis but are recommended if clinical symptoms are atypical. [8]

Diagnostic and Statistical Manual of Mental Disorders (DSM-V) Criteria for Rumination Syndrome

- Repeated belching for at least a month is a hallmark. [8]
- The repeated regurgitation is not due to an underlying general medical condition (e.g., GERD, pyloric stenosis, etc.). [8]
- The behavior does not occur exclusively during anorexia nervosa, bulimia nervosa, binge-eating disorder (BED), or avoidant/restrictive food intake disorder. [8]
- If occurring in the presence of another mental disorder (e.g., intellectual developmental disorder) or general medical condition (including pregnancy), it is severe enough to warrant added clinical attention. [8]

Clinical characteristics

When doctors suspect a patient of having rumination syndrome, the predominant symptom is the rapid 0nset of effortless postprandial regurgitation, typically within 10 minutes of finishing a meal. [31,32] Regurgitation can be produced, even if the patient only ingested liquids, which favors the regurgitation of previously ingested solid foods. [33] Episodes tend to persist for 1 or 2 hours after the meal, and even when they occur within that period, the regurgitated material consists of partially digested foods that are recognizable by their flavor. [3] Regurgitation is often triggered by a sensation of abdominal discomfort. [3]

To distinguish rumination from vomiting, regurgitation episodes in rumination syndrome are usually not preceded by nausea and when a patient vomits, it is difficult to keep the content in the mouth due to the intensity of the impulse, rapidly expelling it. [3]

Some individuals with rumination syndrome have reported postprandial dyspeptic symptoms such as bloating, or heartburn ([34]) and early satiety was reported in 3/4 of patients. [27] Other symptoms, such as heartburn, abdominal pain, diarrhea, and/or constipation, are less frequent but do not rule out the diagnosis. [3] On the other hand, nocturnal regurgitation, dysphagia, or symptoms that are not close to meals make the diagnosis less likely. [33]

In some patients, doctors have described a provocative event before the diagnosis of rumination, such as Illness or psychosocial stress related to divorce, death in the family, or problems at school or work. [35]

Complications

Rumination syndrome is considered a mild disease ([15,36]) but can cause mental and physical problems that affect the patient's quality of life. [35] Frequent regurgitations can also result in significant weight loss (especially in adolescents) and can lead to the diagnosis of an eating disorder in the form of rumination syndrome. [37]

Among the complications associated with this syndrome, dental erosions have been detected in up to 77% of children ([38]) and halitosis has been described as a reason for referral. [15] Research has found that patients with rumination syndrome often have accompanying anxiety, depression, and somatization needing long-term cognitive behavioral therapy to help with symptoms. [8]

Treatment

The therapeutic strategy begins with an adequate explanation to the patients about the nature of the pathology, commenting to them that it corresponds to a benign functional disorder, describing the underlying mechanisms that produce it so that the patients take an active role in the management of the condition. [3]

The available therapies focus on increasing pressure in the lower esophageal sphincter or decreasing gastric pressure produced by the contraction of the striated musculature of the abdominal wall. [3] Diaphragmatic breathing is the first-line treatment. [8] Diaphragmatic breathing reduces the postprandial intragastric pressure and increases the pressure of the gastroesophageal juncture zone, so restoring the pressure gradient to that level. [17] It works by beginning a mechanism that competes with the acquired and unperceived contractions of the abdominothoracic muscles. [8] The patients are

instructed to place one hand on the abdomen and the other on the chest. They are then told to inhale slowly through their nose, only raising the hand on their stomach and keeping the hand on their chest still as they inhale. [3] The patient then exhales slowly through the mouth. [3] Each inhalation and exhalation should be slow and complete, to carry out 6 to 8 respirations per minute. [3] This technique can be taught to patients in either a supine or seated position, "as patients normally eat". [39] The patients are typically instructed to do the diaphragmatic breathing exercises immediately after a meal and continue them for ten to fifteen min or more until the regurgitative sensation is resolved. [3]

Pharmacological treatment for rumination syndrome should be reserved for patients whose initial behavioral therapy has failed. [8] Pauwelle et al. indicated in a small cross-over study that baclofen 10 mg three times a day reduces flow events and improves patient-reported symptoms in rumination syndrome. [40,41] Baclofen is a gamma-aminobutyric acid type B (GABAB) that can reduce the transitory relaxations of the lower esophageal sphincter and increasing the pressure of the lower esophageal sphincter in healthy individuals and patients with gastroesophageal reflux disease. [42,43] Baclofen crosses the blood-brain barrier (BBB) and has a variety of side effects related to the central nervous system, including confusion, dizziness, lightheadedness, sleepiness, weakness, and tremors. [3] In general, a 5 to 10 mg initial dose at bedtime is recommended and can be increased to 10 mg, three times a day, with careful monitoring in relation to secondary effects. [3]

Patients with rumination syndrome have also used Tricyclic antidepressants (TCAs) together with diaphragmatic breathing for at least 3 months. [3] The most widely used tricyclic antidepressant was nortriptyline, starting at a dose of 10 mg at night, with a weekly increase of 10 mg, until achieving symptom improvement, with a minimum of adverse effects. [35] Tack et al. indicated in a cross-over study for functional dyspepsia that buspirone has positive gastric fundus relaxation properties, which might benefit patients with rumination disorder. [25]

Chewing gum use is associated with fewer rumination episodes, but no randomized trials are demonstrating the effectiveness of this intervention. [44,45]

Conclusion

Rumination syndrome is a clinically recognized entity, with lots of clinical criteria included in the Rome IV criteria, ([3] but often, patients with rumination syndrome go undetected and untreated. [24] Diagnosis can often be delayed because of a lack of clinician knowledge to assess for rumination syndrome, and patients can experience protracted symptoms without proper treatment. [24] Treatment is based on a detailed explanation of the condition to the patient and a solid doctor-patient relationship,

encouraging adherence to diaphragmatic breathing exercises with or without biofeedback in referral centers, and using baclofen in second-line treatment. [3]

References

1. Parry-Jones B. Merycism or Rumination Disorder a Historical Investigation and Current Assessment. Vol. 165, British Journal of Psychiatry. 1994.
2. O'brien MD, Bruce BK, Camilleri M. The Rumination Syndrome: Clinical Features Rather Than Manometric Diagnosis. Vol. 108, GASTROENTEROLOGY. 1995.
3. Chahuan J, Rey P, Monrroy H. Rumination syndrome. A review article [Internet]. Vol. 86, Revista de Gastroenterología de México. 2021. Available from: www.elsevier.es/rgmx
4. pubmed-24064412.
5. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. American Psychiatric Association; 2013. 947 p.
6. Drossman DA, Hasler WL. Rome IV - Functional GI disorders: Disorders of gut-brain interaction. Gastroenterology. 2016 May 1;150(6):1257–61.
7. Vijayvargiya P, Iturrino J, Camilleri M, Shin A, Vazquez-Roque M, Katzka DA, et al. Novel association of rectal evacuation disorder and rumination syndrome: Diagnosis, comorbidities, and treatment. United European Gastroenterol J. 2014 Feb 1;2(1):38–46.
8. pubmed-35015429.
9. Thompson WG, Irvine EJ, Pare P, Ferrazzi S, Rance L. Functional Gastrointestinal Disorders in Canada First Population-Based Survey Using Rome II Criteria with Suggestions for Improving the Questionnaire. 2002.
10. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology. 2021 Jan 1;160(1):99-114.e3.
11. Almansa C, Rey E, Sánchez RG, Sánchez ÁÁ, Díaz-Rubio M. Prevalence of Functional Gastrointestinal Disorders in Patients With Fibromyalgia and the Role of Psychologic Distress. Clinical Gastroenterology and Hepatology. 2009 Apr;7(4):438–45.
12. Parkman HP, Yates K, Hasler WL, Nguyen L, Pasricha PJ, Snape WJ, et al. Clinical features of idiopathic gastroparesis vary with sex, body mass, symptom onset, delay in gastric emptying, and gastroparesis severity. Gastroenterology. 2011;140(1):101-115.e10.
13. Fleisher DR. Functional vomiting disorders in infancy: Innocent vomiting, nervous vomiting, and infant rumination syndrome.
14. Malcolm A, Thumshirn MB, Camilleri M, Williams DE. Rumination Syndrome. Mayo Clin Proc [Internet]. 1997 Jul;72(7):646–52. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0025619611635714
15. Levine DF, Wingate DL, Pfeffer JM, Butcher P. Habitual rumination: a benign disorder. Vol. 287, BRITISH MEDICAL JOURNAL. 1983.
16. Kessing BF, Bredenoord AJ, Smout AJPM. Objective manometric criteria for the rumination syndrome. American Journal of Gastroenterology. 2014 Jan;109(1):52–9.
17. Halland M, Parthasarathy G, Bharucha AE, Katzka DA. Diaphragmatic breathing for rumination syndrome: Efficacy and mechanisms of action. Neurogastroenterology and Motility. 2016 Mar 1;28(3):384–91.
18. Tack J, Blondeau K, Boecxstaens V, Rommel N. Review article: The pathophysiology, differential diagnosis and management of rumination syndrome. Vol. 33, Alimentary Pharmacology and Therapeutics. 2011. p. 782–8.
19. Thumshirn M, Camilleri M, Hanson RB, Williams DE, Schei AJ, Kammer PP. Gastric mechanosensory and lower esophageal sphincter function in rumination syndrome. 1998.
20. Barba E, Burri E, Accarino A, Malagelada C, Rodriguez-Urrutia A, Soldevilla A, et al. Biofeedback-guided control of abdominothoracic muscular activity reduces regurgitation episodes in patients with rumination. Clinical Gastroenterology and Hepatology. 2015 Jan 1;13(1):100-106.e1.
21. Gourcerol G, Dechelotte P, Ducrotte P, Leroi AM. Rumination syndrome: When the lower oesophageal sphincter rises. Digestive and Liver Disease. 2011 Jul;43(7):571–4.
22. pubmed-3752757.
23. Thomas JJ, Murray HB. Cognitive-behavioral treatment of adult rumination behavior in the setting of disordered eating: A single case experimental design. International Journal of Eating Disorders. 2016 Oct 1;49(10):967–72.
24. Murray HB, Juarascio AS, Di Lorenzo C, Drossman DA, Thomas JJ. Diagnosis and Treatment of Rumination Syndrome: A Critical Review. Vol. 114, American Journal of Gastroenterology. Wolters Kluwer Health; 2019. p. 562–78.
25. Thumshirn M, Camilleri M, Hanson RB, Williams DE, Schei AJ, Kammer PP. Gastric mechanosensory and lower esophageal sphincter function in rumination syndrome. 1998.
26. Halland M, Talley NJ, Jones M, Murray JA, Cameron R, Walker MM. Duodenal Pathology in Patients with Rumination Syndrome: Duodenal Eosinophilia and Increased Intraepithelial Lymphocytes. Dig Dis Sci. 2019 Mar 15;64(3):832–7.
27. Halland M, Talley NJ, Jones M, Murray JA, Cameron R, Walker MM. Duodenal Pathology in Patients with Rumination Syndrome: Duodenal Eosinophilia and Increased Intraepithelial Lymphocytes. Dig Dis Sci. 2019 Mar 15;64(3):832–7.

28. Rommel N, Tack J, Arts J, Caenepeel P, Bisschops R, Sifrim D. Rumination or belching-regurgitation? Differential diagnosis using oesophageal impedance-manometry. Neurogastroenterology and Motility. 2010 Apr;22(4).
29. Mousa HM, Montgomery M, Alioto A. Adolescent Rumination Syndrome. Vol. 16, Current Gastroenterology Reports. Current Medicine Group LLC 1; 2014. p. 1–6.
30. Barba E, Accarino A, Soldevilla A, Malagelada JR, Azpiroz F. Randomized, Placebo-Controlled Trial of Biofeedback for the Treatment of Rumination. American Journal of Gastroenterology. 2016 Jul 1;111(7):1007–13.
31. Stanghellini V, Chan FKL, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology. 2016 May 1;150(6):1380–92.
32. Cain ME, Doornberg JN, Duit R, Clarnette J, Jaarsma R, Jadav B. High incidence of screw penetration in the proximal and distal tibiofibular joints after intramedullary nailing of tibial fractures—A prospective cohort and mapping study. Injury. 2018 Apr 1;49(4):871–6.
33. Halland M, Pandolfino J, Barba E. Diagnosis and Treatment of Rumination Syndrome. Clinical Gastroenterology and Hepatology. 2018 Oct 1;16(10):1549–55.
34. Tucker E, Knowles K, Wright J, Fox MR. Rumination variations: Aetiology and classification of abnormal behavioural responses to digestive symptoms based on high-resolution manometry studies. Vol. 37, Alimentary Pharmacology and Therapeutics. 2013. p. 263–74.
35. Robles A, Romero YA, Tatro E, Quezada H, McCallum RW. Outcomes of Treating Rumination Syndrome with a Tricyclic Antidepressant and Diaphragmatic Breathing. American Journal of the Medical Sciences. 2020 Jul 1;360(1):42–9.
36. Talley NJ. Rumination Syndrome. Vol. 7, Gastroenterology & Hepatology. 2011.
37. Eckern M, Stevens W, Mitchell J. The Relationship Between Rumination and Eating Disorders. Vol. 26, Int J Eat Disord. 1999.
38. Monagas J, Ritwik P, Kolomensky A, Acosta J, Kay D, Clendaniel L, et al. Rumination Syndrome and Dental Erosions in Children. J Pediatr Gastroenterol Nutr. 2017 Jun 1;64(6):930–2.
39. Chitkara DK, van Tilburg M, Whitehead WE, Talley NJ. Teaching diaphragmatic breathing for rumination syndrome. Vol. 101, American Journal of Gastroenterology. 2006. p. 2449–52.
40. Pauwels A, Broers C, van Houtte B, Rommel N, Vanuytsel T, Tack J. A randomized double-blind, placebo-controlled, cross-over study using baclofen in the treatment of rumination syndrome. American Journal of Gastroenterology. 2018;113(1):97–104.
41. Blondeau K, Boecxstaens V, Rommel N, Farré R, Depeyper S, Holvoet L, et al. Baclofen Improves Symptoms and Reduces Postprandial Flow Events in Patients With Rumination and Supragastric Belching. Clinical Gastroenterology and Hepatology. 2012 Apr;10(4):379–84.
42. Curcic J, Schwizer A, Kaufman E, Forras-Kaufman Z, Banerjee S, Pal A, et al. Effects of baclofen on the functional anatomy of the oesophago-gastric junction and proximal stomach in healthy volunteers and patients with GERD assessed by magnetic resonance imaging and high-resolution manometry: A randomised controlled double-blind study. Aliment Pharmacol Ther. 2014 Nov 1;40(10):1230–40.
43. Lidums I, Lehmann A, Checklin H, Dent J, Holloway RH, Preclinical ǂ, et al. Control of Transient Lower Esophageal Sphincter Relaxations and Reflux by the GABA B Agonist Baclofen in Normal Subjects.
44. Rhine D, Tarbox J. CHEWING GUM AS A TREATMENT FOR RUMINATION IN A CHILD WITH AUTISM. J Appl Behav Anal. 2009 Jun;42(2):381–5.
45. Weakley MM, Petti TA, Karwisch G. Case study: Chewing gum treatment of rumination in an adolescent with an eating disorder. J Am Acad Child Adolesc Psychiatry. 1997;36(8):1124–7.

Article Topic: Avoidant/Restrictive Food Intake Disorder (ARFID).

Author: Zena Amjad Haddadin.

Editor: Ihdaa Mahmoud Bani Khalaf, Sadeen Sameer.

Reviewer: Ethar Hazaimeh.

Keywords: Avoidant, Restrictive food intake, ARFID, nutritional insufficiency, food avoidance.

Overview

Abnormal eating or weight-control behaviors are the hallmarks of eating disorders, which are serious psychiatric conditions. Eating disorders significantly negatively affect physical health and are linked to higher mortality rates than the general population.[1]

The American Psychiatric Association (APA) published the latest Diagnostic and Statistical Manual of Mental Disorders Edition 5 (DSM-5) in May 2013. This updated edition introduces a new classification to eating disorders which includes an additional section "feeding and eating disorders" that replaces and unifies two earlier parts, "eating disorders" and "feeding/eating disorders of infancy or early childhood," found in the DSM-4.[2]

The DSM-4 diagnosis of “feeding and eating disorders of infancy or early childhood” presented a few gaps such as the age restriction of only including children under the age of 6 and the demand for weight loss to be present to make the diagnosis. This problem led to a group of people being left with an “eating disorder not otherwise specified” (EDNOS) diagnosis. Because of that, the DSM-5 includes the new diagnosis “Avoidant restrictive food intake disorder” (ARFID) to cover all age groups.[3] According to the Eating Disorders Consultation Group for revision of the International Classification of Diseases (ICD-10), ARFID is considered one of the 6 main subtypes of “feeding and eating disorders” and it mainly focuses on patients suffering from eating disturbances that are accompanied by clinical and psychosocial consequences.[4]

Epidemiology

A retrospective study was conducted among patients aged between 8 and 18 to evaluate if they meet the DSM-5 diagnostic criteria of avoidant restrictive food intake disorder. The sample included 2,231 patients seeking treatment in 19 different pediatric gastroenterology clinics in Boston between January 1st, 2008, and December 31st, 2008.

The results showed that the prevalence of ARFID among this sample was 1.5% (33 individuals) with more than half of the patients being males (67%).[5] In another retrospective study, the sample targeted patients aged 8-17 years in an eating disorder clinic at a Canadian tertiary care pediatric hospital. The study reviewed cases between January 2000 and May 2017. Of the 1078 patients evaluated, 7% (77) were diagnosed with ARFID, from whom 73% (56) were females.[6]

ARFID's 3-month prevalence was 0.3% in 2014 and 0.3% in 2015, according to Australian interview-based research of males and females aged 15 and older.[7]

Etiology and pathogenesis

Avoidant restrictive food intake disorder is an eating disorder involving food avoidance or restriction that may be driven by one or more of the following factors:[8]

1) lack of interest in food

2) sensitivity to food texture, taste, or smell.

3) A traumatizing experience such as vomiting, choking, or experiencing any form of gastrointestinal distress.

Nevertheless, these behaviors cannot be brought on by a lack of food or by socially acceptable customs; they cannot be driven by a fear of gaining weight or by an excessive value placed on one's appearance, as in anorexia nervosa (AN) or bulimia nervosa (BN); and they cannot be better explained by another medical or psychological condition.[9] Food avoidance or restriction must be more extreme than what would be customary for the co-occurring disease if another medical or psychiatric disorder is present.[3]

In individuals that have had a traumatic food encounter and then started avoiding similar food to prevent it from happening again, the avoidance temporarily lessens worry, but over time it increases anxiety by limiting the chance for future corrective learning to take place. These people frequently tend to anxiety, and their food avoidance extends beyond the index item to comparable foods, then to entire food groups, and in some of the most extreme situations, to avoidance of all solid foods.[8]

A classic example that can be used to demonstrate how all 3 previously mentioned elements can simultaneously take part in developing the disorder would be a young individual who has long-term selective eating (also known as sensory sensitivity) and chronic poor appetite (also known as lack of interest in eating) who experiences abrupt weight loss after an acute choking incident (thus developing a fear of aversive consequences).[10]

However, there may be other motivations contributing to developing this disorder, so it is feared that following these criteria may lead to the neglect of some cases.[9] Moreover, current knowledge of many eating disorders proposes that their cause may be related to both environmental and genetic factors.[11] Studies have shown a close relationship between anorexia nervosa and avoidant restrictive feeding disorder, in fact, many Avoidant restrictive food intake disorder cases end up developing into anorexia nervosa suggesting that both disorders may share a common etiology.[12-14]

Clinical presentation and Diagnosis

Patients exhibiting Avoidant restrictive food intake disorder symptoms frequently seek out general pediatric, endocrinologic, or gastrointestinal (GI) treatments at first since in many cases physical problems like low weight and delayed growth become obvious before disordered eating habits catch attention.[15] ARFID can be misinterpreted for picky eating, but the presence of functional alterations such as concurrently low weight or an inability to grow in line with their developmental trajectory may indicate the presence of an eating disorder.[16]

Signs and Symptoms

The clinical presentation of Avoidant restrictive food intake disorder may greatly vary among patients, it may present as decreased weight, dependence on nutritional supplements or tube feeding to meet calorie needs, nutritional deficiency, and/or psychosocial impairment. As mentioned previously, the person must not have any concerns related to their body image and weight in order to make the diagnosis of ARFID.[9] This explains why ARFID patients are more accepting and cooperative when using nasogastric feeding when compared to anorexia nervosa patients.[14] They may even have the intention to increase their appetite and gain the weight needed to become healthier, indifferent to the body changes they may face.[14]

On physical exam, the clinical signs of ARFID can sometimes resemble those of anorexia nervosa, some of the findings that may be seen include xeroderma, lanugo hair, thin appearance, bradycardia, hypothermia, pale skin, and delayed capillary refill time.[3]

The pediatric age group suffering from ARFID can often be divided according to the duration of their complaints into acute (rapid and recent weight loss after a traumatizing experience), subacute (general abdominal distress and weight loss), and chronic (poor growth and selectivity for a long time).[3]

The current diagnostic criteria stated in the DSM-5 require the presence of at least 1 of the 3 contributing factors mentioned earlier, along with no body weight dissatisfaction.[17] Dietary history, clinical and biological evaluations (such as assessment of dietary intake,

physical examination, and laboratory tests), and the presence of clinical effects on physical health are used to diagnose substantial nutritional deficits in ARFID children.[18]

DSM-5 Diagnostic Criteria[19]

Avoidant Restrictive Food Intake Disorder

1. An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet proper nutritional and/or energy needs associated with one (or more) of the following:
    1. Significant weight loss (failure to achieve expected weight gain or faltering growth in children).
    2. Significant nutritional deficiency.
    3. Dependence on enteral feeding or oral nutritional supplements.
    4. Marked interference with psychosocial functioning.
2. The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.
3. The eating disturbance does not occur exclusively during anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one's body weight or shape is experienced.
4. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder. When the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention.

Comorbidities and Complications

People with eating disorders typically have psychiatric comorbidities (>70%). Mood and anxiety disorders, neurodevelopmental disorders, alcohol, and substance use disorders, and personality disorders are the most typical psychiatric comorbidities.[20] [21] eating disorders are more common in people with diabetes.[16]

Studies have demonstrated that Avoidant restrictive food intake disorder is more commonly seen among males and younger age groups.[22] [23] [13]

When compared to other eating disorders, ARFID showed higher rates of psychiatric comorbidities including OCD, anxiety disorders, learning disability, autism spectrum disorder, and cognitive impairment [2]

The result of the long-term avoidance of a variety of food can eventually lead to the inability to supply the body with its nutritional demands causing insufficient growth and

weight loss. However, this does not mean that low weight is needed to make the diagnosis, research has suggested that an ARFID diagnosis can be made in normal and overweight individuals.[24]

Treatment and management

Early detection of Avoidant restrictive food intake disorder requires a low threshold of suspicion, and treatment planning depends on making the distinction between ARFID and other eating disorders.[3]

Limited data is available about the treatment and management of ARFID cases. However, a few considerations should be kept in mind before starting any treatment. Factors that need to be reviewed include the degree of nutritional insufficiency, the impact of the condition on the patient's social and psychological well-being, any weight changes or growth disturbances, and lastly whether the patient has been struggling with ARFID for a short or prolonged period. Knowing the disorder's duration is crucial since the treatment's success depends on it.[2] Short terms patients tend to have a better prognosis when compared to long-term sufferers. The reason behind this might be that people who have been suffering from this disorder for a brief time still remember how their balanced diet used to be and tend to find it much easier to return to their normal eating habits.[2]

Family-based treatment

Treatment options available include family-based treatment (FBT) which encourages the parents to control the child or adolescent's diet by making sure to increase the quantity and the variability of food in each meal.[25]

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) has also been mentioned in several case reports and case series which involves eating meals regularly, exposure and response prevention, monitoring food intake, and relaxation training.[25] [26] [27] For example, a case study describes the presentation and treatment of a 42-year-old man who claimed to be a restrictive eater throughout his childhood. [28] Since adolescence, he had failed to fulfill the recommended nutritional intake with one meal at night and 10 to 20 standard alcoholic beverages. Ten cognitive behavioral therapy sessions were provided. At the 1-month follow-up, improvements in food intake and alcohol consumption were noticed at the completion of treatment, as well as reductions in depression, anxiety, and stress. However, at the 3-month follow-up, excessive drinking had returned, along with an increase in negative affect and eating-related impairment, suggesting that this population may benefit from longer-term therapy.[28]

Tube feeding

An alternative available for hospitalized ARFID patients is tube feeding. Although it can be vital in certain cases, a study has suggested the risk of developing dependence on tube feeding and how it can negatively affect the patient's oral intake.[29]

Pharmacotherapy

Lastly, studies have suggested the effectiveness of giving drugs as an adjuvant therapy in the treatment of ARFID to ease meal consumption and promote weight gain.[30] [31] [32] In a retrospective study of 14 children and adolescents, an increase in weight was noticed after prescribing mirtazapine to them.[30] Added research showed that mirtazapine use in ARFID patients was associated with a higher rate of weight gain when compared to the use of a standard weight restoration program.[30] In a similar study on 9 patients, the outcome of administering olanzapine was also a significant increase in weight. The effectiveness of D-cycloserine (DCS) was also tested in a double-blind randomized placebo-controlled trial and the results showed that patients given DCS had experienced fewer disturbances when it comes to their mealtime and faster bite swallowing when compared to placebo patients.[25]

Conclusion

Eating disorders are a growing issue that should be seriously addressed and dealt with. Investigations and care should be provided as soon as possible to minimize the complications and to have an overall better outcome. Avoidant restrictive food intake disorder is a new diagnosis that was first introduced in the DSM-5 describing a group of patients that lack body image concerns making it unique from other eating disorders previously mentioned in the DSM-4. Even with growing research, no standard treatment for all ARFID patients is found and little is known about the management of adults.[10]

References

1. Voderholzer U, Haas V, Correll CU, Körner T. Medical management of eating disorders: an update. *Curr Opin Psychiatry*. 2020;33(6):542-553. doi:10.1097/YCO.0000000000000653
2. Zimmerman J, Fisher M. Avoidant/Restrictive Food Intake Disorder (ARFID). *Curr Probl Pediatr Adolesc Health Care*. 2017;47(4):95-103. doi:10.1016/j.cppeds.2017.02.005
3. Mammel KA, Ornstein RM. Avoidant/restrictive food intake disorder: a new eating disorder diagnosis in the diagnostic and statistical manual 5. *Curr Opin Pediatr*. 2017;29(4):407-413. doi:10.1097/MOP.0000000000000507
4. Kurz S, van Dyck Z, Dremmel D, Munsch S, Hilbert A. Early-onset restrictive eating disturbances in primary school boys and girls. *Eur Child Adolesc Psychiatry*. 2015;24(7):779-785. doi:10.1007/s00787-014-0622-z
5. Eddy KT, Thomas JJ, Hastings E, et al. Prevalence of DSM-5 avoidant/restrictive food intake disorder in a pediatric gastroenterology healthcare network. *Int J Eat Disord*. 2015;48(5):464-470. doi:10.1002/eat.22350
6. Norris ML, Spettigue W, Hammond NG, et al. Building evidence for the use of descriptive subtypes in youth with avoidant restrictive food intake disorder. *Int J Eat Disord*. 2018;51(2):170-173. doi:10.1002/eat.22814

7. Hay P, Mitchison D, Collado AEL, González-Chica DA, Stocks N, Touyz S. Burden and health-related quality of life of eating disorders, including Avoidant/Restrictive Food Intake Disorder (ARFID), in the Australian population. *J Eat Disord*. 2017;5:21. doi:10.1186/s40337-017-0149-z
8. Brigham KS, Manzo LD, Eddy KT, Thomas JJ. Evaluation and Treatment of Avoidant/Restrictive Food Intake Disorder (ARFID) in Adolescents. *Curr Pediatr Rep*. 2018;6(2):107-113. doi:10.1007/s40124-018-0162-y
9. Katzman DK, Norris ML, Zucker N. Avoidant Restrictive Food Intake Disorder. *Psychiatr Clin North Am*. 2019;42(1):45-57. doi:10.1016/j.psc.2018.10.003
10. Thomas JJ, Lawson EA, Micali N, Misra M, Deckersbach T, Eddy KT. Avoidant/Restrictive Food Intake Disorder: a Three-Dimensional Model of Neurobiology with Implications for Etiology and Treatment. *Curr Psychiatry Rep*. 2017;19(8):54. doi:10.1007/s11920-017-0795-5
11. Bulik CM. Exploring the gene-environment nexus in eating disorders. *J Psychiatry Neurosci*. 2005;30(5):335-339.
12. Kennedy HL, Dinkler L, Kennedy MA, Bulik CM, Jordan J. How genetic analysis may contribute to the understanding of avoidant/restrictive food intake disorder (ARFID). *J Eat Disord*. 2022;10(1):53. doi:10.1186/s40337-022-00578-x
13. Norris ML, Robinson A, Obeid N, Harrison M, Spettigue W, Henderson K. Exploring avoidant/restrictive food intake disorder in eating disordered patients: a descriptive study. *Int J Eat Disord*. 2014;47(5):495-499. doi:10.1002/eat.22217
14. Kennedy GA, Wick MR, Keel PK. Eating disorders in children: is avoidant-restrictive food intake disorder a feeding disorder or an eating disorder and what are the implications for treatment? *F1000Research*. 2018;7:88. doi:10.12688/f1000research.13110.1
15. Schöffel H, Hiemisch A, Kiess W, Hilbert A, Schmidt R. Characteristics of avoidant/restrictive food intake disorder in a general paediatric inpatient sample. *Eur Eat Disord Rev J Eat Disord Assoc*. 2021;29(1):60-73. doi:10.1002/erv.2799
16. Treasure J, Duarte TA, Schmidt U. Eating disorders. *Lancet (London, England)*. 2020;395(10227):899-911. doi:10.1016/S0140-6736(20)30059-3
17. Bryant-Waugh R. Avoidant/Restrictive Food Intake Disorder. *Child Adolesc Psychiatr Clin N Am*. 2019;28(4):557-565. doi:10.1016/j.chc.2019.05.004
18. Feillet F, Bocquet A, Briend A, et al. Nutritional risks of ARFID (avoidant restrictive food intake disorders) and related behavior. *Arch Pediatr*. 2019;26(7):437-441. doi:10.1016/j.arcped.2019.08.005
19. Zvolensky MJ, Garey L, Shepherd JM, Eifert GH. *Somatic Symptom and Related Disorders*.; 2019. doi:10.4324/9780429028267-15
20. Keski-Rahkonen A, Mustelin L. Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences, and risk factors. *Curr Opin Psychiatry*. 2016;29(6):340-345. doi:10.1097/YCO.0000000000000278
21. Udo T, Grilo CM. Psychiatric and medical correlates of DSM-5 eating disorders in a nationally representative sample of adults in the United States. *Int J Eat Disord*. 2019;52(1):42-50. doi:10.1002/eat.23004
22. Fisher MM, Rosen DS, Ornstein RM, et al. Characteristics of avoidant/restrictive food intake disorder in children and adolescents: a "new disorder" in DSM-5. *J Adolesc Heal Off Publ Soc Adolesc Med*. 2014;55(1):49-52. doi:10.1016/j.jadohealth.2013.11.013
23. Nicely TA, Lane-Loney S, Masciulli E, Hollenbeak CS, Ornstein RM. Prevalence and characteristics of avoidant/restrictive food intake disorder in a cohort of young patients in day treatment for eating disorders. *J Eat Disord*. 2014;2(1):21. doi:10.1186/s40337-014-0021-3
24. Białek-Dratwa A, Szymańska D, Grajek M, Krupa-Kotara K, Szczepańska E, Kowalski O. ARFID-Strategies for Dietary Management in Children. *Nutrients*. 2022;14(9). doi:10.3390/nu14091739
25. Thomas JJ, Wons OB, Eddy KT. Cognitive-behavioral treatment of avoidant/restrictive food intake disorder. *Curr Opin Psychiatry*. 2018;31(6):425-430. doi:10.1097/YCO.0000000000000454
26. Thomas JJ, Brigham KS, Sally ST, Hazen EP, Eddy KT. Case 18-2017 - An 11-Year-Old Girl with Difficulty Eating after a Choking Incident. *N Engl J Med*. 2017;376(24):2377-2386. doi:10.1056/NEJMcpc1616394
27. Bryant-Waugh R. Avoidant restrictive food intake disorder: an illustrative case example. *Int J Eat Disord*. 2013;46(5):420-423. doi:10.1002/eat.22093
28. Steen E, Wade TD. Treatment of co-occurring food avoidance and alcohol use disorder in an adult: Possible avoidant restrictive food intake disorder? *Int J Eat Disord*. 2018;51(4):373-377. doi:10.1002/eat.22832
29. Dovey TM, Wilken M, Martin CI, Meyer C. Definitions and Clinical Guidance on the Enteral Dependence Component of the Avoidant/Restrictive Food Intake Disorder Diagnostic Criteria in Children. *JPEN J Parenter Enteral Nutr*. 2018;42(3):499-507. doi:10.1177/0148607117718479
30. Gray E, Chen T, Menzel J, Schwartz T, Kaye WH. Mirtazapine and Weight Gain in Avoidant and Restrictive Food Intake Disorder. *J Am Acad Child Adolesc Psychiatry*. 2018;57(4):288-289. doi:10.1016/j.jaac.2018.01.011
31. Brewerton TD, D'Agostino M. Adjunctive Use of Olanzapine in the Treatment of Avoidant Restrictive Food Intake Disorder in Children and Adolescents in an Eating Disorders Program. *J Child Adolesc Psychopharmacol*. 2017;27(10):920-922. doi:10.1089/cap.2017.0133
32. Sharp WG, Allen AG, Stubbs KH, et al. Successful pharmacotherapy for the treatment of severe feeding aversion with mechanistic insights from cross-species neuronal remodeling. *Transl Psychiatry*. 2017;7(6):e1157. doi:10.1038/tp.2017.126

Article topic: Female Sexual Interest / Arousal Disorder.

Author name: Mailaa Obeidat.

Editor name: Ihda Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: Female sexual interest, arousal disorder, Hypoactive sexual desire disorder.

Introduction

Attention is considered to be an important part of the sexual stimulation cycle, and researchers have differentiated between the roles of initial (involuntary) and subsequent (voluntary) attention paid to sexual stimuli as part of the facilitation of sexual desire. (1) Sexual problems affect people of all genders and ages, with prevalence being especially high among women. (2) Low sexual desire is a type of female sexual dysfunction known as hypoactive sexual desire disorder or sexual interest/arousal disorder (FSD). (3) Women benefit from behavioral and pharmacological interventions. (4) The first struggle in providing this benefit is the detection and diagnosis of the disorder. (4) However, the private and personal nature of the sexual activity and the potential for feelings of shame, inadequacy, and embarrassment create unique challenges to effective communication about sexual health for both patient and doctor. (4) However, hypoactive sexual desire disorder (HSDD) was subdivided into male hypoactive sexual interest disorder and female sexual interest or arousal disorder. (4)

Epidemiology

The most common sexual disorder affecting women in the US is known as hypoactive sexual desire disorder (HSDD), which is characterized by a lack of or decline in sexual fantasies and desire that is linked to distress. (4) HSDD affects about one in ten premenopausal women and is more common than a major depressive disorder (MDD), which has a prevalence rate of 7.1%. (4) Furthermore, HSDD has a neurobiological basis in the dysregulation of sex hormones and neurotransmitters and can result in significant psychological problems, sexual distress, and impact on the mental and emotional well-being of women and their partners. (5)

8.9% of women between the ages of 18 and 44, 12.3% between the ages of 45 and 64, and 7.4% of women over 65 have HSDD. (4) Although low sexual interest rises with age, distress falls; therefore, the prevalence of HSDD stays constant with age. (4)

Etiology and Pathogenesis

Postmenopausal estrogen deficiency leads to changes in urogenital tissue. (6) Sexual dysfunction and urinary dysfunction are the most inevitable but least publicized problems of estrogen deficiency, and these are important quality-of-life issues that patients and healthcare providers are often reluctant to discuss. (6) In addition to estrogen deficiency, oophorectomies women may suffer from androgen deficiency and problems with libido. (6) While the relationship with one's partner is the quintessential factor in female sexuality, hormone deficiency is important, especially in reference to genital atrophy. (6)

Moreover, sexual function can be directly or indirectly impacted by pregnancy, alcohol or nicotine consumption, pelvic organ prolapse, urinary incontinence, post-menopause, stress, mood disorders, body image problems, low self-esteem, feelings of inadequacy, age, level of education, the quality of long-term relationship with the partner, chronic or neurological diseases, and side effects of cancer treatment (adjuvant or neoadjuvant). (7)

Most women with breast cancer have negative feelings and psychopathological, biological, and social symptoms, such as anger, fear, fatigue, mood, sleep, and sexual disorders. Moreover, a cancer treatment that involves surgical interventions, neoadjuvant chemotherapy, anti-hormonal therapy, radiation, or targeted therapies, may result in psychosocial effects and sexual dysfunctions. (8)

Risk factors

Consistently significant risk factors for female sexual problems were poor physical health, poor mental health, stress, abortion, genitourinary diseases, female genital mutilation, relationship dissatisfaction, sexual abuse, and being religious. (16) Consistently important protective factors included: older age at marriage, exercising, daily affection, intimate communication, having a positive body image, and sex education. Some factors had an unclear effect: age, education, employment, parity, being in a relationship, frequency of sexual intercourse, race, alcohol consumption, smoking, and masturbation. (16)

Diagnosis

There is no consensus as to the routine diagnostic algorithm for females with sexual dysfunction. (9) The basic features of diagnosis include history (sexual, psychosocial, and medical), physical examination (external and internal genitalia), psychologic interview (psychologic issues, partner relationship), and laboratory testing (estrogen,

testosterone, glucose, CBC, creatinine, LFTs, cholesterol, UA, Pap smear, vaginal cultures as considered proper). (9) Patient (and partner) education (anatomy, physiology, epidemiology, risk factors, etc.) as well as reversing modifiable causes such as medical conditions, medication-related sexual dysfunction, and lifestyle changes should be performed prior to the initiation of treatment. (9)

DSM-5

HSDD and female sexual arousal disorder (FSAD) are combined into a single syndrome called female sexual interest/arousal disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) fifth edition (FSIAD). (10) FSIAD is defined in the DSM-5 as significantly reduced sexual interest/arousal as manifested by one of the three following characteristics for a minimum of six months: (11)

1. no/reduced interest in sexual activity.

2. no/reduced sexual/erotic thoughts.

3. absent/reduced initiation of sexual activity and unreceptive to partner's attempts to initiate.

4. no /reduced sexual excitement/pleasure during sexual activity in almost all or all (75-100%) sexual encounters.

5. no / reduced sexual interest/arousal in response to internal or external sexual/erotic cues (written, verbal, visual).

6.no/reduced genital or nongenital sensations during sexual activity in almost all or all (75-100%) sexual encounters.

Clinical Presentation

Because FSIAD is a new diagnosis, there are few studies describing the consequences experienced by women with it. (17) Women with FSIAD may resemble those who have previously been diagnosed with hypoactive sexual desire disorder (HSDD) and female sexual arousal disorder, but recent research suggests that their symptoms are more severe than those of those who meet the earlier standards for HSDD. (18) In the limited studies available, women with FSIAD reported lower health-related quality of life, including more depressive symptoms, and lower sexual and relationship satisfaction compared with healthy control subjects. (19). Moreover, interpersonal factors reported by women, like a partner's sexual difficulties and poor sexual compatibility, play a critical role in women's experience of low desire. (20) Arousal disorders have a

biopsychosocial etiology and are frequently present in conjunction with other sexual issues. (21)

Treatment

As the underlying reason for decreased sexual desire may be multifactorial, a proper treatment plan may be multifaceted. Psychosocial, behavioral, and biological causes and contributing factors are all potential targets of intervention. (4)

Sex therapy, psychotherapy, (11), and the treatment of postmenopausal women's vulvovaginal atrophy, vaginal dryness, and dyspareunia are modalities that may directly benefit patients. (12) The role of the primary care physician and the threshold for referral to a behavioral health doctor or sexual medicine expert will depend upon the clinician’s comfort and interest in treating sexual problems, the patient’s willingness to see other clinicians, and the cost and availability of sexual medicine consultation. (4)

Knowledge and communication between partners are essential foundations for any intervention. (13) It is necessary to assess the patient’s and partner’s beliefs about sex and sexual functioning, address myths and mistaken beliefs, and enhance understanding with essential and correct information about sex and sexual functioning. (13) Also, it is essential to assess the patient’s ability to communicate their experience, feelings, and preferences with their partners. (4) Upon this foundation, efforts to reduce inhibitory processes can focus on, among other things, negative beliefs and feelings about sex, body image concerns, problems with relationships, including pressure to perform, or general deficits in a loving environment in which the woman feels safe and valued. (13)

Visibly, influencing the excitatory and inhibitory neuromodulatory processes affecting sexual responsiveness by psychopharmacological drugs may be a tool to treat FSIAD. (14) The search for drugs that can facilitate sexual interest and arousal—also called aphrodisiacs—has a long history. (14)

Flibanserin has recently been approved in the United States for treating HSDD in premenopausal women. (15) Flibanserin is a centrally acting postsynaptic 5-HT1A (serotonin) receptor agonist and a 5-HT2A antagonist that produces a decrease in serotonin activity and an increase in dopamine and norepinephrine activity in brain pathways associated with sexual desire. (15) In several large trials in women with a diagnosis of hypoactive sexual desire disorder, it was shown that the use of flibanserin (compared to a placebo) resulted in a significantly larger increase in the number of monthly so-called “satisfying sexual events” (SSEs). (15)

Conclusion

Basic science and clinical research in FSD are needed to overcome the gender gap, achieve a more balanced therapeutic perspective between psychologic and physiologic factors, and give female patients an enhanced opportunity for relief from a persistent or recurrent sexual condition that causes personal distress. (9)

References

1. Bradshaw J, Brown N, Kingstone A, Brotto L. Asexuality vs. sexual interest/arousal disorder: Examining group differences in initial attention to sexual stimuli. PLoS One. 2021;16(12):e0261434.
2. Jabs F, Brotto LA. Examining the Treatment Relevance of the Approach-Avoidance Motivation Model for Sexual Interest/Arousal Disorder in Women and Non-Binary Individuals. J Sex Res. 2022 Nov;1–12.
3. Witherow-Párkányi M. Female sexual interest/arousal disorder: history of diagnostic considerations and their implications for clinical practice. Psychiatr Hung. 2022;37(2):133–49.
4. Parish SJ, Hahn SR. Hypoactive Sexual Desire Disorder: A Review of Epidemiology, Biopsychology, Diagnosis, and Treatment. Sex Med Rev. 2016 Apr;4(2):103–20.
5. Kingsberg SA, Clayton AH, Pfaus JG. The Female Sexual Response: Current Models, Neurobiological Underpinnings and Agents Currently Approved or Under Investigation for the Treatment of Hypoactive Sexual Desire Disorder. CNS Drugs. 2015 Nov;29(11):915–33.
6. Freedman MA. Female sexual dysfunction. Int J Fertil Womens Med. 2002;47(1):18–21.
7. Sousa Rodrigues Guedes T, Barbosa Otoni Gonçalves Guedes M, de Castro Santana R, Costa da Silva JF, Almeida Gomes Dantas A, Ochandorena-Acha M, et al. Sexual Dysfunction in Women with Cancer: A Systematic Review of Longitudinal Studies. Int J Environ Res Public Health. 2022 Sep;19(19).
8. Lim-Watson MZ, Hays RD, Kingsberg S, Kallich JD, Murimi-Worstell IB. A Systematic Literature Review of Health-related Quality of Life Measures for Women with Hypoactive Sexual Desire Disorder and Female Sexual Interest/Arousal Disorder. Sex Med Rev. 2022 Jan;10(1):23–41.
9. Goldstein I. Female sexual arousal disorder: new insights. Int J Impot Res. 2000 Oct;12 Suppl 4:S152-7.
10. First MB. Diagnostic and statistical manual of mental disorders, 5th edition, and clinical utility. Vol. 201, The Journal of nervous and mental disease. United States; 2013. p. 727–9.
11. Parish SJ, Cottler-Casanova S, Clayton AH, McCabe MP, Coleman E, Reed GM. The Evolution of the Female Sexual Disorder/Dysfunction Definitions, Nomenclature, and Classifications: A Review of DSM, ICSM, ISSWSH, and ICD. Sex Med Rev. 2021 Jan;9(1):36–56.
12. Tan O, Bradshaw K, Carr BR. Management of vulvovaginal atrophy-related sexual dysfunction in postmenopausal women: an up-to-date review. Menopause. 2012 Jan;19(1):109–17.
13. Leiblum SR, Wiegel M. Psychotherapeutic interventions for treating female sexual dysfunction. World J Urol. 2002 Jun;20(2):127–36.
14. Both S. Recent Developments in Psychopharmaceutical Approaches to Treating Female Sexual Interest and Arousal Disorder. Curr Sex Heal reports. 2017;9(4):192–9.
15. Katz M, DeRogatis LR, Ackerman R, Hedges P, Lesko L, Garcia MJ, et al. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. J Sex Med. 2013 Jul;10(7):1807–15.
16. McCool-Myers M, Theurich M, Zuelke A, Knuettel H, Apfelbacher C. Predictors of female sexual dysfunction: a systematic review and qualitative analysis through gender inequality paradigms. BMC Womens Health. 2018 Jun;18(1):108.
17. Rosen NO, Dubé JP, Corsini-Munt S, Muise A. Partners Experience Consequences, Too: A Comparison of the Sexual, Relational, and Psychological Adjustment of Women with Sexual Interest/Arousal Disorder and Their Partners to Control Couples. J Sex Med. 2019 Jan;16(1):83–95.
18. O'Loughlin JI, Basson R, Brotto LA. Women with Hypoactive Sexual Desire Disorder Versus Sexual Interest/Arousal Disorder: An Empirical Test of Raising the Bar. J Sex Res. 2018;55(6):734–46.
19. Sarin S, Amsel R, Binik YM. A Streetcar Named "Derousal"? A Psychophysiological Examination of the Desire-Arousal Distinction in Sexually Functional and Dysfunctional Women. J Sex Res. 2016;53(6):711–29.
20. Witting K, Santtila P, Varjonen M, Jern P, Johansson A, von der Pahlen B, et al. Female sexual dysfunction, sexual distress, and compatibility with partner. J Sex Med. 2008 Nov;5(11):2587–99.
21. Giraldi A, Rellini AH, Pfaus J, Laan E. Female sexual arousal disorders. J Sex Med. 2013 Jan;10(1):58–73.

Article Topic: Anorexia Nervosa.

Author: Ala' Moh'd Al Barbarawi.

Editor: Ihda Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Omar Sanduka, Ethar Hazaimeh.

Keywords: Psychiatry, Mental Illness, Eating disorders, Anorexia Nervosa.

Overview

Anorexia Nervosa is a serious mental disorder that can affect individuals of all ages, races, and genders. [1] It primarily affects young women in adolescence and can continue into adulthood. [2] Individuals suffering from this disorder have an intense fear of weight gain and a disturbed body image, which drives severe dietary restrictions or other abnormal weight loss behaviors such as purging or excessive physical activity. [1,4-6]

Definition

Anorexia nervosa is defined as the restriction of energy intake compared to body requirements, which leads to significantly low body weight that is not contributable to organic causes. Individuals with this illness also display an intense fear of gaining weight and have behaviors that interfere with weight gain. [4]

Epidemiology

According to the DSM 5, the 12-month prevalence among young females is around 0.4% [4] while the lifetime prevalence in women is 2-4%. [7-9] The female-to-male ratio is 10:1, although there are fewer studies on anorexia nervosa in males. [4] This disorder is most seen in the age group between 10 to 25 years. [10]

Comorbidity

Comorbidities include bipolar, depressive, and anxiety disorders. Obsessive-compulsive disorder (OCD) is described in patients with the restricting subtype of anorexia nervosa. On the other hand, in the binge-eating/purging subtype, alcohol and other substance use disorders may be comorbid. [4]

Suicide Risk

The suicide rate is reported to be 12 per 100,000 per year. Patients with anorexia nervosa should be evaluated for suicide-related ideation and behaviors as well as other risk factors for suicide, including a history of suicide attempt(s). [4]

Pathogenesis

Several factors contribute to the etiology of Anorexia Nervosa.

Genetic Factors

Studies show a strong familial correlation and heritability. Three Genome-Wide Association Studies [11] (GWAS) have been published where multiple gene mutations were found. In the Duncan et al. study, the genome-wide significant finding showed a mutation in the ERBB3 gene. [12]

Neurobiological Factors

- ### Neurocognition and Social Cognition

There are multiple neurocognitive markers for this mental illness including difficulties switching between different tasks or task demands [13] and poor central coherence (i.e., a preference for local, "detail-focused" over global, "bigger picture" processing). [14] Evidence suggests that the stage, duration, and severity of the illness affect the performance of the individual. [15] Affected people also suffer in socio-emotional processing, showing attentional biases, impaired emotion recognition, regulation and expressivity, and poor theory of mind. [16]

- ### Structural Neuroimaging

Patients have been reported to have global reductions in grey and white matter, increased cerebrospinal fluid, and decreased grey matter in the left hypothalamus, reward-related regions of the basal ganglia, and the somatosensory cortex. [14]. Studies done on recovered patients before and after treatment suggest that brain tissue abnormalities may recover with weight regain. [17,18]

Developmental factors

Developmental risk factors include adverse prenatal and neonatal events, such as dysmaturity or prematurity, [19,20] as well as feeding and sleeping difficulties in infancy.

[20] Other risk factors include personality traits associated with anxiety, depression, perfectionism, and autism spectrum. [20] The hormonal changes and dysregulations that occur during puberty and adolescence represent the period of the first onset of anorexia nervosa. [21]

Environmental factors

Females are at higher risk for anorexia nervosa. [20] The illness is increasing in low-income and middle-income countries, which may be due to cultural transitions associated with industrialization, urbanization, and globalization. [8] Another risk factor is body dissatisfaction which is linked to the development of any eating disorder. [22] Despite the worldwide sociocultural pressures to be thin, the incidence of anorexia nervosa in women is low. [23]

DSM-5 Diagnostic Criteria [4]

1. Restriction of energy intake compared to requirements leads to significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than minimally expected.
2. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
3. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Coding note

The ICD-9-CM code for anorexia nervosa is 307.1, which is assigned regardless of the subtype. The ICD-10-CM code depends on the subtype:

- (F50.01) Restricting type: During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.
- (F50.02) Binge-eating/purging type: During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Specify if:

- **In partial remission:** After full criteria for anorexia nervosa were previously met, Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met.
- **In full remission:** After full criteria for anorexia nervosa were previously met, none of the criteria have been met for a sustained period.

Specify current severity

The minimum level of severity is based, for adults, on the current body mass index (BMI) (see below) or, for children and adolescents, on the BMI percentile. The ranges below are derived from World Health Organization categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used. The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision.

- **Mild**: BMI ≥ 17 kg/m2
- **Moderate**: BMI 16–16.99 kg/m2
- **Severe**: BMI 15–15.99 kg/m2
- **Extreme**: BMI < 15 kg/m2

Diagnostic Markers [4]

- **Hematology**: Leukopenia with a decrease in all cell types, but usually with apparent lymphocytosis. Mild anemia and thrombocytosis, and rarely bleeding problems
- **Serum chemistry:** elevated blood urea nitrogen reflecting dehydration. Hypomagnesemia, hypozincemia, hypophosphatemia, and hyperamylasemia can be observed. Hyperchloremic, hypokalemic metabolic alkalosis can be caused by self-induced vomiting while mild metabolic acidosis is observed in laxative abuse.
- **Endocrine**: T3 levels are decreased, while T4 is in normal-low range. Low estrogen in females and low testosterone in males.
- **ECG**: Sinus bradycardia is common, and significant prolongation in QTc is seen in some patients.
- **Bone mass**: The risk of fracture is significantly elevated due to low bone mineral density.
- **Resting energy expenditure**: significant reduction.
- **Physical signs and symptoms**: caused by starvation. Amenorrhea is common which is a consequence of weight loss. In prepubertal females, menarche may be delayed. Other complaints include constipation, abdominal pain, cold intolerance, and lethargy. The most remarkable finding is emaciation. Hypotension, hypothermia, and bradycardia are commonly present. Salivary

gland hypertrophy and dental enamel erosions can be caused by self-induced vomiting.

Treatment

There are multiple treatment modalities including behavioral, pharmacological, and nutritional treatments that can be implemented for adolescent and adult patients.

Behavioral treatments

Family-based treatment (FBT) Family-based treatment

FBT is a three-phase treatment for adolescent patients and their families over 16 1-hour sessions and 9 months (initially of 10h for 6 months).

- First phase: therapy is focused on attempts to absolve the parents from the responsibility of causing the disorder and complimenting them on the positive aspects of their parenting.
- Second phase: parents were helped to transition eating and weight control back to the adolescent in an age-appropriate manner.
- Third phase: focused on establishing a healthy relationship between the adolescent and the parents. 24 1-h sessions were provided over the 1 year. [24]

Specialist supportive clinical management (SSCM)

This modality combines clinical management (i.e., giving information, advice, and encouragement) with a supportive therapy designed to build a positive therapeutic relationship and to influence change. The content includes assessment, identification, and regular review of target symptoms; psychoeducation; monitoring of physical status; establishing a goal weight range; and nutritional education and advice. [25]

- Maudsley model of anorexia treatment for adults (MANTRA) This treatment is based on cognitive-interpersonal treatment. It proposes that these four broad factors are central to the maintenance of anorexia nervosa [26]:

1. A thinking style characterized by inflexibility, excessive attention to detail, and fear of making mistakes, [27]
2. Socio-emotional impairment (e.g., avoidance of emotional experience, regulation, and expression)
3. Positive beliefs on how the mental disorder helps the person in their life.
4. Unhelpful reactions of close others (e.g., overinvolvement, criticism, accommodation to symptoms).

These aspects are targeted in treatment, to improve weight, the eating disorder and other symptoms, and psychosocial adjustment. The treatment style is motivational. [26]

- **Enhanced cognitive behavior therapy (CBT-E):** this is a personalized approach for eating disorders consisting of four stages. Stage one is focused on gaining a mutual understanding of the person's eating problem and helping him or her modify and stabilize their pattern of eating. In stage two, progress is systematically reviewed, and plans are made for the main treatment. Stage three focuses on the processes that are maintaining the person's eating problem (e.g., addressing concerns about shape and eating). In stage four, the emphasis shifts to the future. [28]
- Focal psychodynamic psychotherapy (FPT): At the beginning of this treatment, the therapist identifies psychodynamic relevant foci using a standardized psychodynamic diagnostic interview (OPD-II). It is divided into three treatment phases. Phase one focuses mainly on pro-anorectic behavior, ego-syntonic beliefs (attitudes and behavior viewed as acceptable), and self-esteem. Phase two focuses on relevant relationships and the association between interpersonal relationships and eating (anorectic) behavior. The last phase consists of the transfer to everyday life, treatment termination, and parting. The patient's weight is assessed and documented before every treatment session. [29]

Pharmacological Treatment

According to systematic reviews, antidepressants neither improve weight gain nor reduce eating disorders. [31] Other drugs that are currently under investigation include tumor necrosis factor, dronabinol (a cannabinoid receptor agonist), and ghrelin agonists to promote appetite. [32]

Nutritional Treatment

Dieticians are an important part of a multidisciplinary treatment team. Admission or a day-patient eating disorder unit is indicated in patients who are underweight and malnourished. [33] They should receive a combined program of supervised refeeding and anorexia nervosa-related psychotherapy. Primarily, it is essential to accurately assess nutritional and fluid intake and to document premorbid weight and the course of weight loss. Recommended weight gain rates range from 500 g to 1400 g per week depending on the duration of weight loss and malnutrition, the age of the patient, somatic comorbidity, and the severity of purging behavior. [34,35]

Particularly in the initial stages of refeeding, a serious and potentially fatal medical complication is a refeeding syndrome. The highest-risk patients are those who have been malnourished and emaciated for a long time. Refeeding syndrome is a state of hypophosphatemia, hypomagnesemia, and hypokalemia. [35,36] According to the RANZP

protocol (2014), adult patients should start with a refeeding of 6000 kJ/day, increased by 2000 kJ/day every 3 days, until an adequate intake to meet the person's needs for weight restoration is reached. Moreover, electrolytes should be checked regularly, and this diet should be supplemented by 500mg phosphate twice daily and at least 100 mg daily thiamine for the first week, and thereafter as clinically indicated for people at elevated risk of refeeding syndrome. [37]

Osteoporosis prevention and treatment

Weight restoration is the most efficient strategy to improve bone density and, in women, menstrual function. Transdermal estrogen-replacement therapy only partially increases bone density in adolescents. [30]

Differential Diagnosis [4]

- Medical Conditions (e.g., gastrointestinal disease, hyperthyroidism, occult malignancies, and acquired immunodeficiency syndrome)
- Major Depressive Disorder
- Schizophrenia
- Substance Use Disorders
- Social Anxiety Disorder, OCD, body dysmorphic disorder
- Bulimia Nervosa
- Avoidant/Restrictive Food Intake Disorder

Conclusion

In conclusion, this article provides a broad overview of anorexia nervosa, and it emphasizes the significant roles of environmental, genetic, and developmental factors in contributing to the development of the disorder. There are many physiological consequences of anorexia nervosa, including hormonal imbalances, metabolic changes, and potential long-term health complications. Many treatment approaches have been discussed such as cognitive-behavioral therapy, nutritional counseling, and family-based interventions, which highlight the importance of a multidisciplinary approach to manage Anorexia Nervosa effectively.

References

1. Zipfel S, Giel KE, Bulik CM, Hay P, Schmidt U. Anorexia nervosa: Aetiology, assessment, and treatment. The Lancet Psychiatry [Internet]. 2015;2(12):1099–111. Available from: http://dx.doi.org/10.1016/S2215-0366(15)00356-9
2. Jansingh A, Danner UN, Hoek HW, van Elburg AA. Developments in the psychological treatment of anorexia nervosa and their implications for daily practice. Curr Opin Psychiatry. 2020 Nov;33(6):534–41.
3. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®) [Internet]. Available from: https://books.google.jo/books/about/Diagnostic_and_Statistical_Manual_of_Men.html?id=-JivBAAAQBAJ&printsec=frontcover&source=kp_read_button&redir_esc=y#v=onepage&q&f=false

4. Impact of exercise on energy metabolism in anorexia nervosa [Internet]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4081773/
5. Gümmer R, Giel KE, Schag K, Resmark G, Junne FP, Becker S, et al. High Levels of Physical Activity in Anorexia Nervosa: A Systematic Review. Eur Eat Disord Rev J Eat Disord Assoc. 2015 Sep;23(5):333–44.
6. Smink FRE, van Hoeken D, Hoek HW. Epidemiology, course, and outcome of eating disorders. Curr Opin Psychiatry. 2013 Nov;26(6):543–8.
7. Smink FRE, van Hoeken D, Hoek HW. Epidemiology of eating disorders: incidence, prevalence and mortality rates. Curr Psychiatry Rep. 2012 Aug;14(4):406–14.
8. Galmiche M, Déchelotte P, Lambert G, Tavolacci MP. Prevalence of eating disorders over the 2000-2018 period: a systematic literature review. Am J Clin Nutr. 2019 May;109(5):1402–13.
9. eating disorders [Internet]. Available from: https://www.amboss.com/us/knowledge/Eating_disorders
10. Titova OE, Hjorth OC, Schiöth HB, Brooks SJ. Anorexia nervosa is linked to reduced brain structure in reward and somatosensory regions: a meta-analysis of VBM studies. BMC Psychiatry. 2013 Apr;13:110.
11. Baker JH, Schaumberg K, Munn-Chernoff MA. Genetics of Anorexia Nervosa. Curr Psychiatry Rep. 2017;19(11):1–8.
12. Tchanturia K, Davies H, Roberts M, Harrison A, Nakazato M, Schmidt U, et al. Poor cognitive flexibility in eating disorders: examining the evidence using the Wisconsin Card Sorting Task. PLoS One. 2012;7(1):e28331.
13. Lang K, Lopez C, Stahl D, Tchanturia K, Treasure J. Central coherence in eating disorders: an updated systematic review and meta-analysis. world J Biol psychiatry Off J World Fed Soc Biol Psychiatry. 2014 Dec;15(8):586–98.
14. Lang K, Stahl D, Espie J, Treasure J, Tchanturia K. Set shifting in children and adolescents with anorexia nervosa: an exploratory systematic review and meta-analysis. Int J Eat Disord. 2014 May;47(4):394–9.
15. Caglar-Nazali HP, Corfield F, Cardi V, Ambwani S, Leppanen J, Olabintan O, et al. A systematic review and meta-analysis of "Systems for Social Processes" in eating disorders. Neurosci Biobehav Rev. 2014 May;42:55–92.
16. King JA, Geisler D, Ritschel F, Boehm I, Seidel M, Roschinski B, et al. Global cortical thinning in acute anorexia nervosa normalizes following long-term weight restoration. Biol Psychiatry [Internet]. 2015;77(7):624–32. Available from: http://dx.doi.org/10.1016/j.biopsych.2014.09.005
17. Van den Eynde F, Suda M, Broadbent H, Guillaume S, Van den Eynde M, Steiger H, et al. Structural magnetic resonance imaging in eating disorders: a systematic review of voxel-based morphometry studies. Eur Eat Disord Rev J Eat Disord Assoc. 2012 Mar;20(2):94–105.
18. Tenconi E, Santonastaso P, Monaco F, Favaro A. Obstetric complications and eating disorders: a replication study. Int J Eat Disord. 2015 May;48(4):424–30.
19. Jacobi C, Hayward C, de Zwaan M, Kraemer HC, Agras WS. Coming to terms with risk factors for eating disorders: application of risk terminology and suggestions for a general taxonomy. Psychol Bull. 2004 Jan;130(1):19–65.
20. Herpertz-Dahlmann B, Seitz J, Konrad K. Aetiology of anorexia nervosa: from a "psychosomatic family model" to a neuropsychiatric disorder? Eur Arch Psychiatry Clin Neurosci. 2011 Nov;261 Suppl:S177-81.
21. Stice E, Marti CN, Durant S. Risk factors for onset of eating disorders: evidence of multiple risk pathways from an 8-year prospective study. Behav Res Ther. 2011 Oct;49(10):622–7.
22. Schmidt U. Aetiology of eating disorders in the 21(st) century: new answers to old questions. Eur Child Adolesc Psychiatry. 2003;12 Suppl 1:I30-7.
23. Le Grange D, Lock J, Agras WS, Bryson SW, Jo B. Randomized Clinical Trial of Family-Based Treatment and Cognitive-Behavioral Therapy for Adolescent Bulimia Nervosa. J Am Acad Child Adolesc Psychiatry. 2015 Nov;54(11):886-94.e2.
24. McIntosh VVW, Jordan J, Luty SE, Carter FA, McKenzie JM, Bulik CM, et al. Specialist supportive clinical management for anorexia nervosa. Int J Eat Disord. 2006 Dec;39(8):625–32.
25. Schmidt U, Magill N, Renwick B, Keyes A, Kenyon M, Dejong H, et al. The Maudsley Outpatient Study of Treatments for Anorexia Nervosa and Related Conditions (MOSAIC): Comparison of the Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA) with specialist supportive clinical management (SSCM) in outpatients with. J Consult Clin Psychol. 2015 Aug;83(4):796–807.
26. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. Am J Psychiatry. 2001 Dec;158(12):1982–8.
27. De Jong M, Schoorl M, Hoek HW. Enhanced cognitive behavioural therapy for patients with eating disorders: A systematic review. Curr Opin Psychiatry. 2018;31(6):436–44.
28. Zipfel S, Wild B, Groß G, Friederich H-C, Teufel M, Schellberg D, et al. Focal psychodynamic therapy, cognitive behaviour therapy, and optimised treatment as usual in outpatients with anorexia nervosa (ANTOP study): randomised controlled trial. Lancet (London, England). 2014 Jan;383(9912):127–37.
29. Misra M, Klibanski A. Endocrine consequences of anorexia nervosa. lancet Diabetes Endocrinol. 2014 Jul;2(7):581–92.
30. Aigner M, Treasure J, Kaye W, Kasper S. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. world J Biol psychiatry Off J World Fed Soc Biol Psychiatry. 2011 Sep;12(6):400–43.
31. Tortorella A, Brambilla F, Fabrazzo M, Volpe U, Monteleone AM, Mastromo D, et al. Central and peripheral peptides regulating eating behaviour and energy homeostasis in anorexia nervosa and bulimia nervosa: a literature review. Eur Eat Disord Rev J Eat Disord Assoc. 2014 Sep;22(5):307–20.
32. Pike KM, Walsh BT, Vitousek K, Wilson GT, Bauer J. Cognitive behavior therapy in the posthospitalization treatment of anorexia nervosa. Am J Psychiatry. 2003 Nov;160(11):2046–9.
33. Hay P, Chinn D, Forbes D, Madden S, Newton R, Sugenor L, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. Aust N Z J Psychiatry. 2014 Nov;48(11):977–1008.

34. Eating Disorders: Core Interventions in the Treatment and Management of Anorexia Nervosa, Bulimia Nervosa and Related Eating Disorders. Leicester (UK); 2004.
35. Bulik CM, Klump KL, Thornton L, Kaplan AS, Devlin B, Fichter MM, et al. Alcohol use disorder comorbidity in eating disorders: a multicenter study. J Clin Psychiatry. 2004 Jul;65(7):1000–6.
36. Keski-Rahkonen A, Hoek HW, Susser ES, Linna MS, Sihvola E, Raevuori A, et al. Epidemiology and course of anorexia nervosa in the community. Am J Psychiatry. 2007 Aug;164(8):1259–65.
37. Zipfel S, Löwe B, Reas DL, Deter HC, Herzog W. Long-term prognosis in anorexia nervosa: lessons from a 21-year follow-up study. Vol. 355, Lancet (London, England). England; 2000. p. 721–2.
38. Anorexia nervosa image [Internet]. Available from: https://www.herbaldaily.in/shopbydisease/anorexia-nervosa

Article: Neuroleptic Malignant Syndrome.

Author: Reem Tayih.

Editor: Ihda Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: Neuroleptic Malignant Syndrome, Antipsychotics, Differential Diagnosis, Pathophysiology

Overview

Neuroleptic Malignant Syndrome (NMS) is an idiosyncratic life-threatening medical emergency that requires immediate care. [1] NMS is conceptualized as a disorder triggered in the brain by neuroleptic blockage of the D_2 dopamine receptors in the hypothalamus and brainstem regulatory systems that in turn causes the generalized systemic hypermetabolic syndrome. [2] The most common cause of Neuroleptic Malignant Syndrome (NMS) is the use of Antipsychotic medications, more often first-generation typical Antipsychotics. The typical clinical presentation includes symptoms such as muscular rigidity, altered consciousness, hyperthermia, and autonomic instability. [3] Despite the fact that it is uncommon, NMS remains a critical consideration in the differential diagnosis of patients presenting with hyperthermia and altered mental status because it requires prompt recognition to prevent consequential morbidity and death. [3]

Epidemiology

Incidence rates throughout the years ranged from 0.02%-3%, [4] which is significant. Patients of both sexes and all ages (from children to the elderly) seem to be affected by Neuroleptic Malignant Syndrome (NMS), but young adult males predominate. [2] Instantaneous management and treatment of NMS are crucial since reported mortality rates for NMS vary between 5%-20%. [5] Symptom severity and the occurrence of medical complications are the strongest predictors of mortality. [6] Fortunately, the incidence rate is decreasing due to the development of newer drugs (atypical Antipsychotics) and increased awareness of the condition. [7]

Pathophysiology of NMS

The pathophysiology of Neuroleptic Malignant Syndrome is not completely understood. [20] Several theories have been suggested, with the most common being:

- Blockade of Dopamine receptors
- Genetic predisposition for reduced function of D2 receptors [21]
- Autonomic dysfunction and Sympathoadrenal hyperactivity

Theories suggest that the blockade of D2-like receptors such as D3, D4, etc. induces the tremendous release of glutamate, which in turn causes the development of muscle rigidity and neurological signs. [22,17] The musculoskeletal symptoms are most likely to be caused by the blockade of D2 receptors, causing the abnormal function of basal ganglia like that of Parkinson's disease. [23] Nevertheless, this theory doesn't fully explain the symptoms that accompany NMS, so other theories have been suggested such as the Sympathoadrenal hyperactivity hypothesis. [24,23]

The release of calcium is increased from the sarcoplasmic reticulum with antipsychotic use. [25] This can result in increased muscle contractility, which can play a role in muscle rigidity, and the development of fever. Some antipsychotic drugs, such as typical antipsychotics, are known to block D2 receptors; several studies have shown that when dopamine drugs are withdrawn, symptoms similar to NMS are present. [26]

Clinical Presentation and Diagnostic Criteria

The main risk factor for developing neuroleptic malignant syndrome is the use of antipsychotic medications, especially high potency, and long-acting IM depot forms. [8] Symptoms of NMS develop over several days, and they include hyperthermia, muscle rigidity, altered mental status, and autonomic rigidity. [9] Laboratory investigations are crucial to exclude any other complications. Laboratory abnormalities are associated with NMS, although none are sufficient to make a diagnosis. [10]

For instance, patients with NMS might have rhabdomyolysis, resulting in elevated levels of creatine kinase, transaminases, aldolase, and lactic acid dehydrogenase concentrations, this increases the risk of subsequent myoglobinuric renal failure. [11] Patients may also have metabolic acidosis, hypoxia, decreased serum iron concentrations, increased serum catecholamines, and leukocytosis. [12, 1] The results of CSF analysis are normal in most cases (95% of cases). [1] Neuroimaging tends to be within the normal range, and electroencephalography may show generalized slowing. [13] Several analyses show that the development of altered mental status and neurological signs appears before systemic signs. [1]

The DSM-5 criteria for NMS are: (14)

Major criteria (all required)

- Exposure to dopamine-blocking agent
- Severe muscle rigidity
- Fever

Other criteria (at least 2 required)

- Diaphoresis
- Dysphagia
- Tremor
- Incontinence
- Altered level of consciousness
- Mutism
- Tachycardia
- Elevated or labile blood pressure
- Leukocytosis
- Elevated creatine phosphokinase

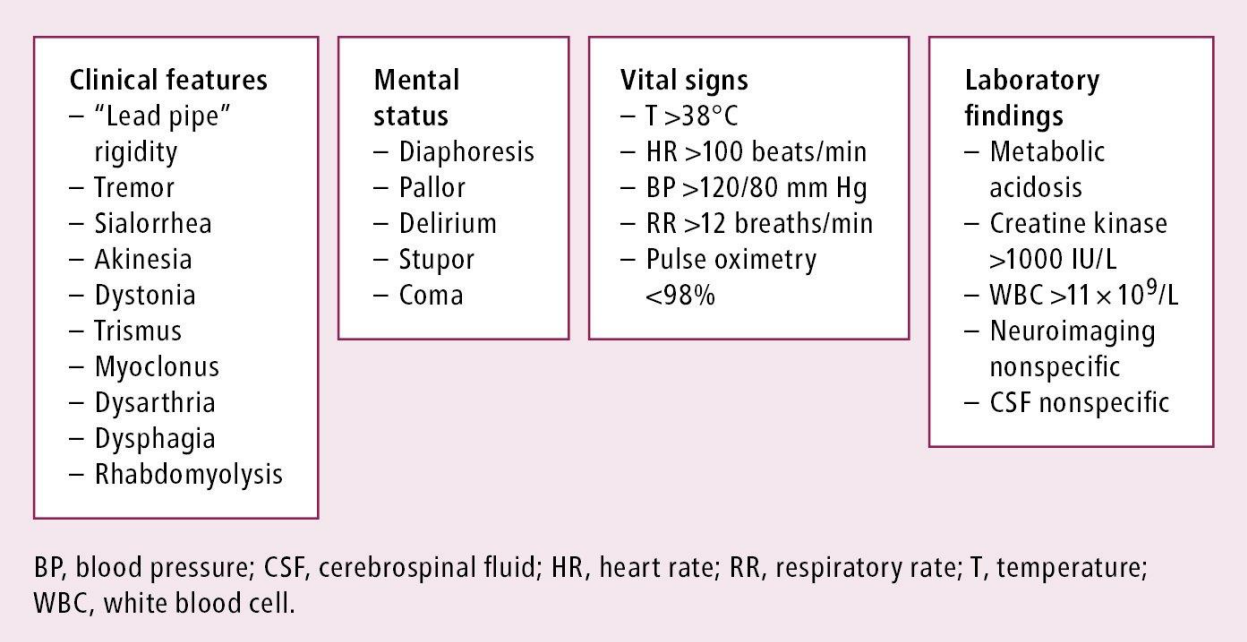


Figure 1 Clinical Presentations of Neuroleptic Malignant Syndrome (NMS). (15)

Medications associated with Neuroleptic Malignant Syndrome

Usually, antipsychotic medications are associated with Neuroleptic Malignant Syndrome (NMS). [3] This syndrome appears with the use of typical Antipsychotics more often, especially the intramuscular depot form. [8] Antiemetic drugs are also associated with NMS, but less than Antipsychotics. [16]

The following table shows examples of drugs that can cause NMS:[3,17,18]

Typical Antipsychotics	Atypical Antipsychotics	Antiemetic Drugs
Haloperidol	Olanzapine	Droperidol
Chlorpromazine	Clozapine	Domperidone
Bromperidol	Quetiapine	Promethazine
Thioridazine	Aripiprazole	Metoclopramide

Table (1) Common drugs associated with Neuroleptic Malignant Syndrome (NMS) (19).

Differential Diagnosis

Serotonin Syndrome is a common differential diagnosis of Neuroleptic Malignant Syndrome (NMS) due to overlapping symptoms, however, it is easily distinguished due to the difference in causative agents. [18] Hyperthermia and muscle rigidity are usually less severe in Serotonin Syndrome than in NMS; In addition to that, Serotonin Syndrome has gastrointestinal symptoms that set it apart from NMS. [27,28] Malignant Catatonia may also present with fever, muscle rigidity, and altered mental status. [29,30] Not only that, but Malignant Catatonia presents with psychological symptoms such as agitation and psychosis. [31] Acute encephalitis, meningitis, and brain abscesses must be differentiated from NMS since they all have common symptoms such as fever and altered mental status; it is crucial since clinicians need to know whether to initiate treatment of CNS infections. [32] Intoxication with drugs such as amphetamines, cocaine, MDMA, and phencyclidine has similar symptoms to NMS. [33,3]

Infectious
Meningitis or encephalitis
Postinfectious encephalomyelitis syndrome
Brain abscess
Sepsis
Psychiatric or neurological
Idiopathic malignant catatonia
Agitated delirium
Benign extrapyramidal side effects
Nonconvulsive status epilepticus
Structural lesions, particularly involving the midbrain
Toxic or pharmacological
Anticholinergic delirium
Salicylate poisoning
Malignant hyperthermia (inhalational anesthetics, succinylcholine)
Serotonin syndrome (monoamine oxidase inhibitors, triptans, linezolid)
Substances of abuse (amphetamines, hallucinogens)
Withdrawal from dopamine agonists, baclofen, sedative-hypnotics, and alcohol
Endocrine
Thyrotoxicosis
Pheochromocytoma
Environmental
Heatstroke

Figure (2) Common differential diagnoses of NMS (34)

Pharmacological Treatment Options

Neuroleptic Malignant Syndrome (NMS) is considered a neurological emergency, and interventions should be immediately initiated due to its high morbidity and death rates. [3] In most cases, Neuroleptic Malignant Syndrome (NMS) is treated in the intensive care unit. [35] First-line treatment is the removal of the causative agent, which is the antipsychotic (or other offending agents). The morbidity and mortality risk associated with Neuroleptic Malignant Syndrome (NMS) outweighs the risk of untreated psychosis and agitation resulting from the sudden discontinuation of antipsychotic medications. [36]

The second key stage is the commencement of medical therapies. Initiation of IV fluids to restore hydration and correct electrolyte imbalances is necessary since elevated levels of CPK pose a risk to the kidneys. [3] Neuroleptic Malignant Syndrome (NMS) is also associated with hyperthermia, which can be managed with cooling blankets or ice packs. [3] Fluid alkalization using bicarbonate has been shown to be useful in preventing renal failure. [1] Several complications arise due to Neuroleptic Malignant Syndrome (NMS), such as renal failure and disseminated intravascular coagulation (DIC) secondary to rhabdomyolysis,[1] Deep vein thrombosis and pulmonary embolism can also arise due to severe dehydration and lack of mobilization, difficulty in swallowing can also cause aspiration pneumonia, and other complications include cardiopulmonary failure, seizures, myocardial infarction, sepsis, and arrhythmias.[37][38]

Several pharmacological interventions have been proposed for the management of Neuroleptic Malignant Syndrome, such as dantrolene sodium, benzodiazepines, and bromocriptine. [39] Benzodiazepines are widely used in the treatment of Neuroleptic Malignant Syndrome (NMS) since they help control agitation and promote muscle relaxation. [40] Adjunctive Dantrolene therapy is associated with the prolongation of clinical recovery. [41] In addition to that, treatment of Neuroleptic Malignant Syndrome (NMS) with Dantrolene monotherapy is correlated with higher overall mortality. [41] Although Dantrolene is not an evidence-based treatment of choice in cases of Neuroleptic Malignant Syndrome (NMS), it might be useful if premedication consisted of a neuroleptic monotherapy. [41] Bromocriptine is the second-line pharmacological treatment of Neuroleptic Malignant Syndrome (NMS) after the withdrawal of the causative agent. [42] A study has shown that Bromocriptine has a therapeutic effect of 94% when used as monotherapy and a therapeutic effect of 88% when used as a combination therapy. [43] Antipyretics may also be used to treat hyperthermia due to Neuroleptic Malignant Syndrome (NMS). [44]

Stage	Clinical presentation	Proposed treatment	Treatment setting
I: Drug-induced	Rigidity, tremor	Reduce or switch antipsychotics Anticholinergic agents	Psychiatric ward
Parkinsonism			
II Drug-induced	Rigidity; mutism; stupor	Discontinue, reduce or switch antipsychotics	Psychiatric
catatonia		Use lorazepam (up to 8 mg/day)	ward/MAU
III Mild, early NMS	Mild rigidity; catatonia or confusion; temperature	Discontinue antipsychotics	MAU
	538 °C (100.4 °F); heart rate .5100 bpm	Use lorazepam (up to 8 mg/day)	
IV: Moderate NMS	Moderate rigidity; catatonia or confusion; temperature	Discontinue antipsychotics	ICU
	38-40 °C (1004-104 °F); heart rate 100-120 bpm	Intensive care	
		Lorazepam (up to 8 mg/day), bromocriptine (up to 15 mg/day) or amantadine (up to 300 mg/day); ECT as second-line therapy	
V: Severe NMS	Severe rigidity; catatonia or coma; temperature AO °C	Discontinue antipsychotics	ICU
	(104 °F); heart rate 120 bpm	Intensive care	

Table 2 Treatment stages of Neuroleptic Malignant Syndrome (NMS) [45] [36] [46]

Conclusion

Neuroleptic Malignant Syndrome (NMS) is a rare, uncommon syndrome associated with the use of medications such as Antipsychotics (e.g. Olanzapine, Haloperidol, etc.). This syndrome has deliberating life-threatening symptoms that require immediate management. It has a mortality rate of up to 10%, so clinicians should be careful while prescribing certain medications. It can be managed through several psychopharmacological interventions such as benzodiazepines, dantrolene sodium, and bromocriptine. Despite its lethality, it is treated successfully most of the time with the right interventions.

References

1. Friedman JH, Fernandez HH. Neuroleptic malignant syndrome. Drug-Induced Mov Disord. 2004;(June):165–92.
2. Oruch R, Pryme IF, Engelsen BA, Lund A. Neuroleptic malignant syndrome: An easily overlooked neurologic emergency. Neuropsychiatr Dis Treat. 2017;13:161–75.
3. Berman BD. Neuroleptic Malignant Syndrome: A Review for Neurohospitalists. The Neurohospitalist. 2011;1(1):41–7.
4. Oneib B, Zaimi O. Neuroleptic malignant syndrome: clinical expression, complication, course, and atypical clinical picture. Middle East Curr Psychiatry. 2021;28(1):1–6.
5. Sahin A, Cicek M, Gonenc Cekic O, Gunaydin M, Aykut DS, Tatli O, et al. A retrospective analysis of cases with neuroleptic malignant syndrome and an evaluation of risk factors for mortality. Turkish J Emerg Med [Internet]. 2017;17(4):141–5. Available from: https://doi.org/10.1016/j.tjem.2017.10.001
6. McNamara D. The Neuroleptic Malignant and Serotonin Syndromes. CPD J Acute Med. 2002;1(3):101–4.
7. Ware MR, Feller DB, Hall KL. Neuroleptic malignant syndrome: Diagnosis and management. Prim Care Companion J Clin Psychiatry. 2018;20(1).
8. Simon L V., Hashmi MF, Callahan AL. Neuroleptic Malignant Syndrome. StatPearls [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482282/#_NBK482282_pubdet_
9. Krivosic-horber R, Adnet P, Guevart E, Theunynck D, Lestavel P. Neuroleptic malignant syndrome and malignant hyperthermia: In vitro comparison with halothane and caffeine contracture tests. Br J Anaesth [Internet]. 1987;59(12):1554–6. Available from: http://dx.doi.org/10.1093/bja/59.12.1554
10. Benzer TI, Mancini MC. Neuroleptic Malignant Syndrome Workup [Internet]. 2022. Available from: https://emedicine.medscape.com/article/816018-workup
11. Gurrera RJ, Romero JA. Enzyme elevations in the neuroleptic malignant syndrome. Biol Psychiatry. 1993;34(9):634–40.
12. Tse L, Barr A, Scarapicchia V, Vila-Rodriguez F. Neuroleptic Malignant Syndrome: A Review from a Clinically Oriented Perspective. Curr Neuropharmacol. 2015;13(3):395–406.
13. Özdemir İ, Kuru E, Safak Y, Tulacı RG. A neuroleptic malignant syndrome without rigidity. Psychiatry Investig. 2018;15(2):226–9.
14. Association. AP. Desk Reference to the Diagnostic Criteria from DSM-5 (R). American Psychiatric Association Publishing; 2013.
15. Jaeschke R, Gajewski P, O'Byrne PM. McMaster Textbook of Internal Medicine. 2020.
16. Friedman LS, Elia JAD, Weinrauch LA. Metoclopramide-Induced Neuroleptic Malignant Syndrome. 2015;8–10.
17. Moscovich M, Nóvak FTM, Fernandes AF. Neuroleptic malignant syndrome. 2011;(August 2014).
18. Turner AH, Nguyen CT, Kim JJ, McCarron RM. Differentiating serotonin syndrome and neuroleptic malignant syndrome. Curr Psychiatr. 2019;18(2):30–6.
19. Chandran GJ, Mikler JR, Keegan DL. Neuroleptic malignant syndrome: Case report and discussion. C Can Med Assoc J. 2003;169(5):439–42.
20. Loynes J, Tann S, Redick D, Hickman R. Neuroleptic malignant syndrome. Tenn Med. 1999;92(10).
21. Mihara K, Kondo T, Suzuki A, Yasui-Furukori N, Ono S, Sano A, et al. Relationship between functional dopamine D2 and D3 receptors gene polymorphisms and neuroleptic malignant syndrome. Am J Med Genet - Neuropsychiatr Genet. 2003;117 B(1):57–60.
22. Communication S. Journal of. 1993;63–72.
23. Martínez HR, Cantú-Martínez L, González HC, De León Flores L, Villarreal HJ, Onofre-Castillo J. Epilepsy, parkinsonism, and neuroleptic malignant syndrome in a child. J Child Neurol. 2006;21(12):1073–5.
24. Hasan S, Buckley P. Novel antipsychotics and the neuroleptic malignant syndrome: A review and critique. Am J Psychiatry. 1998;155(8):1113–6.

25. López JR, Sánchez V, López MJ. Sarcoplasmic ionic calcium concentration in neuroleptic malignant syndrome. Cell Calcium. 1989;10(4):223–33.
26. Serrano-Dueñas M. Neuroleptic malignant syndrome-like, or - dopaminergic malignant syndrome - due to levodopa therapy withdrawal. Clinical features in 11 patients. Park Relat Disord. 2003;9(3):175–8.
27. Tormoehlen LM, Rusyniak DE. Neuroleptic malignant syndrome and serotonin syndrome [Internet]. 1st ed. Vol. 157, Handbook of Clinical Neurology. Elsevier B.V.; 2018. 663–675 p. Available from: http://dx.doi.org/10.1016/B978-0-444-64074-1.00039-2
28. Dosi R, Ambaliya A, Joshi H, Patell R. Serotonin syndrome versus neuroleptic malignant syndrome: A challenging clinical quandary. BMJ Case Rep. 2014;
29. Rubin T. Psychiatry 1989; 146:324-328). Psychiatry Interpers Biol Process. 1989;(March):324–8.
30. Ghaziuddin N, Hendriks M, Patel P, Wachtel LE, Dhossche DM. Neuroleptic Malignant Syndrome/Malignant Catatonia in Child Psychiatry: Literature Review and a Case Series. J Child Adolesc Psychopharmacol. 2017;27(4):359–65.
31. Philbrick L. C atatonia. J Neuropsychiatry Clin Neurosci. 1994;1–13.
32. Hall JM, Jacobson JL. Neuroleptic Malignant Syndrome. Crit Care Secrets Fifth Ed. 2012;565–70.
33. Velamoor VR, Swamy GN, Parmar LRS, Williamson P, Caroff SN. Management of suspected neuroleptic malignant syndrome. Can J Psychiatry. 1995;40(9):545–50.
34. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Psychopharmacol Bull. 1988;24(1):25–9.
35. Velamoor VR. Neuroleptic malignant syndrome. Drug Saf. 1998;19(1):73–82.
36. Pileggi DJ, Cook AM. Neuroleptic Malignant Syndrome: Focus on Treatment and Rechallenge. Ann Pharmacother. 2016;50(11):973–81.
37. Bhanushali MJ, Tuite PJ. The evaluation and management of patients with neuroleptic malignant syndrome. Neurol Clin. 2004;22(2):389–411.
38. Lenler-Petersen P, Hansen BD, Hasselstrøm L. A rapidly progressing lethal case of neuroleptic malignant syndrome. Intensive Care Med. 1990;16(4):267–8.
39. Dhib-Jalbut S, Hesselbrock R, Mouradian MM, Means ED. Bromocriptine treatment of neuroleptic malignant syndrome. J Clin Psychiatry. 1987 Feb;48(2):69–73.
40. Guzofski S, Peralta R. Neuroleptic Malignant Syndrome, with Attention to Its Occurrence with Atypical Antipsychotic Medication: A Review. Jefferson J Psychiatry. 2006;20(1).
41. Reulbach U, Dütsch C, Biermann T, Sperling W, Thuerauf N, Kornhuber J, et al. Managing an effective treatment for neuroleptic malignant syndrome. Crit Care. 2007;11(1):1–6.
42. Wait SD, Ponce FA, Killory BD, Wallace D, Rekate HL. Neuroleptic malignant syndrome from central nervous system insult: 4 Cases and a novel treatment strategy. J Neurosurg Pediatr. 2009;4(3):217–21.
43. Putra PY, Setiawati Y. Neuroleptic Malignant Syndrome: A Review of Diagnosis and Treatment Neuroleptic Malignant Syndrome: A Review of Diagnosis and Treatment LITERATURE REVIEW Neuroleptic Malignant Syndrome: A Review of Diagnosis and Treatment. 2021;(6).
44. Langan Martin J, Martin DJ. Neuroleptic Malignant Syndrome [Internet]. Life-Threatening Effects of Antipsychotic Drugs. Elsevier Inc.; 2016. 223–240 p. Available from: http://dx.doi.org/10.1016/B978-0-12-803376-0.00010-1
45. Schönfeldt-Lecuona C, Cronemeyer M, Hiesener L, Connemann BJ, Gahr M, Sartorius A, et al. Comparison of International Therapy Guidelines with Regard to the Treatment of Malignant Catatonia. Pharmacopsychiatry. 2020;53(1):14–20.
46. Wadoo O, Ouanes S, Firdosi M. Neuroleptic malignant syndrome: a guide for psychiatrists. BJPsych Adv. 2020;27:1–10.

Article topic: Disinhibited social engagement disorder (DSED).

Author: Batool Fahad Alkasasbeh.

Editor: Ihda Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: **Disinhibited social engagement disorder, Attachment, young children, caregiver.**

Introduction

Children with a disinhibited social engagement disorder are known to show a lack of normative reticence with strangers, to be physically or verbally overly familiar, to not check their caregiver after venturing away, or to willingly go off with an unfamiliar adult (2).

It can make it difficult for kids to form relationships with peers and adults, and it can place them in risky and perilous situations like riding on a stranger's lap or leaving without telling their parents (2).

There is now broad consensus that in early childhood, attachment disorders result from inadequate caregiving environments and encompass two clinical patterns, an emotionally withdrawn/inhibited phenotype, and an indiscriminately social/disinhibited phenotype (3).

Using continuous measurements to monitor symptoms and categorically diagnose *Reactive Attachment Disorder (RAD) and Disinhibited Social Engagement Disorder (DSED) in* maltreated children and those who are currently or were formerly institutionalized, some research on attachment disorders in early children has been done (3).

Epidemiology

The prevalence of DSED also is not completely clear because the condition has not been subjected to large, community-based studies explicitly designed to estimate prevalence (4). Nevertheless, DSED occurs only in a minority of children who have been severely neglected and subsequently placed in foster care or those raised in institutions. Even in such high-risk populations, the condition occurs in fewer than 20% of children (5–7).

The DSM notes that prevalence is up to 2% in low-income community populations in the United Kingdom (8).

Etiology

Along with other trauma and stress-related disorders, attachment disorders include the specification of etiology in the criteria. Thus, social neglect is noted as a necessary but not sufficient requirement for the diagnosis to be entertained (9).

There may be one or several causes of DSED. Cases frequently involve the lack of quality, long-term caregiving. Some kids with DSED are from institutionalized environments, such as orphanages. Children in foster care who are frequently moved between homes or who are never adopted may also develop DSED (10).

Studies of children who have been maltreated, and those raised in institutions, have confirmed that indiscriminate behavior, the central feature of the phenotype, is increased compared to that in children who have not experienced such extremes of care (7,11–19).

In a study exploring genetic vulnerability to indiscriminate behavior in children who experienced deprivation, Bakersman-Kranenberg et al. (2011) examined whether the serotonin transporter gene (5HTT) moderated the association between institutional care and both disorganized attachment and indiscriminate behavior among young children raised in Ukranian institutions. They found that the long allele of the genotype protected against the development of disorganized attachment but did not protect against the development of indiscriminate behavior (3).

The DSM-5 Diagnostic criteria

The Diagnostic and Statistical Manual of Mental Disorders *(DSM-5)* defines disinhibited social engagement disorder as "*a pattern of behavior in which a child actively approaches and interacts with unfamiliar adults.*" (American Psychiatric Association, 2013) (20).

The *DSM-5* gives the following criteria for Disinhibited Social Engagement Disorder (21):

A. A pattern of behavior in which a child actively approaches and interacts with unfamiliar adults and shows at least two of the following:

    - Reduced or absent reticence in approaching and interacting with unfamiliar adults.
    - Overly familiar verbal or physical behavior (that is not consistent with culturally sanctioned and age-appropriate social boundaries).
    - Diminished or absent checking back with an adult caregiver after venturing away, even in unfamiliar settings.

- Willingness to go off with an unfamiliar adult with little or no hesitation.

B. The behaviors in Criterion A are not limited to impulsivity (as in Attention-Deficit/Hyperactivity Disorder) but include socially disinhibited behavior.

C. The child has exhibited a pattern of extremes of insufficient care as evidenced by at least one of the following:

- Social neglect or deprivation in the form of persistent lack of having basic emotional needs for comfort, stimulation, and affection met by caregiving adults.
- Repeated changes in primary caregivers that limit the ability to form stable attachments (e.g., frequent changes in foster care).
- Rearing in unusual settings that severely limit opportunities to form selective attachments (e.g., institutions with high child-to-caregiver ratios).

D. The care in Criterion C is presumed to be responsible for the disturbed behavior in Criterion A (e.g., the disturbances in Criterion A began following the pathogenic care in Criterion C).

E. The child has a developmental age of at least nine months.

Specify if Persistent: The disorder has been present for more than 12 months.

Specify current severity: Disinhibited Social Engagement Disorder is specified as severe when a child exhibits all symptoms of the disorder, with each symptom manifesting at relatively elevated levels.

Clinical presentations

Behavioral features of DSED include an inappropriate approach to unfamiliar adults and lack of wariness toward strangers, and a willingness to wander off with strangers. In DSED, children also prove a lack of proper social and physical boundaries, such as interacting with adult strangers in over proximity (experienced by the adult as intrusive) and by actively seeking close physical contact. By the preschool years, verbal boundaries may be violated as the child asks overly intrusive and overly familiar questions of unfamiliar adults (3).

Children with DSED have a history of social neglect, but they are usually effectively brighter and more social than children with RAD. The essence of DSED is socially disinhibited behavior with strangers. Affected children lack restraint around adults whom they do not know, instead approaching and engaging them. They are notably

willing to leave caregivers and accompany or “go off” with strangers without hesitation (4).

Workup and Diagnosis

Not all children who are able to interact with strangers have DSED. Children who typically show manifestations of independence and physical separation from parents may explore away from their caregivers and be attracted to others some of them have naturally outgoing personalities and they like to approach other adults in an overly enthusiastic way (10).

A therapist or psychiatrist is usually responsible for making the diagnosis. The doctor will conduct a thorough psychiatric evaluation across multiple appointments that may occur in one or more places (10).

Observations may be informal. A psychologist may note several behaviors as they occur, such as how the child approaches the psychologist and interacts with them. If the child immediately runs up to the psychologist and wants the psychologist to hold them, that is notable. If the child gets upset in the room, and they do not seek their caregiver out for comfort, or if they reject the caregiver’s attempts to comfort them, that is important. Also, if the caregiver or psychologist praises the child for doing something well, and the child seems to not react or be affected by the praise, that is notable (8).

If the child is diagnosed with DSED, the doctor is going to create a highly individualized treatment plan. The plan will be targeted toward healing the child’s trauma and supporting their ability to form meaningful, close relationships with others (10).

Management

Due to significant impairment in caregiving, the relationship and attachment between the child and caregiver are damaged, therapies focus on repairing that relationship or making a bond between the child and a new caregiver if the unpleasant caregiver is no longer involved in the child’s life, It is important to note, nevertheless, that relatively little research particularly looks at how treatments affect these illnesses (8).

A significant goal of therapy is to improve sensitive caregiving from the caregiver. This involves increasing the caregiver’s ability to ‘tune in’ to the child so that they can be particularly responsive and sensitive to the child’s needs. This can be achieved by either working only with the caregiver or working with the caregiver *and* the child. Treatment is not typically conducted with only the child because that does not allow a clinician to address the core concern appropriately (3).

One of the first things that occur in therapy is trying to understand the relationship between the caregiver and child and provide support to the caregiver (8). The primary objective of the intervention is to help the caregiver and child form an attachment.

In other words, if a caregiver is overwhelmed, frustrated, and defeated, they may not be able to respond consistently and calmly to the child. If they cannot do this, attachment cannot be fostered. Therefore, it is important to acknowledge and support the caregiver's own emotions and responses (8).

The most common treatment methodologies include stress-free psychotherapies such as expressive therapy or play therapy. These treatments allow your child to interact with a professional, trusted, adult counselor in a way that is comfortable for them. They will guide their treatment by playing naturally or engaging in the arts, all while developing proper levels of discretion and attachment (22).

Prognosis

Research has already shown that symptoms of DSED can persist across childhood (15,23), and even into adulthood (24), but the Guyon-Harris et al. study goes deeper:(25) it adds new knowledge by examining different profiles in the course of DSED over time, and takes a closer look at factors that might be associated with reduction or persistence of DSED symptoms (26).

The research reveals that symptoms of DSED can persist throughout childhood and even into adulthood. The study identifies four profiles of DSED development: "minimal" (consistently low symptoms), "persistent modest" (low-to-moderate symptoms persisting over time), "early decreasing" (marked reduction in symptoms in early childhood), and "elevated" (high symptom scores throughout childhood, decreasing in adolescence) (25).

The findings demonstrate that early placement in foster care from an institutional context leads to a significant reduction in DSED symptoms for many children. However, the persistence of DSED symptoms is associated with longer periods of institutional care, older age at placement into foster families, and a higher number of placement disruptions (25).

Conclusion

In conclusion, Disinhibited Social Engagement Disorder (DSED) is a condition characterized by children showing a lack of reticence with strangers, engaging in overly familiar behaviors, and willingly going off with unfamiliar adults. This disorder can hinder the formation of relationships with peers and adults, placing children at risk of

dangerous situations. The prevalence of DSED is not well established, but it is typically observed in a minority of children who have experienced severe neglect or have been raised in institutional environments. The etiology of DSED is complex, involving factors such as social neglect, frequent changes in caregivers, and limited opportunities to form stable attachments. The DSM-5 provides diagnostic criteria for DSED, emphasizing the pattern of socially disinhibited behavior and a history of insufficient care. A diagnosis is typically made through a psychiatric evaluation, considering the child's behavior and interactions with both caregivers and unfamiliar individuals. Treatment focuses on repairing the relationship between the child and caregiver or setting up a bond with a new caregiver, aiming to improve sensitive caregiving and promote secure attachment. Therapy often involves the caregiver and child, with an emphasis on understanding the caregiver-child relationship and providing support. Common treatment approaches include expressive therapy or play therapy, which allows the child to interact with a trusted adult while developing proper boundaries and attachment. The prognosis for children with DSED tends to improve over time, with most symptoms diminishing significantly by the age of twelve.

References

1. DSED [Internet]. Available from: https://www.viquepedia.com/assets/images/sitelogo/DSED.jpg
2. Zephyr L, Cyr C, Monette S, Langlois V, Cyr-Desautels L, Archambault M. Disinhibited social engagement behaviors in young, maltreated children: Dysfunctional behavior of biological parents and child attachment. Child Abuse Negl. 2021 Jan;111:104791.
3. Zeanah CH, Gleason MM. Annual research review: Attachment disorders in early childhood - Clinical presentation, causes, correlates, and treatment. J Child Psychol Psychiatry Allied Discip. 2015;56(3):207–22.
4. Zeanah CH, Chesher T, Boris NW, Walter HJ, Bukstein OG, Bellonci C, et al. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Reactive Attachment Disorder and Disinhibited Social Engagement Disorder. J Am Acad Child Adolesc Psychiatry. 2016;55(11):990–1003.
5. Gleason MM, Fox NA, Drury S, Smyke A, Egger HL, Nelson CA, et al. Validity of evidence-derived criteria for reactive attachment disorder: Indiscriminately social/disinhibited and emotionally withdrawn/inhibited types. J Am Acad Child Adolesc Psychiatry [Internet]. 2011;50(3):216–31. Available from: http://dx.doi.org/10.1016/j.jaac.2010.12.012
6. Hodges J, Tizard B. Social and Family Relationships of Ex-Institutional Adolescents. J Child Psychol Psychiatry. 1989;30(1):77–97.
7. Boris NW, Hinshaw-Fuselier SS, Smyke AT, Scheeringa MS, Heller SS, Zeanah CH. Comparing criteria for attachment disorders: Establishing reliability and validity in high-risk samples. J Am Acad Child Adolesc Psychiatry [Internet]. 2004;43(5):568–77. Available from: http://dx.doi.org/10.1097/00004583-200405000-00010
8. Attachment M 4-DSED and R. No Title [Internet]. Available from: https://opentext.wsu.edu/behavioral-disorders-childhood/chapter/module-4-disinhibited-social-engagement-disorder-and-reactive-attachment/
9. Zeanah CH, Gleason MM. treatment. 2016;56(3):207–22.
10. health line [Internet]. Available from: https://www.healthline.com/health/disinhibited-social-engagement-disorder
11. Reams R. Children birth to three entering the state's custody. Infant Ment Health J. 1999;20(2):166–74.
12. Hinshaw-Fuselier S, Boris NW, Zeanah CH. Reactive attachment disorder in maltreated twins. Infant Ment Health J. 1999;20(1):42–59.
13. Oosterman M, Schuengel C. Autonomic reactivity of children to separation and reunion with foster parents. J Am Acad Child Adolesc Psychiatry [Internet]. 2007;46(9):1196–203. Available from: http://dx.doi.org/10.1097/chi.0b013e3180ca839f
14. Pears KC, Bruce J, Fisher PA, Kim HK. Indiscriminate friendliness in maltreated foster children. Child Maltreat. 2010;15(1):64–75.
15. Tizard B, Rees J. the Effect of Early Institutional Rearing on the Behaviour Problems and Affectional Relationships of Four-Year-Old Children. J Child Psychol Psychiatry. 1975;16(1):61–73.
16. Rutter M, Colvert E, Kreppner J, Beckett C, Castle J, Groothues C, et al. Early adolescent outcomes for institutionally-deprived and non-deprived adoptees. I: Disinhibited attachment. J Child Psychol Psychiatry Allied Discip. 2007;48(1):17–30.

17. Bruce J, Tarullo AR, Gunnar MR. Disinhibited social behavior among internationally adopted children. Dev Psychopathol. 2009;21(1):157–71.
18. Chisholm K. A Three Year Follow-up of Attachment and Indiscriminate Friendliness in Children Adopted from Romanian Orphanages. Child Dev. 1998;69(4):1092–106.
19. O'Connor TG, Rutter M, Andersen-Wood L, Beckett C, Bredenkamp D, Castle J, et al. Attachment disorder behavior following early severe deprivation: Extension and longitudinal follow-up. J Am Acad Child Adolesc Psychiatry [Internet]. 2000;39(6):703–12. Available from: http://dx.doi.org/10.1097/00004583-200006000-00008
20. Disorders D-5 CTS-R. No Title [Internet]. Available from: https://www.theravive.com/therapedia/disinhibited-social-engagement-disorder-dsm--5-313.89-(f94.2)
21. DSM-5 Criteria for Disinhibited Social Engagement Disorder [Internet]. Available from: https://www.cebc4cw.org/search/topic-areas/dsm-5-criteria-for-disinhibited-social-engagement-disorder/
22. DSED T. No Title [Internet]. Available from: http://disinhibitedsocialengagementdisorder.com/
23. Zeanah CH, Smyke AT, Dumitrescu A. Attachment Disturbances in Young Children. II: Indiscriminate Behavior and Institutional Care. J Am Acad Child Adolesc Psychiatry [Internet]. 2002;41(8):983–9. Available from: http://dx.doi.org/10.1097/00004583-200208000-00017
24. Kennedy M, Kreppner J, Knights N, Kumsta R, Maughan B, Golm D, et al. Adult disinhibited social engagement in adoptees exposed to extreme institutional deprivation: Examination of its clinical status and functional impact. Br J Psychiatry. 2017;211(5):289–95.
25. Minnis H. What Happens to Disinhibited Social Engagement Disorder Over Time? J Am Acad Child Adolesc Psychiatry [Internet]. 2018;57(5):304–5. Available from: https://doi.org/10.1016/j.jaac.2018.03.001
26. Guyon-Harris KL, Humphreys KL, Fox NA, Nelson CA, Zeanah CH. Course of Disinhibited Social Engagement Disorder From Early Childhood to Early Adolescence. J Am Acad Child Adolesc

Article topic: Obstructive Sleep Apnea.

Author: Ihda Mahmoud Bani Khalaf.

Editor: Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: Obstructive, Sleep Disorder, Apnea, Psychiatry.

Overview

A sleep disorder called obstructive sleep apnea (OSA) is characterized by frequent episodes of the airway becoming completely or partially blocked while a person is asleep. (1) It happens when there are frequent episodes of upper airway obstruction and collapses while you are sleeping coupled with arousals that may or may not cause oxygen desaturations. The oropharynx in the back of the throat collapses because of these OSA events, causing arousal, oxygen desaturation, or both, leading to fragmented sleep. (1)

Studies show that OSA is common. According to a 2015 study conducted in Switzerland, 23% of women and 50% of men had at least moderate OSA. (2) According to the Sleep Heart Health study from 2002, 9% of women and 24% of men have OSA that is at least mild. (3) According to the Wisconsin Sleep Study Cohort, 17% of men and 9% of women who are between the ages of 50 and 70 have at least moderate OSA, compared to 10% of men and 3% of women in that age group. (4) In the United States, it is estimated that 82% of men and 93% of women have OSA but are not yet diagnosed. (5)

Although patients differ in the number and combination of symptoms they report, there are several typical sleep and daytime symptoms linked to OSA (Table 1). (6) Snoring is one of the most typical sleep-related symptoms. Excessive daytime sleepiness or fatigue are common OSA daytime symptoms. While fatigue refers to feeling worn out, low on energy, and unmotivated, excessive daytime sleepiness refers to feeling very drowsy or very sleepy at times. Another sign is feeling exhausted despite getting the recommended 7 to 9 hours of sleep.

Sleep	Daytime
Snoring	Excessive sleepiness

Gasping	Fatigue
Snorting	Morning headaches
Not breathing	Memory or concentration issues
Fragmented sleep	Mood disturbances or irritability
Sleep maintenance insomnia (inability to stay asleep or wake and not returning to sleep)	Decreased libido
Nocturia	
Bedwetting	
Night sweats	

Table 1: obstructive sleep apnea symptoms (6)

Epidemiology

Around the world, Obstructive sleep apnea is common. (7) Furthermore, some recent studies even point to an increase in prevalence, which is due to the rising prevalence of overweight and obese people. (7) Updated population prevalence estimates based on long-term data from the Wisconsin cohort study do in fact lend credence to this idea. When compared to 5% of men and 4% of women in 1993, 13% of men and 6% of women in the 30-70 age range had moderate to severe sleep-disordered breathing in the late 2000s (apnea-hypopnea index (AHI) 15). (4) The authors concluded that there had been a 14-55% increase in the prevalence of OSA since the early 1990s, depending on the age and gender subgroup.

The ratio is typically even higher in populations of sleep clinics, (8) even though Obstructive Sleep Apnea is typically two to three times more common in men than in women in studies of the general population. Uncertainty about the cause of this disparity suggests that it may be due to the different symptom profiles that cause men to seek medical care earlier than women. Health professionals may also underdiagnose certain subgroups, such as premenopausal women, young and lean people, and patients without severe snoring or obvious Ehlers-Danlos syndromes (EDS). (9)

Etiology and Pathogeneses

Some pathophysiological factors, such as increased upper airway collapsibility, a narrower upper airway, and skeletal abnormalities, are prevalent in both adult and pediatric OSA. Despite these factors, there might be various etiological factors that contribute to the disease. (10)

The peak of incidence occurs between the ages of 2 and 5 years in preschoolers, which is also the time when the adenoids and tonsils develop most in comparison to the oro-pharyngeal space. (11) There is no direct correlation between the size of the adenoids and tonsils and the severity of respiratory sleep disorder, even though adenotonsillar hypertrophy is a significant risk factor for pediatric OSA. (12) Specifically in the second childhood (6–9 years) and during adolescence, obesity is becoming a more significant and frequent risk factor for pediatric OSA. (13)

Risk factors

Both non-modifiable and modifiable factors affect the risk of OSA. Risk factors that cannot be changed include race, age, and male sex. A higher risk of OSA may be caused by cranial facial anatomy that results in narrow airways, genetic predisposition, a family history of OSA, or both. Obesity, drugs that relax muscles and narrow the airway (opioids, benzodiazepines, alcohol), endocrine conditions (hypothyroidism, polycystic ovary syndrome), smoking, nasal congestion, or obstruction are all modifiable risk factors. (9)

Sex

Men have a higher risk of developing OSA than women, though once a woman enters menopause, her risk approaches that of men. It was discovered that postmenopausal women receiving hormone replacement therapy had lower rates of OSA, indicating that a loss of hormones increases the risk of OSA. (14,15) Women also have more OSA during rapid eye movement (REM) sleep and less OSA when sleeping supine, whereas most men have OSA when sleeping supine. (8,16) Women with similar body mass indexes (BMI) have OSA that is less severe than men. (8) Men and women experience different symptoms; men are more likely to snore and have seen apneas, while women are more likely to experience insomnia and excessive daytime sleepiness. (8) This could explain the higher mortality rate in women and the delayed diagnosis in men.

Age

Age increases the risk of OSA. The prevalence of moderate OSA was 23% in men under the age of 72 and 30% in men over the age of 80 in a study of men aged 65 or older. (17) In contrast, 10% of men between the ages of 30 and 40 had moderate OSA. (4) Age-related decline in slow wave sleep, or deep sleep, which protects against sleep-disordered breathing and airway collapse, may be the cause of an increased risk of OSA. (18) Additionally, older adults report less daytime fatigue and sleepiness. (19)

Race

Blacks (20%) and American Indians (23%) had a slightly higher risk of moderate to severe OSA than did whites (17%), according to the Sleep Heart Health Study. (3) According to a different study, the prevalence of OSA was 30% in white people, 32% in black people, 38% in Hispanic people, and 39% in Chinese people. (20) Although another study found no racial differences in older patients, (21) it was reported that young blacks (25 years) had a higher prevalence of OSA than whites. (22) These variations in craniofacial anatomy may be the cause of these racial differences.

Obesity

Obesity (BMI > 30 kg/m2) and its correlates of a higher waist-to-hip ratio and neck circumference are associated with an increased risk of OSA. (3) In comparison to a 10% weight loss, a 10% increase in body weight causes a six-fold increase in moderate to severe OSA and an increase in the apnea-hypopnea index (AHI; the number of breaths pauses or respiratory events per hour) of 32%. (23)

Diagnosis

The diagnosis of OSA and the requirement for treatment are determined by the results of polysomnography (PSG) or home sleep apnea test (HSAT). The American Academy of Sleep Medicine established the most recent OSA diagnostic standards in 2014. (Table 2) (24)

Polysomnogram or home sleep apnea test reveals

- ≥ 15 predominantly obstructive respiratory events per hour of sleep OR
- ≥ 5 predominantly obstructive respiratory events per hour of sleep and at least 1 of the following:
  - Daytime sleepiness, nonrestorative sleep, fatigue, or insomnia

– Waking with breath-holding, gasping, or choking

– Observed loud snoring, breathing interruption, or both

– Hypertension, mood disorder, cognitive dysfunction, ischemic heart disease, stroke, congestive heart failure, atrial fibrillation, or diabetes type 2

Table 2: obstructive sleep apnea diagnostic criteria (24)

The gold standard of OSA evaluation is polysomnography (PSG). (1) The more recent home sleep apnea test (HSAT), while convenient for some patients as a confirmatory test, may understate the severity of breathing disorders that are related to sleep. (25)

Respiratory events captured on a PSG or HSAT

The occurrence of obstructive respiratory events during sleep, such as apneas, hypopneas, and respiratory event-related arousals, is the basis for the OSA diagnostic criteria. (1)

Apneas. A respiratory event known as apnea causes a complete lack of airflow, as indicated by a thermal sensor reduction of more than 90% for 10 or more seconds. Obstructive, central, or mixed apneas are possible (Figure 1). When the airway is blocked and breathing effort is felt in the chest and abdomen, obstructive apneas happen (Figure 2). There is no airflow and no respiratory effort in central apnea, which means the brain is not telling the body to breathe. Lack of airflow with and without respiratory effort is brought on by mixed apneas. (1)

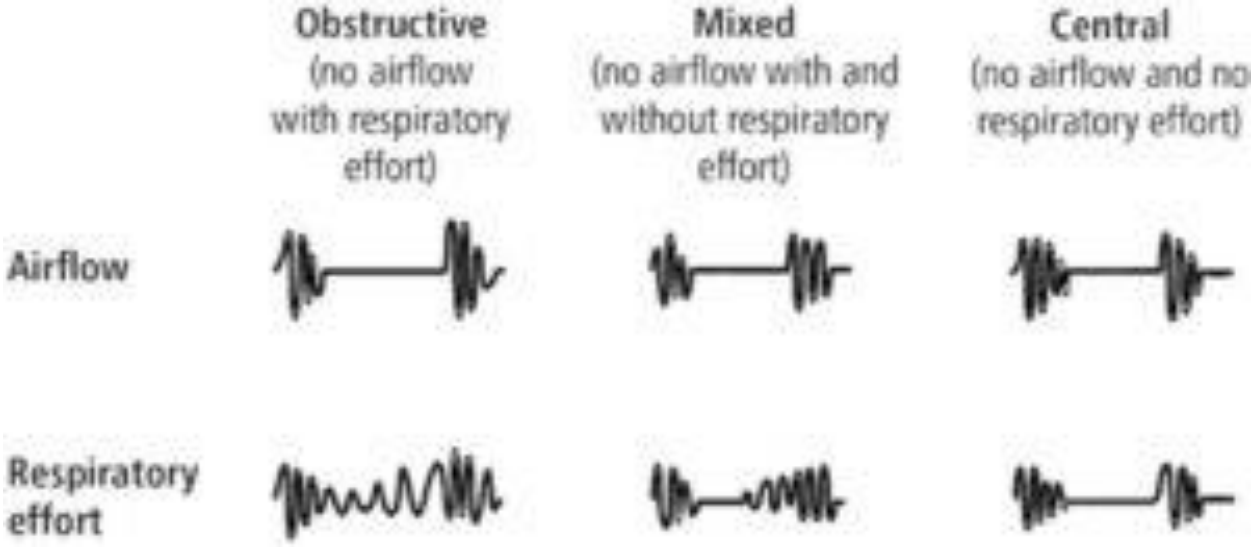


Figure 1: Apneas can be obstructive, mixed, or central (1)

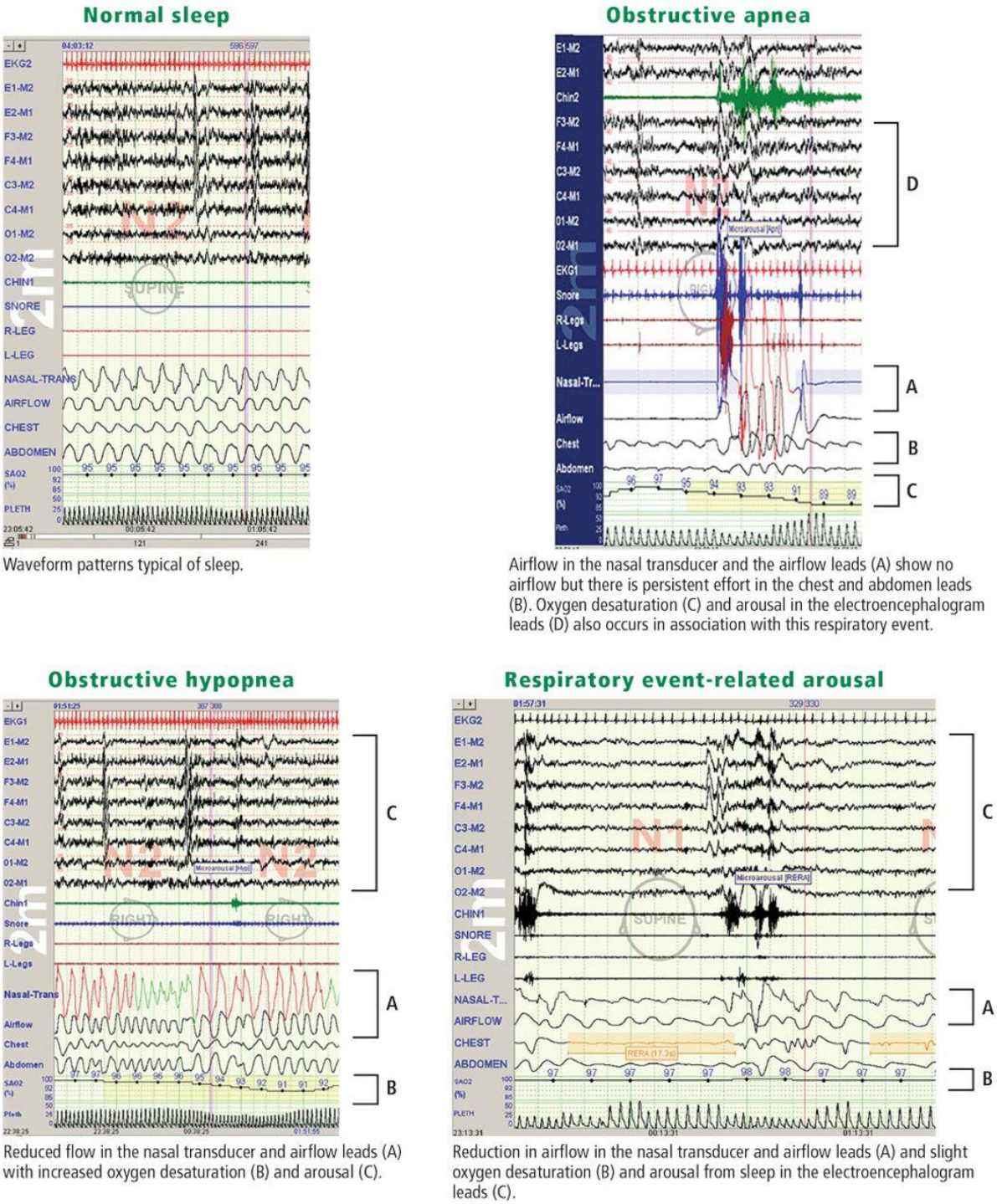


Figure 2: Polysomnogram excerpts with normal sleep, obstructive apnea, obstructive hypopnea, and respiratory event-related arousal waveform findings. (1)

Severity

The severity of OSA should be included in the diagnosis (mild, moderate, or severe), as it may influence whether the patient receives treatment. AHI, respiratory disturbance index, or respiratory event index are used to quantify severity (Table 3). (26) A value of 5 to 14.9 for any of the 3 indices is regarded as mild, 15 to 29.9 as moderate, and 30 or higher as severe.

Index	Calculation
Apnea–hypopnea index (AHI)	(Apneas + Hypopneas) / Total Sleep Time, hours
Respiratory disturbance index	(AHI + Respiratory event-related arousal) / Total Sleep Time, hours
Respiratory event index	(Apneas + Hypopneas) / Total monitoring time, hours

Table 3: Respiratory event index is typically used for home sleep apnea testing as it is based on monitoring time as distinct from actual sleep time. (26)

OSA in pediatric patients

The ICSD-3 recommends two methods for determining whether a child has OSA: one is clinically based on the presence of one or more symptoms (excessive daytime sleepiness, behavioral changes, snoring, shortness, paradox, or blocked breath during sleep). (24)

One or more obstructive apneas, mixed apneas, or hypopneas for sleep time, or 25% of TST with hypercapnia ($PaCO_2$ > 50 mmHg) in association with one or more of the following parameters: snoring, flattening of the flow curve, or thoracoabdominal paradox movement, constitute the second criteria. (24)

DSM 5 Diagnostic Criteria (27)

1. Either (1) or (2):
2. Evidence by polysomnography of at least five obstructive apneas or hypopneas per hour of sleep and either of the following sleep symptoms:
3. Nocturnal breathing disturbances: snoring, snorting/gasping, or breathing pauses during sleep.

4. Daytime sleepiness, fatigue, or unrefreshing sleep despite sufficient opportunities to sleep that is not better explained by another mental disorder (including a sleep disorder) and is not attributable to another medical condition.
5. Evidence by polysomnography of 15 or more obstructive apneas and/or hypopneas per hour of sleep regardless of accompanying symptoms.

Specify current severity:

Mild: Apnea hypopnea index is less than 15.

Moderate: Apnea hypopnea Index is 15-30.

Severe: Apnea hypopnea index is greater than 30.

Physical examination

Physical exam findings that might point to OSA include the following: (6)

- greater than 17 inches for men and 16 inches for women in the neck circumference
- greater than 30 BMI
- Tongue position Friedman class 3 or higher (Figure 3)
- Features of the mouth (macroglossia, enlarged or present tonsils)
- nasal deviations (turbinate hypertrophy, deviated septum).

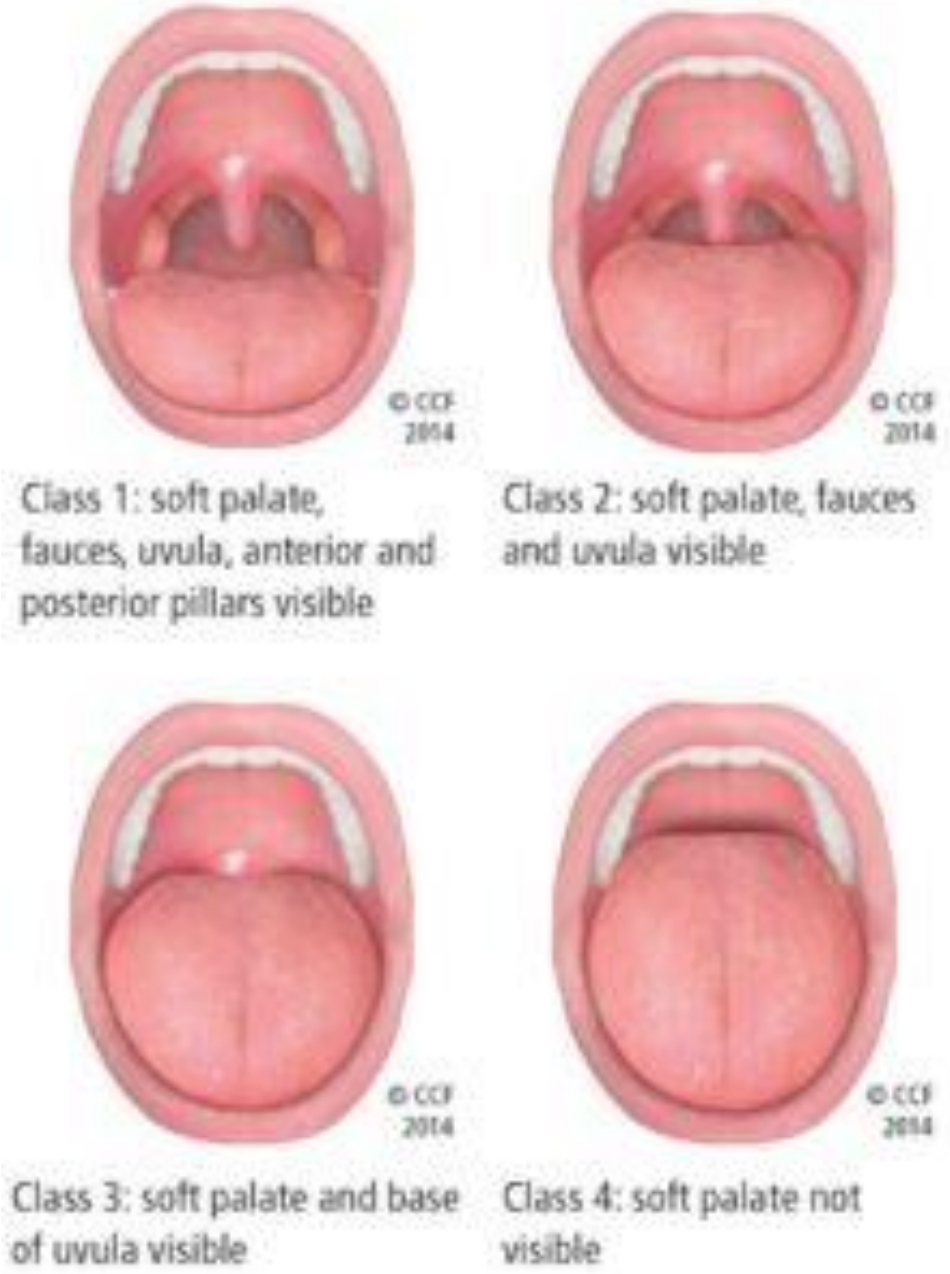


Figure 3: Friedman palate positions (classes 1, 2, 3, and 4). (6)

Management and Treatment

The goal of treating OSA is to lessen symptoms, enhance the quality of life, lessen the burden of co-morbidities, and reduce mortality. As a result, the treatment plan for a specific patient should be customized based on the severity of OSA and any associated co-morbidities. (7)

Treatments for OSA include changing one's behavior, losing weight, taking medication, applying continuous positive airway pressure, using oral appliances (such as tongue-retaining devices, orthodontic appliances, or mandibular advancing appliances), and

having surgery (e.g., tracheostomy, uvulopalatopharyngoplasty, laser-assisted uvulopalatoplasty, surgically assisted rapid maxillary expansion, maxillomandibular advancement, and hypoglossal nerve stimulation). (31)

The potential causes of OSA are addressed by behavioral therapies. All OSA patients should refrain from using alcohol and sedatives. By reducing apneic episodes and snoring, weight loss has a positive effect on airway patency for some patients. Avoiding the supine position while you sleep may help some patients experience fewer sleep apnea episodes. The effectiveness of suggested pharmacotherapeutic treatments for OSA has not been established, and the role of pharmacotherapy in treating OSA is still unknown. (31)

Nasal continuous positive airway pressure (CPAP), in which the upper airway is splinted open to improve patency during sleep, is the first-line treatment for OSA. When used properly and regularly, CPAP effectively reduces sleepiness symptoms and enhances the quality-of-life indicators in people with moderate to severe OSA. (32) With a success rate of about 75%, CPAP is regarded as the best treatment option for moderate-to-severe OSA. Sadly, reported nonadherence rates (where adherence is defined as using a CPAP for at least 4 hours each night) range from 46% to 83%. (33) However, patients who reject or are unable to tolerate CPAP must have other treatment options.

Prevention

Since obesity is the single biggest risk factor for developing OSA, preventing or reducing overweight and obesity is the most efficient way to lower OSA rates in a population. OSA appears to be significantly reduced following significant weight loss in several RCTs, and this holds true for both dietary and surgical approaches. (28–30) There is, however, a dearth of evidence demonstrating that weight loss techniques can significantly lower OSA occurrence over time.

Conclusion

Despite our growing understanding of OSA, there are still unanswered questions and issues with suggested OSA treatments. By assisting in the provision of the highest caliber of healthcare to OSA patients, multidisciplinary teams made up of dentists, orthodontists, and oral-maxillofacial surgeons can lay the groundwork for addressing these issues. Effective OSA management depends on team members staying in touch and following up.

References

1. Rundo JV. Obstructive sleep apnea basics. Cleve Clin J Med. 2019 Sep;86(9 Suppl 1):2–9.

2. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015 Apr;3(4):310–8.
3. Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med. 2002 Apr;162(8):893–900.
4. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013 May;177(9):1006–14.
5. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep. 1997 Sep;20(9):705–6.
6. Epstein LJ, Kristo D, Strollo PJJ, Friedman N, Malhotra A, Patil SP, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin sleep Med JCSM Off Publ Am Acad Sleep Med. 2009 Jun;5(3):263–76.
7. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Prim. 2015 Jun;1:15015.
8. Redline S, Kump K, Tishler P V, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. Am J Respir Crit Care Med. 1994 Mar;149(3 Pt 1):722–6.
9. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. JAMA. 2004 Apr;291(16):2013–6.
10. Chan KC, Au CT, Hui LL, Ng S-K, Wing YK, Li AM. How OSA Evolves From Childhood to Young Adulthood: Natural History From a 10-Year Follow-up Study. Chest. 2019 Jul;156(1):120–30.
11. Alsubie HS, BaHammam AS. Obstructive Sleep Apnoea: Children are not little Adults. Paediatr Respir Rev. 2017 Jan;21:72–9.
12. Lam Y, Chan EYT, Ng DK, Chan C, Cheung JMY, Leung S, et al. The correlation among obesity, apnea-hypopnea index, and tonsil size in children. Chest. 2006 Dec;130(6):1751–6.
13. Choi JH, Kim EJ, Choi J, Kwon SY, Kim TH, Lee SH, et al. Obstructive sleep apnea syndrome: a child is not just a small adult. Ann Otol Rhinol Laryngol. 2010 Oct;119(10):656–61.
14. Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med. 2003 May;167(9):1181–5.
15. Shahar E, Redline S, Young T, Boland LL, Baldwin CM, Nieto FJ, et al. Hormone replacement therapy and sleep-disordered breathing. Am J Respir Crit Care Med. 2003 May;167(9):1186–92.
16. Collop NA, Adkins D, Phillips BA. Gender differences in sleep and sleep-disordered breathing. Clin Chest Med. 2004 Jun;25(2):257–68.
17. Mehra R, Stone KL, Blackwell T, Ancoli Israel S, Dam T-TL, Stefanick ML, et al. Prevalence and correlates of sleep-disordered breathing in older men: osteoporotic fractures in men sleep study. J Am Geriatr Soc. 2007 Sep;55(9):1356–64.
18. Van Cauter E, Leproult R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA. 2000 Aug;284(7):861–8.
19. Groth M. Sleep apnea in the elderly. Clin Geriatr Med. 2005 Nov;21(4):701–12, vi.
20. Chen X, Wang R, Zee P, Lutsey PL, Javaheri S, Alcántara C, et al. Racial/Ethnic Differences in Sleep Disturbances: The Multi-Ethnic Study of Atherosclerosis (MESA). Sleep. 2015 Jun;38(6):877–88.
21. Redline S, Tishler P V, Hans MG, Tosteson TD, Strohl KP, Spry K. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. Am J Respir Crit Care Med. 1997 Jan;155(1):186–92.
22. Song Y, Ancoli-Israel S, Lewis CE, Redline S, Harrison SL, Stone KL. The association of race/ethnicity with objectively measured sleep characteristics in older men. Behav Sleep Med. 2011 Dec;10(1):54–69.
23. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA. 2000 Dec;284(23):3015–21.
24. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014 Nov;146(5):1387–94.
25. Iber C, Ancoli-Israel S, Chesson A QS. The ASSM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications 1st ed Winchester, IL: American Academy of Sleep Medicine. Am Acad Sleep Med. 2007;
26. Younes M, Kuna ST, Pack AI, Walsh JK, Kushida CA, Staley B, et al. Reliability of the American Academy of Sleep Medicine Rules for Assessing Sleep Depth in Clinical Practice. J Clin sleep Med JCSM Off Publ Am Acad Sleep Med. 2018 Feb;14(2):205–13.
27. Sutton WS. Neurocognitive disorders. Handbook of Geropsychiatry for the Advanced Practice Nurse: Mental Health Care for the Older Adult. 2020. 133–158 p.
28. Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. Arch Intern Med. 2009 Sep;169(17):1619–26.
29. Dixon JB, Schachter LM, O'Brien PE, Jones K, Grima M, Lambert G, et al. Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. JAMA. 2012 Sep;308(11):1142–9.
30. Araghi MH, Chen Y-F, Jagielski A, Choudhury S, Banerjee D, Hussain S, et al. Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-analysis. Sleep. 2013 Oct;36(10):1553–62, 1562A-1562E.
31. Chang H-P, Chen Y-F, Du J-K. Obstructive sleep apnea treatment in adults. Kaohsiung J Med Sci. 2020 Jan;36(1):7–12.
32. Antic NA, Catcheside P, Buchan C, Hensley M, Naughton MT, Rowland S, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. Sleep. 2011 Jan;34(1):111–9.

33. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc. 2008 Feb;5(2):173–8.

Article topic: Premenstrual Dysphoric Disorder (PMDD).

Authors: Mohammad Kamal Daradkeh, Ahed Fahmi Mohammad Daoud.

Editors: Mohammad Omari, Haneen A. Banihani, Ihda Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Overview

Premenstrual dysphoric disorder (PMDD) is a common mood disorder with distinct affective, cognitive, and physical symptoms affecting millions of women during their reproductive age [1]. According to DSM-5 criteria, these symptoms occur in the last week before menses and continue within 3-4 days after menses, confirmed by specific tools for a daily rating of symptoms for at least two menstrual cycles [1]. Despite sharing the cyclicity of psychological and physical symptoms that impair the patient's social and occupational life, Premenstrual dysphoric disorder should be considered a separate entity from premenstrual syndrome (PMS) in aspects of hopelessness, tension, extreme moodiness, and marked irritability, as these severe affective symptoms lead the women with PMDD to seek medical help more than women with PMS [2]. Different studies showed an association between PMDD and decreased work productivity that leads to absence, adding to the economic burden of the disorder [3]. Interestingly, women with PMDD were at increased risk of reporting suicidal ideations, thoughts, plans, and attempts than PMS patients and the general population, although that didn't implicate any significant suicide risk profile in terms of frequency and completion [4].

PMDD is characterized by at least five symptoms, affective, that are present in the luteal phase of most menstrual cycles. In addition, behavioral and somatic symptoms can accompany the main affective symptoms, such as changes in appetite or food cravings, changes in sleep, loss of energy, or physical complaints (i.e., breast tenderness or bloating), which can overlap with other mood disorders. Yet, it is distinguished by its predictable cyclicity, confined to the premenstrual period [1]. It is thought that the altered sensitivity to the fluctuating serum levels of ovarian hormones that occur during the menstrual period, especially progesterone, in the brain-sensitive regions involved in top-down control and mesolimbic emotional processing, plays a role in the symptomatology of this disorder, according to some studies [5-7].

PMDD affects 1.8 - 5.8 % of women of childbearing age. The incidence of new cases over a 40-month follow-up period is 2.5%. Onset can occur at any point after menarche. Many individuals, as they approach menopause, report worsening symptoms but cease after that, although cyclical hormone replacement can trigger the re-expression of symptoms [1].

Etiology and Pathogenesis

Recently, the etiology behind PMDD has been an active area of investigation and an important subject for randomized controlled clinical trials [8]. It can be divided into genetic, biological, environmental, or psychosocial factors. There are no studies examining the familial association based on DSM-5 criteria for PMDD because of the difficulty in obtaining prospective symptom reporting in a large sample of first-degree relatives of multiple generations [9]. However, the heritability of premenstrual symptoms can range from 35.1% to 56%, according to old studies [10,11].

Progestrone and Allopregnanolone

More substantial evidence for its pathogenesis was found by studying progesterone, its primary active metabolite, Allopregnanolone (ALLO) levels, and its effect on (GABA) A receptor function. ALLO is a positive modulator of the (GABA) A receptor with anxiolytic, anesthetic, and sedative properties like that of alcohol and benzodiazepines[12], so the rapid withdrawal of high serum levels of progesterone and ALLO at the end of the luteal phase may lead to upregulation of the receptor and may play a role in the anxiety and depressive-like behavior [13], [14]. Giving their (GABA) A sensitivity to progesterone and ALLO, especially in regions involved in aggression and cognitive control (i.e., angulate cingulate gyrus (ACC) and medial prefrontal cortex (mPFC)), PMDD patients randomized to selective progesterone receptor modulator (SPRM) treatment, which works by progesterone antagonism, had shown lower aggression scores and enhanced brain reactivity to negative stimuli compared with placebo group suggesting a beneficial role of progesterone antagonism and anovulation[6].

Given the CNS sensitivity of PMDD patients, the decline in the estrogen serum level in the luteal phase may add to the symptomatology of PMDD in terms of mood, cognition, sleep, eating, and other aspects [15], considering the possible estradiol-enhancing effects on the serotonergic system through increasing serotonin transporter mRNA expression[16], and decreasing monoamine oxidase A (MAOA) [17]. Moreover, patients with PMDD experience serotonergic abnormalities exacerbated in the luteal phase; one of them is the deficiency of the whole blood level of total serotonin 5-HT [18], adding evidence to the increased sensitivity to estrogen among patients with PMDD. One study found that single nucleotide polymorphisms in the estrogen receptor alpha (ESR1) gene were associated with an increased risk for PMDD [19].

Women with PMDD who carriers of the Val66Met polymorphism of the Met allele of the brain-derived neurotrophic factor (BDNF) are had lower front cingulate cortex activation during the luteal phase [20]; in addition, they had significantly higher serum BDNF levels, especially during luteal phase [21]. However, further investigation is

needed as the obvious association is inconclusive despite the evidence of cyclicity across the menstrual cycle [22].

Immune System Dysregulation

Some evidence suggests the role of immune system dysregulation, as the luteal phase is associated with increased production of soluble interleukin 6 receptor (IL-6R) and increased expression of proinflammatory IL-6 and tumor necrosis factor alpha (TNF-A) [23,24]. C-reactive protein (CRP) level follows a cyclic pattern, as a tenfold increase in progesterone was associated with a 20-23% CRP increase [25,26].

The most relevant environmental factors associated with PMDD include stress, interpersonal trauma, seasonal allergies, and sociocultural aspects of female sexual behavior and gender roles [1]. Looking at the literature, the role of stress as an etiology of PMDD is controversial. Some studies found an association between traumatic history, physical and emotional abuse, and PMDD [27,28], but others demonstrated no increased risk compared with healthy counterparts [29]. The GABAergic sedative effect of ALLO promotes homeostasis during periods of acute stress [30], but the response becomes blunted with chronic stress [31], so administering exogenous ALLO may correct chronic stress-induced depressive and anxiety-like behaviors [32].

Estrogen

Estrogen plays a vital role in normal sexual and reproductive development in women. It comes in multiple forms, but the most important is estradiol, secreted in significant amounts by ovaries and small quantities by the adrenal cortex and pregnancy; it's released from the placenta, too [17].

In some trials, they found that polymorphism in the alpha gene in estrogen receptor is associated with the risk of PMDD and demonstrated a low estradiol level among women with PMDD [8].

A study that tests the effect of alteration in hormonal levels among PMDD demonstrates an increase in the risk of mood symptoms among women whose estrogen is in a lower concentration, such as in the premenstrual phase, postpartum, and post-menopause.

Tamoxifen, a medication that suppresses estrogen function, contributes to depression's pathophysiology. These results suggest that withdrawal from estrogen contributes to mood symptoms with PMDD [62].

Estrogen facilitates higher cognitive functions by affecting brain regions like the prefrontal cortex and hippocampus. These regions are most known for their involvement in regulating one's mood and cognition and initiating a complex set of

signal transduction pathways via estrogen receptors [18]. By these signals, estrogen can modulate the function of various neurotransmitters, such as serotonin and GABA [63].

Clinical presentation and complications

The fundamental features of premenstrual dysphoric disorder are mood lability, irritability, dysphoria, and anxiety, which are present in the premenstrual period and resolve shortly after menses [1]. Many women may complain of physical symptoms such as headache, fatigue, cramps, backache, weight gain, acne, constipation, diarrhea [33], and behavioral changes. The symptoms should be confirmed by a prospective daily rating for at least two menstrual cycles accomplished via tools such as the Daily Record of Severity of Problems (DRSP) [34]. The symptoms would be manifested as long as cyclic ovarian hormonal activity persists, meaning that a significant part of women affected could be adolescents [35]. Building on that, PMDD is not found in periods of hypothalamic amenorrhea, pregnancy, breastfeeding, and following menopause [36,37]. Rarely, delusions and hallucinations have been described in the late luteal phase of the menstrual cycle [1].

Like many disorders included in DSM-5, The condition is disabling as it can impair the function of women in different settings. Clinically significant distress with or without a noticeable and marked impairment in the ability to function socially or occupationally in the final week before menses is of major concern, as impairment in social functioning may be manifested by marital discord and problems with children, other family members, or friends. In addition, PMDD had significant effects on concentration [1].

Diagnosis and workup

According to DSM-5 American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders criteria:[1]

Criterion A: In most menstrual cycles, at least five symptoms must be present in the final week before the onset of menses (luteal phase), start to improve within a few days after the beginning of menses, and become minimal or absent in the week post menses (follicular phase) At least one (or more) of the following symptoms must be present:

Criterion B:

1. Marked affective lability (e.g., mood swings, feeling suddenly sad or tearful, or increased sensitivity to rejection).
2. Marked irritability or anger or increased interpersonal conflicts and problems.
3. Marked depressed mood, feelings of hopelessness, or self-deprecating(disapproval) thoughts.

4. Marked anxiety, tension, and/or feelings of being keyed up or on the edge.

Criterion C: At least one (or more) of the following symptoms must additionally be present, to reach a total of five symptoms when combined with symptoms from Criterion B above.

1. Decreased interest in usual activities of life (e.g., work, school, friends, hobbies).
2. Subjective difficulty in concentration.
3. Lethargy, easy fatigability, or marked lack of energy.
4. Marked change in appetite, overeating, or specific food cravings.
5. Hypersomnia or insomnia.
6. A sense of being overwhelmed or out of control.
7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," or weight gain.

Note: The symptoms in Criteria A-C must have been met for most menstrual cycles that occurred in the preceding year.

Criterion D: The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).

Criterion E: The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).

Criterion F: Criterion A should be confirmed by prospective daily rating tools during at least two symptomatic cycles, although the diagnosis may be made provisionally prior to this confirmation.

Criterion G: The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or another medical condition (e.g., hyperthyroidism).

Importantly, physical, and behavioral symptoms in the absence of mood and/or anxiety symptoms make the diagnosis of PMDD insufficient [1]. The Premenstrual Tension Syndrome Rating Scale is a useful tool as it has a self-report and an observer version, both of which have been validated and used widely to measure illness severity [1].

Treatment and management

Selective serotonin reuptake inhibitors (SSRIs) are the first line of treatment for patients with PMDD, given that they have shown efficacy in multiple controlled clinical trials [38-41], and their action in stabilizing the serotonin level, which is thought to be deficient in these patients, thus playing a major role in pathogenesis and symptomatology of this disorder[18]. It was found that there was no difference in efficacy between SSRIs administration only in symptomatic premenstrual period and with continuous daily administration [38]. In contrast to weeks that are required for response in major depression, SSRIs have been shown to have a shorter duration of onset in PMDD, taking effect within hours to days [42]. Active treatment with sertraline has shown to be effective in treating irritability and anger cardinal symptoms of PMDD [43], with weaker effects on depressive and somatic symptoms [38]. Treatment of PMDD patients with comorbid bipolar disorder poses challenges, as SSRIs have a risk of treatment-emergent manic episodes [44].

Oral contraceptives (OCPs), according to some clinical trials, have been shown to significantly improve PMDD symptoms through a combination of drospirenone and ethinyl estradiol (EE) dosed for 24 active days and 4 inactive days for a 28-day cycle [45,46]. On the other hand, other studies have found that the combination with 21 active days and 7 inactive days dosing didn't show more efficacy than placebo [47]. It is suggested that continuous dosing of OCP without a hormone-free period might be more efficacious than traditional dosing [48], although some studies have shown no difference [49].

Gonadotropin-releasing hormone agonist (GnRHa) Leuprolide is effective, although the significant side effects of ovarian suppression might interfere with compliance and efficacy [50]. Given its major role in pathophysiology, novel pharmacotherapies such as sepranolone, an allopregnanolone antagonist, have been developed and showed a significant reduction in symptoms [51], considering it a promising drug in treating PMDD.

Cognitive behavioral therapy (CBT), especially internet-based, has been shown to decrease the disease burden and its impact on everyday life by increasing cognitive and behavioral coping strategies [52], although it does not produce the effect as rapidly as SSRIs like fluoxetine [53].

Risk factors

Genetics, age of puberty, socioeconomic status, educational level, and cognitive factors were all implicated as risk factors [54-57]. Val66Met polymorphism of the Met allele of the brain-derived neurotrophic factor (BDNF) is one of the popular studied genes that

may increase the risk in the susceptible carriers [20], [58]. The age of puberty is inversely correlated with developing premenstrual symptoms, and late menarche has a lower risk of developing PMDs [56].

PMDD was significantly higher among older women with low socioeconomic status and lower-educated women [54,55]. A study has shown that negative cognitive styles are a crucial factor in the development of PMDD [57].

Prognosis

Earlier results have demonstrated that the diverse types of impairment and reduced quality of life found with PMDD were comparable in severity to that found in MDD and dysthymia, with worse impairment in social activities and hobbies than in dysthymia, and similar relational impairment in social, marital, and parental relationships in comparison with women diagnosed with MDD. In contrast, women with MDD had more significant occupational and social impairment [59]. The emotional, psychological, and physical symptoms were different in their association with impairment, as the psychological symptoms were the strongest predictors of impairment, while the physical was the least associated with a significant functional impairment [60].

Importantly, PMDD as an independent disorder has a good prognosis in cases of proper diagnosis and management [61]. On the other hand, the increased reporting of suicidal ideations, thoughts, and tries among women with PMDD can be a leading cause of significant morbidity and mortality [4].

References

[1] American Psychiatric Association. and American Psychiatric Association. DSM-5 Task Force., *Diagnostic and statistical manual of mental disorders: DSM-5*. American Psychiatric Association, 2013.

[2] P. M. S. O'Brien *et al.*, "Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: The ISPMD Montreal consensus," *Archives of Women's Mental Health*, vol. 14, no. 1. pp. 13–21, Feb. 2011. doi: 10.1007/s00737-010-0201-3.

[3] M. S. Hunter, J. M. Ussher, S. J. Browne, M. Cariss, R. Jelley, and M. Katz, "A randomized comparison of psychological (cognitive behavior therapy), medical (fluoxetine) and combined treatment for women with premenstrual dysphoric disorder," *Journal of Psychosomatic Obstetrics and Gynecology*, vol. 23, no. 3, pp. 193–199, 2002, doi: 10.3109/01674820209074672.

[4] E. Osborn, J. Brooks, P. M. S. O'brien, and & A. Wittkowski, "Suicidality in women with Premenstrual Dysphoric Disorder: a systematic literature review", doi: 10.1007/s00737-020-01054-8/Published.

[5] M. Gingnell, A. Morell, E. Bannbers, J. Wikström, and I. Sundström Poromaa, "Menstrual cycle effects on amygdala reactivity to emotional stimulation in premenstrual dysphoric disorder," *Hormones and Behavior*, vol. 62, no. 4, pp. 400–406, Sep. 2012, doi: 10.1016/j.yhbeh.2012.07.005.

[6] E. Kaltsouni *et al.*, "Brain reactivity during aggressive response in women with premenstrual dysphoric disorder treated with a selective progesterone receptor modulator," *Neuropsychopharmacology*, vol. 46, no. 8, pp. 1460–1467, Jul. 2021, doi: 10.1038/s41386-021-01010-9.

[7] E. Bannbers *et al.*, "The effect of premenstrual dysphoric disorder and menstrual cycle phase on brain activity during response inhibition," *Journal of Affective Disorders*, vol. 142, no. 1–3, pp. 347–350, Dec. 2012, doi: 10.1016/j.jad.2012.04.006.

[8] L. Hantsoo and C. N. Epperson, "Premenstrual Dysphoric Disorder: Epidemiology and Treatment," *Current Psychiatry Reports*, vol. 17, no. 11, Nov. 2015, doi: 10.1007/s11920-015-0628-3.

[9] K. McEvoy, L. M. Osborne, J. Nanavati, and J. L. Payne, "Reproductive Affective Disorders: A Review of the Genetic Evidence for Premenstrual Dysphoric Disorder and Postpartum Depression," *Current Psychiatry Reports*, vol. 19, no. 12. Current Medicine Group LLC 1, Dec. 01, 2017. doi: 10.1007/s11920-017-0852-0.

[10] J. T. Condon, "The premenstrual syndrome: A twin study," *British Journal of Psychiatry*, vol. 162, no. APR., pp. 481–486, 1993, doi: 10.1192/bjp.162.4.481.
[11] K. S. Kendler, L. M. Karkowski, L. A. Corey, and M. C. Neale, "Longitudinal population-based twin study of retrospectively reported premenstrual symptoms and lifetime major depression," *American Journal of Psychiatry*, vol. 155, no. 9, pp. 1234–1240, 1998, doi: 10.1176/ajp.155.9.1234.
[12] C. Schüle, C. Nothdurfter, and R. Rupprecht, "The role of allopregnanolone in depression and anxiety," *Progress in Neurobiology*, vol. 113. Elsevier Ltd, pp. 79–87, 2014. doi: 10.1016/j.pneurobio.2013.09.003.
[13] S. S. Smith, Y. Ruderman, C. Frye, G. Homanics, and M. Yuan, "Steroid withdrawal in the mouse results in anxiogenic effects of 3α,5β-THP: A possible model of premenstrual dysphoric disorder," *Psychopharmacology*, vol. 186, no. 3, pp. 323–333, Jun. 2006, doi: 10.1007/s00213-005-0168-3.
[14] Y. Li, A. L. Pehrson, D. P. Budac, C. Sánchez, and M. Gulinello, "A rodent model of premenstrual dysphoria: Progesterone withdrawal induces depression-like behavior that is differentially sensitive to classes of antidepressants," *Behavioural Brain Research*, vol. 234, no. 2, pp. 238–247, Oct. 2012, doi: 10.1016/j.bbr.2012.06.034.
[15] S. Shanmugan and C. N. Epperson, "Estrogen and the prefrontal cortex: Towards a new understanding of estrogen's effects on executive functions in the menopause transition," *Human Brain Mapping*, vol. 35, no. 3. pp. 847–865, Mar. 2014. doi: 10.1002/hbm.22218.
[16] P. P. Bertrand, U. T. Paranavitane, C. Chavez, A. Gogos, M. Jones, and M. van den Buuse, "The effect of low estrogen state on serotonin transporter function in mouse hippocampus: A behavioral and electrochemical study," *Brain Research*, vol. 1064, no. 1–2, pp. 10–20, Dec. 2005, doi: 10.1016/j.brainres.2005.10.018.
[17] C. Gundlah, N. Z. Lu, and C. L. Bethea, "Ovarian steroid regulation of monoamine oxidase-A and B mRNAs in the macaque dorsal raphe and hypothalamic nuclei," *Psychopharmacology*, vol. 160, no. 3, pp. 271–282, 2002, doi: 10.1007/s00213-001-0959-0.
[18] H. Kikuchi *et al.*, "Decreased blood serotonin in the premenstrual phase enhances negative mood in healthy women," *Journal of Psychosomatic Obstetrics and Gynecology*, vol. 31, no. 2, pp. 83–89, Jun. 2010, doi: 10.3109/01674821003770606.
[19] A. Miller, H. Vo, L. Huo, C. Roca, P. J. Schmidt, and D. R. Rubinow, "Estrogen receptor alpha (ESR-1) associations with psychological traits in women with PMDD and controls," *Journal of Psychiatric Research*, vol. 44, no. 12, pp. 788–794, Sep. 2010, doi: 10.1016/j.jpsychires.2010.01.013.
[20] E. Comasco *et al.*, "Emotional fronto-cingulate cortex activation and brain derived neurotrophic factor polymorphism in premenstrual dysphoric disorder," *Human Brain Mapping*, vol. 35, no. 9, pp. 4450–4458, 2014, doi: 10.1002/hbm.22486.
[21] E. Oral *et al.*, "Serum brain-derived neurotrophic factor differences between the luteal and follicular phases in premenstrual dysphoric disorder," *General Hospital Psychiatry*, vol. 37, no. 3, pp. 266–272, May 2015, doi: 10.1016/j.genhosppsych.2015.03.001.
[22] D. L. Carbone and R. J. Handa, "Sex and stress hormone influences on the expression and activity of brain-derived neurotrophic factor," *Neuroscience*, vol. 239. pp. 295–303, Jun. 03, 2013. doi: 10.1016/j.neuroscience.2012.10.073.
[23] S. M. O'Brien, P. Fitzgerald, P. Scully, A. M. T. Landers, L. v. Scott, and T. G. Dinan, "Impact of gender and menstrual cycle phase on plasma cytokine concentrations," *NeuroImmunoModulation*, vol. 14, no. 2, pp. 84–90, Sep. 2007, doi: 10.1159/000107423.
[24] H. Northoff, M. W. Löffler, A. Abbasi, and P. Simon, "Gender-and menstrual phase dependent regulation of inflammatory gene expression in response to aerobic exercise The HLA Ligand Atlas View project IFR for SARS CoV-2 View project," 2008. [Online]. Available: https://www.researchgate.net/publication/23993522
[25] A. J. Gaskins *et al.*, "Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: The BioCycle Study," *American Journal of Epidemiology*, vol. 175, no. 5, pp. 423–431, Mar. 2012, doi: 10.1093/aje/kwr343.
[26] K. Wander, E. Brindle, and K. A. O'Connor, "C-reactive protein across the menstrual cycle," *American Journal of Physical Anthropology*, vol. 136, no. 2, pp. 138–146, Jun. 2008, doi: 10.1002/ajpa.20785.
[27] C. E. Pilver, B. R. Levy, D. J. Libby, and R. A. Desai, "Posttraumatic stress disorder and trauma characteristics are correlates of premenstrual dysphoric disorder," *Archives of Women's Mental Health*, vol. 14, no. 5, pp. 383–393, Oct. 2011, doi: 10.1007/s00737-011-0232-4.
[28] Q. Yang *et al.*, "Clinical indications of premenstrual disorders and subsequent risk of injury: a population-based cohort study in Sweden," *BMC Medicine*, vol. 19, no. 1, Dec. 2021, doi: 10.1186/s12916-021-01989-4.
[29] B. Segebladh *et al.*, "Prevalence of violence exposure in women with premenstrual dysphoric disorder in comparison with other gynecological patients and asymptomatic controls," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 90, no. 7, pp. 746–752, Jul. 2011, doi: 10.1111/j.1600-0412.2011.01151.x.
[30] R. R. Klatzkin, A. Leslie Morrow, K. C. Light, C. A. Pedersen, and S. S. Girdler, "Associations of histories of depression and PMDD diagnosis with allopregnanolone concentrations following the oral administration of micronized progesterone," *Psychoneuroendocrinology*, vol. 31, no. 10, pp. 1208–1219, Nov. 2006, doi: 10.1016/j.psyneuen.2006.09.002.
[31] M. Serra, E. Sanna, M. C. Mostallino, and G. Biggio, "Social isolation stress and neuroactive steroids," *European Neuropsychopharmacology*, vol. 17, no. 1. pp. 1–11, Jan. 01, 2007. doi: 10.1016/j.euroneuro.2006.03.004.
[32] J. Evans, Y. Sun, A. McGregor, and B. Connor, "Allopregnanolone regulates neurogenesis and depressive/anxiety-like behaviour in a social isolation rodent model of chronic stress," *Neuropharmacology*, vol. 63, no. 8, pp. 1315–1326, Dec. 2012, doi: 10.1016/j.neuropharm.2012.08.012.
[33] K. A. Lee and C. A. Rittenhouse, "Prevalence of perimentrual symptoms in employed women," *Women and Health*, vol. 17, no. 3, pp. 17–32, Aug. 1991, doi: 10.1300/J013v17n03_02.
[34] J. Endicott, J. Nee, and W. Harrison, "Daily Record of Severity of Problems (DRSP): Reliability and validity," *Archives of Women's Mental Health*, vol. 9, no. 1, pp. 41–49, Jan. 2006, doi: 10.1007/s00737-005-0103-y.
[35] A. J. Rapkin and J. A. Mikacich, "Premenstrual dysphoric disorder and severe premenstrual syndrome in adolescents: Diagnosis and pharmacological treatment," *Pediatric Drugs*, vol. 15, no. 3. pp. 191–202, Jun. 2013. doi: 10.1007/s40272-013-0018-4.

[36] S. Hammarbl=a, U.-B. Ekholm, and T. " rn Bl=a, "Spontaneous anovulation causing disappearance of cyclical symptoms in women with the premenstrual syndrome."
[37] R. L. Reid, "CLINICAL SECTION Clinical Opinion Premenstrual syndrome: A time for introspection."
[38] M. Landén, H. Nissbrandt, C. Allgulander, K. Sörvik, C. Ysander, and E. Eriksson, "Placebo-controlled trial comparing intermittent and continuous paroxetine in premenstrual dysphoric disorder," *Neuropsychopharmacology*, vol. 32, no. 1, pp. 153–161, Jan. 2007, doi: 10.1038/sj.npp.1301216.
[39] K. A. Yonkers, T. Pearlstein, R. Fayyad, and J. A. Gillespie, "Luteal phase treatment of premenstrual dysphoric disorder improves symptoms that continue into the postmenstrual phase," *Journal of Affective Disorders*, vol. 85, no. 3, pp. 317–321, 2005, doi: 10.1016/j.jad.2004.10.006.
[40] L. S. Cohen *et al.*, "Premenstrual Daily Fluoxetine for Premenstrual Dysphoric Disorder: A Placebo-Controlled, Clinical Trial Using Computerized Diaries," 2002.
[41] E. Eriksson *et al.*, "Escitalopram administered in the luteal phase exerts a marked and dose-dependent effect in premenstrual dysphoric disorder," *Journal of Clinical Psychopharmacology*, vol. 28, no. 2, pp. 195–202, Apr. 2008, doi: 10.1097/JCP.0b013e3181678a28.
[42] E. M. Steinberg, G. M. P. Cardoso, P. E. Martinez, D. R. Rubinow, and P. J. Schmidt, "Rapid response to fluoxetine in women with premenstrual dysphoric disorder," *Depression and Anxiety*, vol. 29, no. 6, pp. 531–540, 2012, doi: 10.1002/da.21959.
[43] K. A. Yonkers, S. G. Kornstein, R. Gueorguieva, B. Merry, K. van Steenburgh, and M. Altemus, "Symptom-onset dosing of sertraline for the treatment of premenstrual dysphoric disorder: A randomized clinical trial," *JAMA Psychiatry*, vol. 72, no. 10, pp. 1037–1044, Oct. 2015, doi: 10.1001/jamapsychiatry.2015.1472.
[44] A. Slyepchenko, L. Minuzzi, and B. N. Frey, "Comorbid Premenstrual Dysphoric Disorder and Bipolar Disorder: A Review," *Frontiers in Psychiatry*, vol. 12. Frontiers Media S.A., Aug. 25, 2021. doi: 10.3389/fpsyt.2021.719241.
[45] K. A. Yonkers, C. Brown, T. B. Pearlstein, M. Foegh, C. Sampson-Landers, and A. Rapkin, "Efficacy of a New Low-Dose Oral Contraceptive With Drospirenone in Premenstrual Dysphoric Disorder," 2005.
[46] J. Marr, K. Heinemann, M. Kunz, and A. Rapkin, "Ethinyl estradiol 20 μg/drospirenone 3 mg 24/4 oral contraceptive for the treatment of functional impairment in women with premenstrual dysphoric disorder," *International Journal of Gynecology and Obstetrics*, vol. 113, no. 2, pp. 103–107, 2011, doi: 10.1016/j.ijgo.2010.10.029.
[47] E. W. Freeman *et al.*, "Evaluation of a Unique Oral Contraceptive in the Treatment of Premenstrual Dysphoric Disorder," Mary Ann Liebert, Inc, 2001.
[48] S. v. Carlini and K. M. Deligiannidis, "Evidence-based treatment of premenstrual dysphoric disorder: A concise review," *Journal of Clinical Psychiatry*, vol. 81, no. 2. Physicians Postgraduate Press Inc., Apr. 01, 2020. doi: 10.4088/JCP.19ac13071.
[49] T. A. Eisenlohr-Moul, S. S. Girdler, J. L. Johnson, P. J. Schmidt, and D. R. Rubinow, "Treatment of premenstrual dysphoria with continuous versus intermittent dosing of oral contraceptives: Results of a three-arm randomized controlled trial," *Depression and Anxiety*, vol. 34, no. 10, pp. 908–917, Oct. 2017, doi: 10.1002/da.22673.
[50] K. M. Wyatt, P. W. Dimmock, K. M. K. Ismail, P. W. Jones, and P. M. Shaughn O'brien, "The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis." [Online]. Available: www.blackwellpublishing.com/bjog
[51] M. Bixo *et al.*, "Treatment of premenstrual dysphoric disorder with the GABAA receptor modulating steroid antagonist Sepranolone (UC1010)—A randomized controlled trial," *Psychoneuroendocrinology*, vol. 80, pp. 46–55, Jun. 2017, doi: 10.1016/j.psyneuen.2017.02.031.
[52] C. Weise *et al.*, "Internet-Based Cognitive-Behavioural Intervention for Women with Premenstrual Dysphoric Disorder: A Randomized Controlled Trial," *Psychotherapy and Psychosomatics*, vol. 88, no. 1, pp. 16–29, Mar. 2019, doi: 10.1159/000496237.
[53] T. Nevatte *et al.*, "ISPMD consensus on the management of premenstrual disorders," *Archives of Women's Mental Health*, vol. 16, no. 4, pp. 279–291, Aug. 2013, doi: 10.1007/s00737-013-0346-y.
[54] V. Skrzypulec-Plinta, A. Drosdzol, K. Nowosielski, and R. Plinta, "The complexity of premenstrual dysphoric disorder - risk factors in the population of Polish women," *Reproductive Biology and Endocrinology*, vol. 8, Nov. 2010, doi: 10.1186/1477-7827-8-141.
[55] A. B. de Carvalho *et al.*, "Prevalence and factors associated with Premenstrual Dysphoric Disorder: A community sample of young adult women," *Psychiatry Research*, vol. 268, pp. 42–45, Oct. 2018, doi: 10.1016/j.psychres.2018.06.005.
[56] D. Lu, J. Aleknaviciute, R. Bjarnason, R. M. Tamimi, U. A. Valdimarsdóttir, and E. R. Bertone-Johnson, "Pubertal development and risk of premenstrual disorders in young adulthood," *Human Reproduction*, vol. 36, no. 2, pp. 455–464, Feb. 2021, doi: 10.1093/humrep/deaa309.
[57] A. Śliwerski and E. Bielawska-Batorowicz, "Negative cognitive styles as risk factors for the occurrence of PMS and PMDD," *Journal of Reproductive and Infant Psychology*, vol. 37, no. 3, pp. 322–337, May 2019, doi: 10.1080/02646838.2018.1543943.
[58] J. Marrocco *et al.*, "Epigenetic intersection of BDNF Val66Met genotype with premenstrual dysphoric disorder transcriptome in a cross-species model of estradiol add-back," *Molecular Psychiatry*, vol. 25, no. 3, pp. 572–583, Mar. 2020, doi: 10.1038/s41380-018-0274-3.
[59] U. Halbreich, J. Borenstein, T. Pearlstein, and L. S. Kahn, "The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD)," *Psychoneuroendocrinology*, vol. 28, no. SUPPL. 3, pp. 1–23, 2003, doi: 10.1016/S0306-4530(03)00098-2.
[60] K. M. Schmalenberger, T. A. Eisenlohr-Moul, P. Surana, D. R. Rubinow, and S. S. Girdler, "Predictors of premenstrual impairment among women undergoing prospective assessment for premenstrual dysphoric disorder: A cycle-level analysis," *Psychological Medicine*, vol. 47, no. 9, pp. 1585–1596, Jul. 2017, doi: 10.1017/S0033291716003524.
[61] D. Passow and M. Bolz, “Die prämenstruelle dysphorische Störung (PMDS) alseigenständiges Krankheitsbild,” *Fortschritte der Neurologie Psychiatrie*, vol. 80, no. 7, pp. 382–387, 2012, doi: 10.1055/s-0031-1299473.

[62] Yen JY, Lin HC, Lin PC, Liu TL, Long CY, Ko CH. Early-and late-luteal-phase estrogen and progesterone levels of women with premenstrual dysphoric disorder. Int J Environ Res Public Health. 2019 Nov 2;16(22).
[63] Hara Y, Waters EM, McEwen BS, Morrison JH, Milliken M, Hara LY. Estrogen Effects on Cognitive and Synaptic Health Over the Lifecourse. Physiol Rev [Internet]. 2015;95:785–807. Available from: www.prv.org

Article topic: Acute Stress Disorder (ASD).

Author: Ahmad Naser.

Editor: Haneen A. Banihani.

Reviewer: Ethar Hazaimeh.

Overview

Acute Stress Disorder (ASD) is a severe stress reaction to trauma exposure that may occur in the initial month after the event and requires at least nine out of 14 potential symptoms to be present for a diagnosis. Contrary to what was once believed in the DMS-IV, ASD is not a strong predictor of subsequent Post Traumatic Stress Disorder (PTSD), leading to a huge change in the DMS-V. [1]

While less than 20% of people facing non-interpersonal trauma get ASD, it occurs in up to 50% of people facing interpersonal trauma.[2] The prevalence of ASD, like PTSD, is more common in females.[3]

Pathogenesis and Etiology

ASD is caused by exposure to a traumatic event, which activates the body's stress response system, which triggers the release of stress hormones such as adrenaline and cortisol. This can lead to changes in the brain, including alterations in the amygdala and prefrontal cortex, which are involved in emotional regulation and processing. These changes can result in symptoms such as intrusive thoughts, avoidance behaviors, and hyperarousal, which are characteristic of ASD.[4]

Clinical presentation & Complications

The presentation of ASD is divided into two aspects:[5]

History:

Symptoms of ASD can be subcategorized into

1. Emotional (e.g., shock, grief, anxiety, guilt, numbness, helplessness, shame, emptiness)
2. Cognitive (e.g., nightmares, poor concentration, unwanted memories of the event, self-blame, confusion)

3. Physical (e.g., Difficulty sleeping or staying asleep, Fatigue, Aches and pains, Palpitations, Nausea, change in appetite or libido)
4. Interpersonal (e.g., Withdrawal, work or school problems, the feeling of abandonment)

More severe symptoms include marked depression, marked hyperarousal, extreme numbness, emotional dysregulation, ongoing problems in work or school, and significant problems in self-care.

Signs that the patient may need help include a lack of task-oriented activity, overwhelming emotions, inappropriate self-blame, isolation, and suicidal or homicidal ideation.

Physical Examination

Assessing the mental status is necessary in ASD patients. Usually, it will reveal the following findings:

1. Lack of self-care is reflected in the unclean appearance.
2. Mood changes such as sadness, anxiousness, irritability, apathy, and anger.
3. Suicidal & homicidal ideas.

Workup and Diagnosis

Acute stress disorder is characterized by the development of symptoms lasting from 3 days to 1 month following exposure to one or more traumatic events. The clinical presentation may include intrusion symptoms, negative mood, dissociative symptoms, avoidance symptoms, and arousal symptoms. The individual may experience problems with sleep onset and maintenance, heightened vigilance, concentration difficulties, and a heightened startle response.[2]

Diagnostic Criteria
A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways: 1- Directly experiencing the traumatic event(s). 2- Witnessing, in person, the event(s) as it occurred to others. 3- Learning that the event(s) occurred to a close family member or close friend. Note: In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental. 4- Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains, police officers repeatedly exposed to details of child abuse). Note: This does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.
B. Presence of nine (or more) of the following symptoms from any of the five categories of intrusion, negative mood, dissociation, avoidance, and arousal, beginning or worsening after the traumatic event(s) occurred: **Intrusion Symptoms** 1- Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). Note: In children, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed. 2- Recurrent distressing dreams in which the content and/or affect of the dream are related to the event(s). Note: In children, there may be frightening dreams without recognizable content. 3- Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Note: In children, trauma-specific reenactment may occur in play. 4- Intense or prolonged psychological distress or marked physiological reactions in response to internal or external cues that symbolize or resemble an aspect of the traumatic event(s). **Negative Mood** 5- Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings). **Dissociative Symptoms** 6- An altered sense of the reality of one's surroundings or oneself (e.g., seeing oneself from another's perspective, being in a daze, time slowing). 7- Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs). **Avoidance Symptoms** 8- Efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s). 9- Efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s). **Arousal Symptoms** 10- Sleep disturbance (e.g., difficulty falling or staying asleep, restless sleep). 11- Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal or physical aggression toward people or objects. 12- Hypervigilance. 13- Problems with concentration. 14- Exaggerated startle response.
C. Duration of the disturbance (symptoms in Criterion B) is 3 days to 1 month after trauma exposure. Note: Symptoms typically begin immediately after the trauma, but persistence for at least 3 days and up to a month is needed to meet disorder criteria.
D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The disturbance is not attributable to the physiological effects of a substance (e.g., medication or alcohol) or another medical condition (e.g., mild traumatic brain injury) and is not better explained by brief psychotic disorder.

Table (1) - Diagnostic Criteria for ASD according to DSM-V TR

Treatment and Management

The goal of the treatment of ASD is to alleviate symptoms and prevent possible subsequent PTSD.[3] Treatment of ASD is divided into two areas:

Psychotherapy

Mainly Cognitive Behavioral Therapy (CBT) Which is considered the frontline treatment of ASD.[3] Since it proved a significant efficacy in the treatment of ASD.[6] CBT forms multiple elements that can be addressed all or as a subset during individual sessions conducted weekly. These elements include:[3]

- **Education**
  - Done at the beginning of the treatment to help the patients understand the symptoms they are going through and to explain the specific strategies that will be done.
- **Anxiety management**
  - This helps the patients get comfortable with the therapy strategies by teaching them to master arousal.
- **Prolonged exposure**
  - By teaching the patients how to approach and understand their trauma memories. This element proved to be one of the highest efficacious in treating ASD.[7]
- **Cognitive restructuring**
  - By identifying negative thoughts and appraisals of the patients and challenging them to let them interpret their experiences more realistically.
- **In-vivo exposure**
  - Introducing the patients to the situations that caused them the trauma to prevent avoidance behavior in the future.
- **Relapse prevention**
  - Predict situations where relapse may occur and develop strategies to deal with such situations. Relapse prevention should be done before expected difficult situations and upon symptoms increase.

Pharmacotherapy

Pharmacological treatments are mostly used for the prevention of secondary PTSD.[3] The evidence for the efficacy of pharmacological treatments of ASD and the prevention of subsequent PTSD isn't significant for most drugs (e.g. Propranolol, Dexamethasone, Escitalopram, Gabapentin Oxytocin) [8-10] except for Hydrocortisone which showed the most promise in lowering the incidence and severity of PTSD.[8] However, given its severe effects, it can't be used routinely until further research is conducted.

Risk factors

Factors increasing the risk of acute stress disorder (ASD) following a traumatic event include:[11]

1. Loss of a loved one.
2. Significant injury.
3. Witnessing horrendous images.
4. Dissociation at the time of the traumatic event.
5. Development of serious depressive symptoms within 1 week that last for 1 month or longer.
6. Numbness, depersonalization, a sense of reliving the trauma, and motor restlessness after the event.
7. Preexisting psychiatric problems.
8. Previous trauma.
9. Loss of home or community.
10. Extended exposure to danger.
11. Toxic exposure.
12. Absent social supports or social supports who were also traumatized and thus are incapable of adequate emotional availability.

Recent research

New findings support the use of Propranolol and Hydrocortisone as preventive agents for re-experiencing symptoms of ASD & PTSD as they were found to lessen the occurrence of involuntary memories. This encourages more research to be done studying these drugs as pharmacotherapy for ASD recovery and prevention of PTSD.[12]

References

[1] R. A. Bryant, "The Current Evidence for Acute Stress Disorder.," *Curr. Psychiatry Rep.*, vol. 20, no. 12, p. 111, Oct. 2018, doi: 10.1007/s11920-018-0976-x.

[2] American Psychiatric Association, *DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS - FIFTH EDITION TEXT REVISION*. 2022.

[3] R. A. Bryant, *ACUTE STRESS DISORDER What It Is and How to Treat It*. THE GUILFORD PRESS, 2016.

[4] C. Allene, K. Kalalou, F. Durand, F. Thomas, and D. Januel, "Acute and Post-Traumatic Stress Disorders: A biased nervous system.," *Rev. Neurol. (Paris).*, vol. 177, no. 1–2, pp. 23–38, 2021, doi: 10.1016/j.neurol.2020.05.010.

[5] Medscape and Roy H Lubit, "Acute Stress Disorder Clinical Presentation," 2021. https://emedicine.medscape.com/article/2192581-clinical#showall

[6] J. K. Carpenter, L. A. Andrews, S. M. Witcraft, M. B. Powers, J. A. J. Smits, and S. G. Hofmann, "Cognitive behavioral therapy for anxiety and related disorders: A meta-analysis of randomized placebo-controlled trials.," *Depress. Anxiety*, vol. 35, no. 6, pp. 502–514, Jun. 2018, doi: 10.1002/da.22728.

[7] R. A. Bryant *et al.*, "Treatment of acute stress disorder: a randomized controlled trial.," *Arch. Gen. Psychiatry*, vol. 65, no. 6, pp. 659–667, Jun. 2008, doi: 10.1001/archpsyc.65.6.659.

[8] L. Astill Wright, M. Sijbrandij, R. Sinnerton, C. Lewis, N. P. Roberts, and J. I. Bisson, "Pharmacological prevention and early treatment of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis.," *Transl. Psychiatry*, vol. 9, no. 1, p. 334, Dec. 2019, doi: 10.1038/s41398-019-0673-5.

[9] S. Suliman, S. Seedat, J. Pingo, T. Sutherland, J. Zohar, and D. J. Stein, “Escitalopram in the prevention of posttraumatic stress disorder: a pilot randomized controlled trial.,” *BMC Psychiatry*, vol. 15, p. 24, Feb. 2015, doi: 10.1186/s12888-015-0391-3.
[10] A. Y. Shalev, Y. Ankri, Y. Israeli-Shalev, T. Peleg, R. Adessky, and S. Freedman, “Prevention of posttraumatic stress disorder by early treatment: results from the Jerusalem Trauma Outreach and Prevention study.,” *Arch. Gen. Psychiatry*, vol. 69, no. 2, pp. 166–176, Feb. 2012, doi: 10.1001/archgenpsychiatry.2011.127.
[11] Medscape and Roy H Lubit, “Acute Stress Disorder Etiology,” 2021. https://emedicine.medscape.com/article/2192581-overview#a5
[12] S. K. Kamboj *et al.*, “Reduction in the occurrence of distressing involuntary memories following propranolol or hydrocortisone in healthy women.,” *Psychol. Med.*, vol. 50, no. 7, pp. 1148–1155, May 2020, doi: 10.1017/S0033291719001028.

Article topic: Erectile Disorder

Authors: Imad Hatoum.

Editor: Lubna AL-Rawabdeh.

Reviewer: Ethar Hazaimeh.

Keywords: Alcohol, cardiovascular, hormonal, stress, medications.

Abstract

Background: Among all sexual disorders, erectile disorder (ED) is one of the most known and researched. Attaining less than 10% of men below the age of fifty, and more than 20% above the age of sixty, it is a widespread problem, and therefore an important one to discuss [1].

Methods: medical articles and bibliography were reviewed, combined with expert opinion on the matter.

Results: Erectile dysfunction is, as its name suggests, a problem that prohibits men from having normal erections and thus normal sexual intercourse. The etiologies vary from psychogenic to hormonal to vascular or neurologic, pharmacologic, or even a mix of many. Fortunately, there are many diagnostic tools to detect the condition. Moreover, there is no considerable number of complications, and the treatments are various and available with an incredibly good prognosis.

Introduction

Though sexual health remains taboo in a lot of places around the world, it is one of the main concerns of a vast number of people, especially sexually active ones. Disorders and pathologies about sexual health are remarkably diverse and can have microbial, psychological, or physiological causes. In this article, we will tackle the issue of erectile disorder from different perspectives: it is possible physiological and psychological causes, its presentation, its diagnosis… all the way to the most recent updates about it. This of course is going to be supported by the scientific experiments and studies regarding this matter which is a big problem for a lot of men but also a lot of fear about sexual “performance.”

Overview

Erectile disorder or erectile dysfunction is as the name suggests, a problem affecting people with a penis regarding their sexual activity. As defined by the Diagnostic and Statistical Manual-5 (DSM-5), it is presented by at least one of three symptoms that must appear in 75-100% of occasions of sexual activity, these three symptoms being either the difficulty to reaching erection during sexual activity, or the difficulty to maintain erection during sexual activity, or a decrease in the rigidity of the erection [2]. Furthermore, erectile dysfunction can be either primary as in the case where the person never had a normal erection, or secondary as in the case where a person had normal sexual activity but started having problems later. The erectile disorder presents differently whether the cause is organic or psychogenic, when the problem comes from a physical pathology trauma or substance use, the problem manifests as a decrease in intensity and duration in all circumstances as in the case of morning erections, masturbation, sex, But when the source of the problem is psychogenic, its manifestation depends on the mental state of the person; it can occur in depression, or specifically only when wanting to have sex, etc [3].

Moreover, the reason that makes erectile disorder so known is also its prevalence which is believed to grow with age:

- 1-9% of men under forty.
- Less than 10% for men between 41 and 49, though some studies suggest it can go up to 15%.
- Unsure values concerning men between 50 and 60.
- 20-40% for men between 60 and 70.
- 50-100% for men over 70 or 80 years old [3].

Etiology and Pathogenesis

Concerning the etiology of ED, there are, as we said, organic and psychogenic reasons that we will see in detail in the following.

Organic Etiologies

Imbalance in corporal smooth muscle contraction and relaxation at the origin of ED can result from several reasons. Though an anomaly in the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway or cyclic adenosine monophosphate (cAMP) pathway can be the first and most direct reason that comes to mind, we can also find causes that are neurogenic, vasogenic, veno-occlusive, hormonal, and even pharmacogenomic [4]. ED can also appear because of Peyronie's disease.

- **Cardiovascular disease (CVD) and vascular causes**

Both having a physiopathology linked to endothelial dysfunction makes ED and CVD narrowly linked. While CVD and all its risk factors (such as chronic kidney disease, and diabetes mellitus…) seem to be a cause of ED, ED itself can also be an early indicator of potential cardiovascular accidents [5].

Moreover, perineal trauma can cause focal arterial occlusive disease thus causing ED by reducing the velocity of systolic pressure in the cavernous arteries to zero [9]. This explains the correlation between cycling on a bicycle that puts high pressure on the perineal region and increased risks of ED [9].

- ## Neurogenic causes

Trauma to the nerves can also be a cause of ED. One of the common cases is fractures of the femoral bone causing damage to the pudendal nerve resulting in ED for approximately 40% of men [9]. Other neurological causes can be strokes, dementia, multiple sclerosis, spinal injury, radical prostatectomy, and other clinical or accidental trauma [5] … Sudden loss of sexual functions only occurs in the case of prostatectomy and genital tract trauma, whereas the other causes manifest in a more gradual progressive way [5].

- ## Hormonal and endocrine causes

Low testosterone plays a key role in ED. Hormonal causes include Klinefelter's syndrome, congenital hypogonadotropic hypogonadism which is exceedingly rare with a prevalence of 1/4000-10000 patients, and acquired hypogonadotropic hypogonadism, as well as cryptorchidism [9].

A lot of endocrine diseases may cause ED; we can count mellitus diabetes, hyperprolactinemia, hyperthyroidism, and hypothyroidism as diseases associated with ED [5].] It is important to note that hormonal causes are not common for the young male population.

- ## Pharmacological causes

Though it may not come to mind as particularly important, 25% of cases of ED have pharmacological sources, a number that must not be ignored [5]. The drugs associated with ED are selective serotonin reuptake inhibitors (SSRI), antihypertensive, and specifically thiazides diuretics, anti-androgens due to their direct effects but also ketoconazole, spironolactone, cimetidine, and sympathetic blockers [5]. However, the effect of SSRI concerning ED was discussed in older studies suggesting that it has no more effect than a placebo in concerning this disorder [9]. The usage of finasteride, a drug used to prevent baldness has shown that it can cause ED, as well as regular use of

NSAIDs, and neuroleptics due to their effects causing an increase in prolactin levels and antiepileptics because of their vasogenic activity [9].

Psychogenic etiologies

Depression and ED have a bidirectional relationship, both able to cause one another [6]. Furthermore, we can add stress and relationship issues [5] and hyposexuality [7]. But psychological causes do not stop here, we can also count fear of failure, social pressure regarding sexual performance, familial and religious narratives that are restrictive towards sexuality, mood disorders, sexual identity crisis or instability, fear of sexually transmitted diseases, bad or traumatic earlier sexual experiences, distrust, or hostility towards the partner, etc [3].

The last thing we should notice about the etiology of ED is that it can be a mix of psychogenic and organic causes at once or it can be an organic one amplified by a psychological one. Therefore, a multidisciplinary approach and assessment of the situation remains the most adequate way to deal with ED.

Clinical presentation and complications

The patient will present complaints of unsatisfactory sexual experiences regarding problems with erection manifesting through one of the three symptoms defined by the DSM-5 and exposed earlier (overview).

Regarding the complications of ED, they are usually more psychological leading to stress, frustration, anxiety, low self-esteem, and in the worst cases depression. Aside from these, ED does not seem to cause long-lasting damage.

Diagnosis

After laying out the etiology, it is only natural to think of the ways that should be followed to diagnose this disorder. Taking history combined with physical examination showed a 95% sensitivity, but a 50% specificity [8]. Complementary tests and dosages can be applied to confirm the diagnosis.

Taking history

Based on all the potential causes we explained it is only logical to ask our patients for any history of surgical procedures, psychological trauma and relationship problems, spinal or pelvic or femoral injuries, their drug use, and even their activities of cycling and their duration [9]. We can equally search for any history of endocrine, vascular, or neurological problems that can be of help to make the diagnosis. An interview with the

partner can also be of help. Some questionnaires like the International Index of Erectile Function (IIEF), Sexual Health Inventory for Men (SHIM, or IIEF-5), and Sexual Arousal, Interest, and Drive Scale (SAID) are used to assess libido that we should evaluate while taking history. It is IIEF and SHIM that are more recommended to assess ED as well as the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) [8].

Moreover, to differentiate between a physiological problem and a more psychological one. If the patient did not manifest problems until one night, with no history of genital tract trauma or radical prostatectomy, for example, the problem is more likely to be psychogenic since physiological problems appear more sporadically. The presence of spontaneous erections is also an indicator that the patient's ED is more psychological [8]. Last but not least, check for any other history of sexual disorders and Peyronie's disease.

Physical examination

Regarding physical examination, it is only natural to check for testicular and penile sizes, as well as eunuchoid body habitus to identify an undiagnosed Klinefelter's syndrome [9] or search for penile plaques to find an undiagnosed Peyronie's disease [8]. A check-up on the sexual secondary characteristics can also be of use. The measurement of the femoral and peripheral pulses is important in the search for vascular ED [8]. Furthermore, cremasteric contraction with elevation of the testis is the normal reaction when checking the cremasteric reflex by stroking the inner thighs [8].

Finally, the visual field of the patient should also be evaluated, since problems in the visual field are a pattern recurrent in hypogonadal men [8].

Laboratory dosages and other tests

Hormonal dosages of testosterone, prolactin, and thyroid hormone can be important depending on the etiology the physician is suspecting.

In addition, Nocturnal penile tumescence testing (NPT) can now easily be assessed from home through new monitoring devices [8]. For instance, men with ED but normal nocturnal tumescence have a psychogenic source to their problem.

Furthermore, duplex Doppler ultrasonography and even penile angiography can be used to search for arterial or venous leaks. The test is done while inducing an erection with vasodilating substances [8]. Penile trauma, priapism, Peyronie's disease, or insensibility to drug-like phosphodiesterase-5 (PDE5) inhibitors can all lead to the use of penile ultrasound to make the diagnosis [8].

Treatment

The treatments can be as mixed as the etiologies! Going from drugs, devices or psychological therapy, solutions to ED are various and numerous.

Drugs and physical treatments

Some behavioral measures can be taken as a first step: stopping smoking and recreational drug use, weight loss and exercise all have proven to be of help for men with ED [9].

Aside from these lifestyle changes, the prescription of PDE5 inhibitors remains the initial solution [10]. PDE5 plays a role in the catabolism of cGMP. By inhibiting PDE5, cGMP remains for a longer time in this active form therefore maintaining and strengthening the person's erection. It is important to pay attention to interactions with other medications since PDE5 inhibitors are contraindicated in patients taking alpha-blockers and nitrates [10].

Drugs like sildenafil, vardenafil, tadalafil, and avanafil have been proven to be useful [10]. A study showed sildenafil has shown efficacity in ED for men with mild to moderate depression [6], while tadalafil has shown efficacity for men taking SSRI [9]. PDE5 inhibitors combined with testosterone have been shown to be useful for hypogonadal men [10].

Other solutions may be the use of vacuum devices, penile injections of alprostadil, papaverine, phentolamine combined with vasointestinal peptide (VIP), or papaverine with alprostadil as a third component can also be used [10]. We can also count the use of urethral alprostadil. To induce an erection by a vacuum device remains the least invasive when compared to implants and urethral suppositories.

Finally, surgical procedures such as the implant of penile prostheses known as penile pumps, or procedures like penile revascularization can be done [10]. However, these procedures are better kept as a last resort because of their invasiveness.

Psychological treatment [3]

The psychotherapy of ED is traditionally done in six steps:

- The first psycho-pedagogic step: consists of explaining to the patient the basic anatomy and physiology of erection thus helping him to visualize and understand his problem.
- The second step is where the therapist teaches the patient techniques of relaxation and stabilization.
- A third step of identification of "targets" in the past of the patient like traumatic experiences or memories at the source of the manifestation of ED.

- A fourth step of treatment of these “targets” with adequate and standard protocols.
- The fifth step consists of the usage of the Logie and De Jong “flashforward technique” which aims to project the patient the imagination of sexual intercourse and how it can be fulfilling if normal after raising the beginning of the technique questions like: what is the worse that could happen? These procedures provide the therapist with data to analyze in order to direct and help the patient.
- A sixth step consists of the application of the “sensate focus” of Masters and Johnson where the specialist teaches the patient how to focus on his material sensations and reintroduces the patient to the sexual experience without stress or anxiogenic factors.

Since the etiologies of ED can be mixed, and since ED itself can have a psychological impact, this part of treatment should not be completely neglected.

Prognosis

Treatment success rates are remarkably high and the patient, if treated, is highly likely to have normal sexual intercourse.

Risk factors

Between the risk factors, we can count bicycling for lengthy periods of time very frequently, sleep disorders, and pornography [5] … but we can also add psychological and relationship problems, low levels of education, no previous experience of masturbation, psychological problems, no adequate sexual education, as well as smoking and recreational drug use specifically for men under forty [9].

Of course, we can keep in mind the risk factors for all the conditions associated with ED that we discussed in the etiologies.

Recent update: COVID-19 and ED

A recent study found that the prevalence of ED in patients positive for COVID-19 is higher than the prevalence of the normal population suggesting even that ED and COVID-19 have a bidirectional relationship in helping to develop one another. Proof has been found that COVID-19 has a significant effect on the development of ED [11].

Conclusion

To sum up, we can say that erectile disorder is a way more complex condition than we can expect, having various and mixed etiologies both organic and psychogenic. Fortunately, it is a well-studied and well-known condition that has a lot of treatments making it very curable. The most important thing is for the patient not to feel pressured and incompetent and to understand that their problem is a resolvable one. Sexual education still has a long way to go to be understood and accepted by the public, and it is our duty as medical professionals to make it accessible and helpful to all.

References

[1] Erectile dysfunction, Progres En Urologie: Journal De L'association Francaise D'urologie Et De La Societe Francaise D'urologie. (n.d.).
[2] DSM-5, American Psychiatric Association
[3] Prise en charge des troubles de la sexualité avec la psychothérapie EMDR, (n.d.). https://www.ifemdr.fr/prise-en-charge-des-troubles-de-la-sexualite-avec-la-psychotherapie-emdr/.
[4] Pathophysiology of Erectile Dysfunction, 3 (n.d.) 87–102.
[5] UpToDate, (n.d.). https://www.uptodate.com/contents/epidemiology-and-etiologies-of-male-sexual-dysfunction (accessed September 30, 2023).
[6] Treatment of erectile dysfunction in men with depressive symptoms: results of a placebo-controlled trial with sildenafil citrate, 158 (n.d.) 1623–1630. https://doi.org/10.1176/appi.ajp.158.10.1623.
[7] Psychological factors involved in erectile dysfunction, Zhonghua Nan Ke Xue = National Journal of Andrology. (n.d.).
[8] Evaluation of male sexual dysfunction, (2023). https://medilib.ir/uptodate/show/7468 (accessed September 30, 2023).
[9] Organic Causes of Erectile Dysfunction in Men Under 40, Urologia Internationalis. (n.d.).
[10] UpToDate 2018, (2018). https://ykhoa.org/d/topic.htm?path=evaluation-of-male-sexual-dysfunction (accessed September 30, 2023).
[11] Mask up to keep it up: Preliminary evidence of the association between erectile dysfunction and COVID-19, Journal of Andrology. (n.d.).

Article topic: Tourette Syndrome.

Author: Amr Atef Hasan.

Editor: Said Lahham, Rahmeh Adel.

Reviewer: Ethar Hazaimeh.

Keywords: ***Tic, Urge, Dopamine, Obsessive Compulsive Disorder, risk factors.***

Abbreviations: ***TS: Tourette Syndrome, CTD: chronic tics disorder.***

Abstract

Objective

This article has focused on Tourette Syndrome (TS) and its connection to Obsessive-Compulsive Disorder (OCD), as indicated by a body of genetic epidemiological research that consistently presents compelling evidence of their association. Additionally, the article has provided insights into the risk factors, characteristics, findings from imaging studies, classification, management strategies, and treatment options for this syndrome.

Method

To be considered for inclusion, research papers had to be written in the English language. We conducted searches for relevant articles using databases such as PubMed, Google Scholar, Medscape, and Medline.

Result

Tourette syndrome, a neurodevelopmental disorder, disproportionately affects boys compared to girls and is often associated with attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). It can manifest in both children and adults, although it typically begins around the age of 6 years, and adult-onset tics are uncommon. The diagnostic process for TS often includes a clinical Interview, Physical Examination, Diagnostic Criteria, Observation of Tics, Patient and Family History, and Psychological Assessment.

Conclusion

Although Tourette Syndrome is frequently diagnosed in childhood, its precise origins remain a topic of ongoing investigation. Past research has unveiled disparities in the neurobiological makeup of individuals affected by Tourette Syndrome. In recent years, a slew of studies conducted within the last half-decade has brought fresh insights into genetic variations, alterations in neurophysiological processes, and changes in neural networks that contribute to its onset. This has led to a surge in research across various treatment areas related to Tourette Syndrome. Numerous therapeutic approaches have shown efficacy in controlled trials, such as interventions involving Dopamine D2 receptor antagonists, Dopamine agonists, Cannabinoids, and Habit reversal therapy.

Overview

Tourette Syndrome is a condition characterized by tics, typically manifesting during childhood and often showing improvement in adulthood[1]. It represents a chronic neurodevelopmental disorder marked by motor and vocal tics, significantly affecting the quality of life for those it afflicts.[2]

In 1885, Gilles de la Tourette provided a vivid description of a neuropsychiatric syndrome with distinct clinical features, including multiple motor tics, phonic symptoms, compulsions, and other behavioral phenomena, such as an irresistible urge to echo or imitate. He noted its prevalence in males, early onset, and lifelong duration, guessing that its origins might be linked to inherited neurological vulnerability. Following Tourette's initial report, over the past two decades, many cases and patient series have been documented in the global literature, leaving little doubt that Tourette's syndrome (TS) is a clinically identifiable disorder with a consistent pattern of expression across different cultures.[7]

This concept finds support in multiple lines of evidence, including clinical pharmacology, the presence of tics in other disorders characterized by clear basal ganglia pathology, and imaging data showing developmental abnormalities within the basal ganglia. Additionally, robust backing for the dysfunction of the basal ganglia stems from experimental manipulations of basal ganglia pathways in non-human primates, which produce credible tic-like behaviors.[4]

Tics observed in Tourette syndrome may be linked to various comorbidities, including anxiety, attention deficit hyperactivity disorder (ADHD), and obsessive–compulsive disorder (OCD). Tourette syndrome and chronic tic disorders (CTD) are among the five categories of tic disorders delineated in the fifth edition of the American Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[5]

Furthermore, Tourette syndrome appears to cluster significantly within families, implying that family members may share genetic or environmental risk factors contributing to the condition. The morbid risk of Tourette syndrome among relatives ranges from 10% to 15%, while the prevalence of other tics falls within the range of 15% to 20%. These figures notably exceed the rates of Tourette syndrome and tics observed in control groups.[6] In this article we will shed light on Tourette Syndrome, with a focus on its definition, etiology, clinical classification, management, and treatment.

Clinical Features

The defining characteristic of Tourette's syndrome is the persistent presence of at least two motor tics and one vocal tic that have been present since childhood. *Tics* are described as involuntary, sudden, rapid, recurring, and non-rhythmic movements (referred to as motor tics) or vocalizations, known as vocal or phonic tics. Importantly, this syndrome is now recognized as a global condition, affecting individuals of all races, ethnic backgrounds, and both genders (with a higher prevalence in males, approximately four times more common than in females). Tourette's syndrome can manifest in both children and adults, although it typically begins around the age of 6 years, and adult-onset tics are uncommon.[8]

Motor tics generally precede the development of vocal tics, and simple tics often appear before complex tics. Simple motor tics may manifest as actions such as eye blinking, facial grimacing, shoulder shrugging, neck stretching, and abdominal contractions. Among vocal tics, the most frequently observed ones include sniffing, grunting, and throat clearing. Gilles de la Tourette's original case series featured nine patients who also exhibited complex tics, specifically echolalia (repeating other people's words) and coprolalia (the involuntary use of profane language). It is worth noting that both coprolalia and copropraxia (involuntary production of offensive gestures as complex tics) are relatively rare, occurring in approximately 10% of patients (with higher rates of 20-30% in specialized clinics that see more severe or complex cases).[8]

Etiology

Years of investigation have firmly established the influence of genetic factors on Tourette Syndrome (TS). Multiple studies have demonstrated a familial association with TS. Nevertheless, an illuminating twin study revealed that the concordance rate was 53% for monozygotic twins and 8% for dizygotic twins, underscoring that TS is not solely dictated by genetic factors. Consequently, it is understood to be a complex condition arising from a combination of factors, encompassing genetic predispositions and environmental triggers.[9]

Genetic

Family and twin studies have provided compelling evidence that genetic factors play a significant role in the hereditary transmission of Tourette Syndrome (TS) and related conditions.[14] Symptoms of obsessive-compulsive disorder (OCD) are frequently observed alongside Tourette Syndrome (TS), and family studies have indicated a heightened prevalence of OCD among close relatives of individuals with TS. Initial analyses of TS within families suggested an autosomal dominant inheritance pattern with varying expression, encompassing the presence of OCD. However, recent scrutiny has cast doubt on these findings, as observations suggest that the transmission pattern of TS may align more closely with polygenic influences.[10]

In conditions believed to involve complex genetic inheritance, variations in an individual's DNA, known as polymorphisms, are thought to heighten the susceptibility to the condition and may contribute to the disease through a cumulative impact. These DNA polymorphisms are commonly referred to as Single Nucleotide Polymorphisms (SNP) and Copy Number Variants (CNV).[11]

Expanding upon two studies published in 2018, which reported an increased prevalence of rare, gene-disrupting mutations in 5–10% of Tourette Syndrome (TS) patients, notable findings appeared. Wang and colleagues conducted the most extensive examination of rare, de novo gene-disrupting mutations in TS patients to date. Meanwhile, Yu and colleagues conducted the latest TS genome-wide association study (GWAS), involving 4819 cases and 9488 controls. In their study, they identified a strong candidate TS gene (FLT3) and corroborated prior findings indicating that a huge part of TS heritability can be attributed to the collective influence of common genetic risk variants distributed throughout the genome. These two sets of findings collectively endorse the notion that TS and other tic disorders exist on a continuum rather than being distinct diagnostic entities, a viewpoint supported at the genetic level.[12]

Furthermore, Mufford and colleagues employed the same TS GWAS polygenic risk score (PRS) to investigate genetic data related to subcortical brain volumes in the ENIGMA (Enhancing Neuro Imaging Genetics Through Meta Analysis) consortium. This research linked the genetics of TS with the genetics of brain volumes. In a separate study involving a vast dataset derived from shared GWAS data encompassing over a million individuals with various neurological and psychiatric disorders, it was revealed that TS shares common variant genetic risk with conditions such as obsessive-compulsive disorder (OCD), major depression, and, surprisingly, with migraine, particularly migraine with aura.[12]

In 2021, the TS/OCD working group of the Psychiatric Genomics Consortium conducted a comprehensive genome-wide pathway analysis, involving 1,285 individuals with Tourette Syndrome (TS) and 4,964 ancestry-matched controls. This study revealed

significant differences in three gene sets associated with TS: ligand-gated ion channel signaling, lymphocytic (driven by variants in FLT3), and cell adhesion and trans-synaptic signaling sets. These gene sets align with and substantiate previous hypotheses regarding the potential involvement of neuroinflammation, GABA signaling, and cell adhesion mechanisms in the pathophysiology of TS.[13]

Furthermore, it was recently discovered that a specific genetic variant located on chromosome 13 is linked to Tourette's Syndrome in a single child. This gene, known as SLITRK1, has been implicated in dendrite growth and the regulation of neural development. However, it is important to note that only a small percentage of individuals with Tourette's Syndrome are believed to have this gene mutation.[15]

Environmental risk factors

The influence of environmental factors on the disease mechanisms and clinical manifestation of Tourette Syndrome (TS) can commence during the prenatal and perinatal phases and persist throughout virtually the entire lifespan of the individual, spanning from childhood and adolescence into adulthood. Exposures to adverse conditions, particularly those occurring early on, such as during pregnancy or due to complications during delivery, may have formative effects on the development of brain networks that are pertinent to the generation of tics and associated symptoms.[16]

An extensive and authoritative review, of the immunology of brain development in a general context and specifically within the context of Tourette Syndrome (TS), has been authored by one of the leading experts in this field. An intriguing study was prompted by clinical observations that blinking tics, a commonly observed initial symptom of tic disorders, are frequently mistaken for allergic conjunctivitis (AC) by both families and primary care physicians. Researchers in southwest China conducted a study involving 70 children with provisional tic disorder (PTD) and 70 tic-free controls. Their findings indicated that AC was more than four times more prevalent in individuals with PTD (74%) compared to controls (17%). Importantly, this discrepancy could not be solely attributed to symptom confusion, as quantitative assessments of dry eyes and allergic responses to a skin prick test were also about four times more frequent in patients with PTD. These results introduce intriguing hypotheses about immune-related abnormalities that may contribute to the development of tics.[15]

Additionally, an alternative perspective arises from patient reports indicating that tics sometimes develop after a repeated behavior initiated for a different reason outlasts its initial stimulus and becomes chronic. For example, a child may have initially coughed due to an upper airway infection, but then the cough persisted and transformed into a tic. This suggests that in some cases, tics may emerge when underlying host factors convert externally triggered repetitive behaviors (such as blinking or coughing) into chronic symptoms. Notably, prior research in rodents has demonstrated that a similar

two-hit scenario can lead to the development of a distinct movement disorder, dystonia.[15]

DSM-5 Diagnostic Criteria

The diagnostic criteria for Tourette syndrome, as outlined in DSM-5 (307.23), are as follows:

- Presence of both multiple motor tics and at least one vocal tic at some point during the illness, although they may not necessarily occur simultaneously.
- Tics manifest frequently throughout the day, typically in bouts, occurring almost daily or intermittently for a period exceeding one year. During this duration, there should be no period longer than three consecutive months without any tics.
- The onset of symptoms occurs before reaching 18 years of age.
- The distribution is not attributable to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).[17]

Classification of tics

Tics are conventionally categorized, albeit subjectively, based on their distribution and complexity. While tics typically manifest in areas such as the face, neck, pharynx, shoulders, and central torso, they have the potential to affect any part of the body (Figure 1).[18]

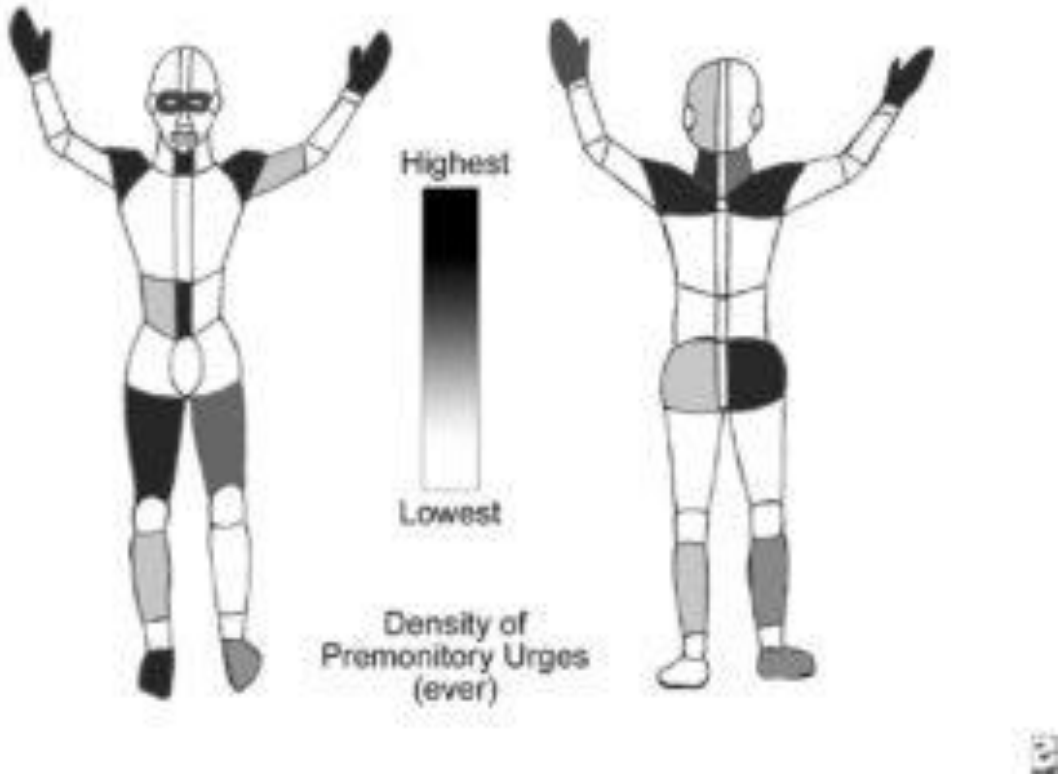


Figure 1: Tourette syndrome and other tic disorders. The graphic shows the relative likelihood of lifetime sensory tics in each region, as based on self-report of patients with Tourette syndrome. Overt tics are distributed similarly.18[/caption]

Albin has seen that stimulating the ventral basal ganglia can elicit socially significant complex gestures, such as stereotyped fear or pleasure displays in rodents. Importantly, these socially meaningful gestures involve the same body regions associated with the ventral basal ganglia.[18] However, it is worth noting that certain tics may not neatly align with traditional classifications.[19]

Simple motor tics are characterized by brief movements involving a single muscle group, while simple vocal tics involve simple sounds. Some examples of simple motor tics encompass eye blinks, facial grimaces, head and neck jerks, and shoulder shrugs. Additionally, brief sustained postures like blepharospasm, oculogyric movements, and sustained mouth opening can also be categorized as simple motor tics. In the realm of simple vocal tics, you might find actions like coughing, sniffing, throat clearing, grunting, and squeaking. **Complex motor tics** involve more purposeful or coordinated patterns of movement, while complex vocal tics manifest as longer, more organized patterns of speech. Complex motor tics can include actions such as turning while walking, echopraxia (mimicking gestures), and copropraxia (performing obscene gestures). On the other hand, complex vocal tics encompass behaviors like repeating words or phrases, echolalia (repeating another person's words or phrases), and coprolalia (uttering obscenities).[21] It is worth mentioning that coprolalia, while it can

cause significant social distress, is rare, occurring in only approximately 10% of patients.[22]

General features of tics

Most tics are simple, purposeless movements. However, tics are not entirely random; they often incorporate elements of personal experience, practice, and social norms. For instance, echolalia or echopraxia, which involves mimicking another person's speech or movements, can occur in up to one-third of patients. It is interesting to note that witnessing someone with tics, such as excessive blinking, can trigger a similar tic in someone who has not experienced it for years. Likewise, simply hearing or learning about tics can increase their severity. At times, tics appear to imitate newly got voluntary behaviors. For example, some individuals have developed a complex tic of "air typing" after learning touch typing, a phenomenon observed in two unrelated individuals by one of the authors. Intriguingly, a man whose personal history was published in 1902 described his tics as frequently involving an urge to engage in precisely what was forbidden, like "clucking" when instructed to remain silent in school. He likened his motor and vocal tics to a "desire for forbidden fruit.[19]

Complex tics can encompass inappropriate actions, such as touching a hot iron or a stranger's breasts. As with many movement disorders, tics tend to worsen during times of emotional stress and significantly diminish during sleep.[20]

Imaging Studies

Structural imaging studies are typically not necessary when evaluating patients with a typical clinical history and examination findings. They are primarily recommended when there are indications of specific illnesses suggested by unusual history or examination results. Currently, functional imaging studies do not have established clinical utility in the assessment of tic disorders. However, there is some potential for future clinical benefits based on data from unpublished reports. For instance, there is emerging evidence that caudate volume in childhood may be inversely associated with the severity of the illness in adulthood.[23]

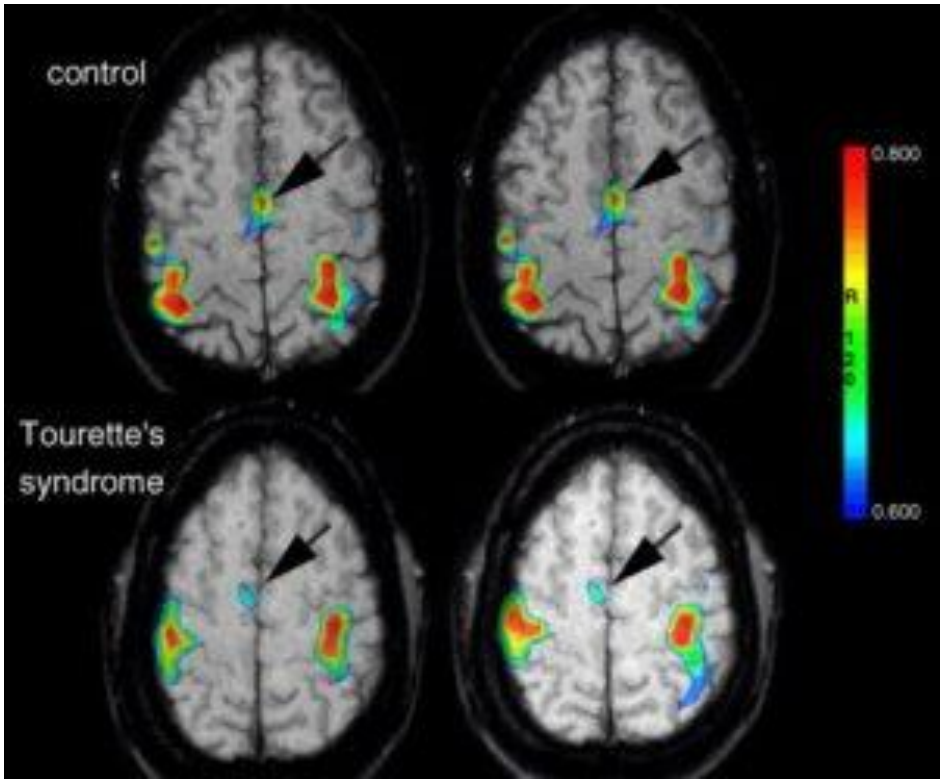


Figure 2: Gilles de la Tourette syndrome and voluntary movement: A functional MRI study.35

Management and treatment

Several fundamental principles should guide our approach to Tourette syndrome (TS). Firstly, it is crucial to acknowledge that current treatments for TS are primarily aimed at alleviating symptoms; there are no known curative or preventive treatments. Secondly, it is important to recognize that tics, while a prominent feature of TS, may not always be the most distressing aspect of the condition. Thirdly, TS is a chronic disorder, and the focus should typically be on achieving long-term benefits rather than seeking rapid improvement at any cost. Lastly, symptoms can fluctuate, improving or worsening over time, even in the absence of treatment.[24]

From these principles, several corollaries appear:

- Treatment may not always be necessary, especially when tics are mild and not significantly affecting the individual's life.
- Treatment should prioritize addressing the most troublesome symptoms or those causing the greatest impairment.
- It is important to approach the perceived success or failure of any treatment with caution, as outcomes may sometimes be coincidental.
- Starting with reasonable trials of single treatment agents is a more prudent approach than hastily resorting to high doses or using multiple medications.

TS has been categorized as both a neurological and a psychiatric disorder. These labels do not pertain to the cause or treatment of TS but rather reflect the historical involvement of neurologists and psychiatrists in researching and managing the condition.[24]

Treatment for tics

Effective treatments for tics, supported by evidence from replicated controlled trials (RCTs), include the following:

Dopamine D2 receptor antagonist therapy

In 1959, shortly after its introduction, chlorpromazine was reported to have a remarkable impact on reducing tic severity. Since then, multiple randomized controlled trials, utilizing various neuroleptic medications such as haloperidol, fluphenazine, and pimozide, have substantiated these initial findings.[25] On average, treatment with neuroleptics results in a reduction of tic severity by 50-80%. Neuroleptic drugs currently stand as the standard for effectiveness in treating tics. Notably, they can be effective at doses significantly lower than those typically used for treating psychosis, and most adverse effects can be managed through pharmacological adjustments.

Regrettably, some patients find it challenging to tolerate acute adverse effects, which most commonly include sedation, weight gain, depression, lethargy, and akathisia. Additionally, prolonged treatment carries a slight risk of tardive dyskinesia. Consequently, researchers have explored alternative treatment options.[26]

Dopamine antagonists, such as fluphenazine (Prolixin) at doses ranging from 1 to 15 mg/day and trifluoperazine (Stellazine) at doses ranging from 2 to 15 mg/day, are less commonly used than haloperidol or pimozide but appear to show equivalent efficacy in suppressing tics and share a similar spectrum of side effects. Some clinicians prefer these medications due to their potential to induce less sedation compared to haloperidol.[28]

Dopamine agonist therapy

Dopamine agonists, which can be categorized into ergoline- and nonergoline DA agonists, have been explored as potential treatments for tics since 1979 when the first positive effects were reported in individuals with Tourette Syndrome (TS).[36] Several studies have delved into the impact of dopamine agonists on tics. Despite initial expectations that these agonists might not be effective due to the success of antagonist treatments, some findings have indeed been promising. Both apomorphine and the partial D2 (and 5-HT1A) agonist buspirone have demonstrated efficacy in the treatment

of tics. Additionally, ropinirole has been shown to have a positive effect on reducing tic frequency and severity.[37]

Cannabinoids

High concentrations of cannabinoid receptors have been identified in the basal ganglia and hippocampus, suggesting a potential role of cannabinoids in regulating movement and behavior.[34] The cannabis plant is rich in various compounds, with delta-9-tetrahydrocannabinol (THC) being the most abundant and psychoactive among the cannabinoids. Cannabis has more than 60 cannabinoid compounds, and some, like cannabidiol, may influence the effects of THC.[33] Cannabinoids have been utilized for medicinal purposes for centuries. Currently, delta-9-tetrahydrocannabinol (THC) and the cannabis extract nabiximols are approved for the treatment of nausea and anorexia, respectively. In the context of Tourette Syndrome (TS), there have been many anecdotal reports suggesting that marijuana may be effective not only in reducing tics but also in addressing associated behavioral issues.[27]

Botulinum toxin for tics

Local intramuscular injections of botulinum toxin can be considered a therapeutic approach when dealing with a select few highly troublesome tics. Case series have suggested that botulinum toxin injections may not only alleviate tics but also provide relief from associated uncomfortable premonitory sensations and pain. This treatment approach is frequently employed for tics affecting the eye blinking, neck, and shoulder regions. In cases of severe vocal tics, intralaryngeal injections may also be utilized. It's important to note that the benefits of botulinum toxin therapy are temporary, typically lasting for a duration of 3 to 6 months.[29]

Habit reversal therapy

Habit Reversal Therapy (HRT) stands as the primary behavioral psychotherapeutic approach for treating Tic Disorders (TD). HRT encompasses three fundamental steps, divided into two stages, and typically spans twelve sessions.[3]

The three core steps are as follows:

- ***Awareness Training*:** This initial step involves guiding individuals, particularly children, to recognize and acknowledge premonitory urges, which are the sensations that precede the occurrence of a tic.
- ***Competing Response Training*:** In this phase, specific competing responses are identified for each tic. For instance, for vocal tics, controlled breathing may be selected as a competing response, while for sniffing tics, nose breathing could serve as the competing response.

- ***Intensive Training*:** This step involves selecting a family member to aid the child in diligently practicing and reinforcing the competing response, ensuring its effectiveness (Figure 3).

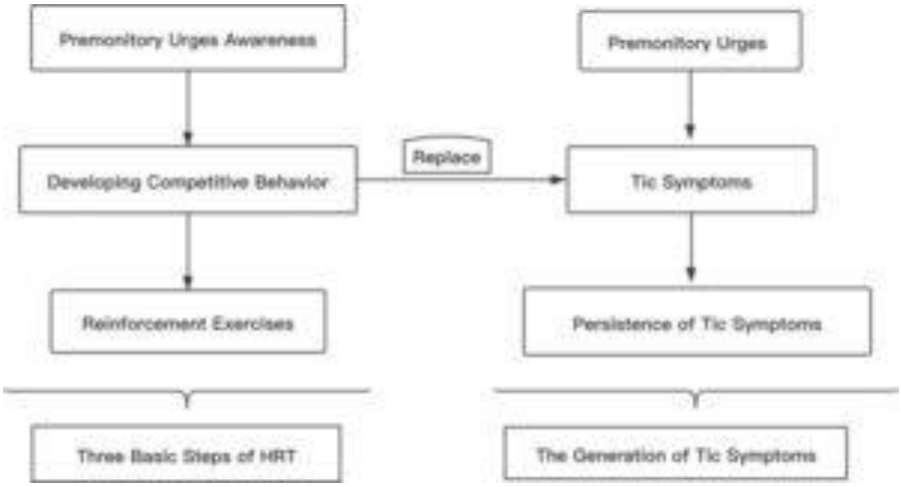


Figure 3: Three basic steps of habit reversal therapy 30.

The treatment process is divided into two stages:

Stage One (Sessions 1–8): This stage encompasses four main components: tic awareness training, competing response training, relaxation techniques, and intensive training.

Stage Two: The second stage primarily serves as a review and consolidation phase, ensuring that the learned techniques are effectively applied and maintained.

These sessions are distributed across twelve sessions as follows:

- **Session 1**: Introduction to the basic process, familiarization with reversal training, and introduction to the methods and procedures.
- **Sessions 2–6**: Weekly sessions focused on developing distinct competitive behaviors tailored to various tic symptoms.
- **Sessions 7 and 8**: Biweekly sessions primarily dedicated to reviewing and consolidating the content covered in sessions 2–6.
- **Sessions 9–12**: Monthly sessions that further reinforce and review the training provided in previous sessions.[30]

Deep brain stimulation for Tourette Syndrome

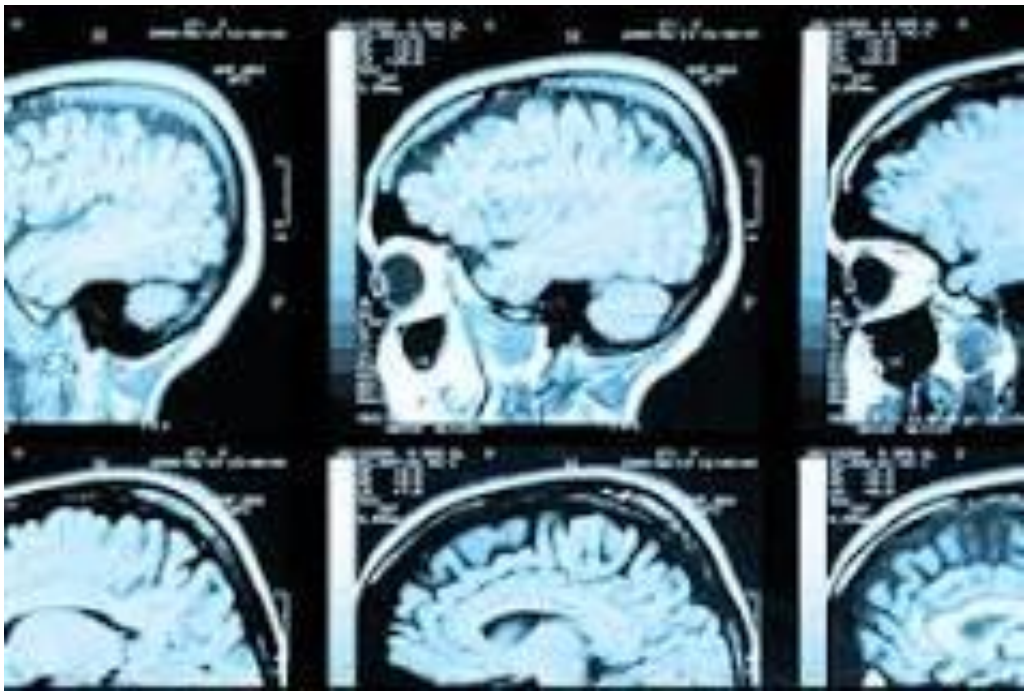


Figure 4: Deep Brain Stimulation: A New Option for Tourette Syndrome.32

Deep Brain Stimulation (DBS) has appeared as a practical choice for certain individuals with Tourette Syndrome (TS) who experience substantial impairment in their quality of life due to motor and/or vocal tics, even after trying various other treatment approaches.[32] (Figure 4)

The current clinical criteria for considering Deep Brain Stimulation (DBS) in a patient with Tourette Syndrome (TS) are primarily rooted in the clinical diagnosis, with an emphasis on high tic severity scores and the persistence of symptoms despite the use of at least three different pharmacological drugs. These drugs typically include alpha-adrenergic agonists, dopamine antagonists, and medication from at least one added class, such as tetrabenazine or clonazepam. While some recommendations may use age as a potential exclusion criterion, particularly limiting DBS for individuals below the age of 18 or 25, it's important to note that age should not be an absolute or inflexible criterion.[32] However, it is advisable to seek guidance and consult with a local ethics committee when contemplating surgery for patients younger than 18 years of age.[31]

Conclusion

While Tourette Syndrome is a common childhood disorder, its exact cause has not yet been fully understood. Previous studies have revealed differences in the neurobiological structures of individuals with Tourette Syndrome.[11] In recent years, research conducted

over the past five years has shed new light on genetic variations and changes in neurophysiology and brain networks that contribute to its development.[3]

Notably, only a limited number of studies have delved into the role of environmental factors in the causation and natural progression of Tourette Syndrome. Nevertheless, the data generated by these studies warrant further investigation in this area.[16]

Tourette Syndrome disproportionately affects boys compared to girls and is often associated with attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). Although the inheritance pattern of Tourette Syndrome frequently appears to be autosomal recessive, pinpointing specific abnormal genes has proven challenging.[1] Over the past several decades, treatment options have significantly advanced, offering greater opportunities to enhance the quality of life for individuals with Tourette Syndrome. Promising pharmacological options on the horizon hold the potential to further reduce tics, ideally with fewer adverse effects.[3]

References

1. Hallett, Mark. "Tourette Syndrome: Update." *Brain & Development* 37, no. 7

(August 2015): 651–55. https://doi.org/10.1016/j.braindev.2014.11.005.

2. Johnson, Kara A., Yulia Worbe, Kelly D. Foote, Christopher R. Butson, Aysegul Gunduz, and Michael S. Okun. "Tourette Syndrome: Clinical Features, Pathophysiology, and Treatment." *The Lancet. Neurology* 22, no. 2 (February 2023): 147–58. https://doi.org/10.1016/S1474-4422(22)00303-9.
3. Frey, Jessica, and Irene A. Malaty. "Tourette Syndrome Treatment Updates: A Review and Discussion of the Current and Upcoming Literature." *Current Neurology and Neuroscience Reports* 22, no. 2 (February 2022): 123–42. https://doi.org/10.1007/s11910-022-01177-8.
4. Albin, Roger L. "Tourette Syndrome as a Disorder of the Social Decision-Making Network." *Frontiers in Psychiatry* 10 (2019): 742. https://doi.org/10.3389/fpsyt.2019.00742.
5. Jiang, Jilong, Mengxin Chen, Huifang Huang, and Yanhui Chen. "The Aetiology of Tourette Syndrome and Chronic Tic Disorder in Children and Adolescents: A Comprehensive Systematic Review of Case-Control Studies." *Brain Sciences* 12, no. 9 (September 6, 2022): 1202. https://doi.org/10.3390/brainsci12091202.
6. Keen-Kim, Dianne, and Nelson B. Freimer. "Genetics and Epidemiology of Tourette Syndrome." *Journal of Child Neurology* 21, no. 8 (August 2006): 665–71. https://doi.org/10.1177/08830738060210081101.
7. Jagger, J., B. A. Prusoff, D. J. Cohen, K. K. Kidd, C. M. Carbonari, and K. John. "The Epidemiology of Tourette's Syndrome: A Pilot Study." *Schizophrenia Bulletin* 8, no. 2 (1982): 267–78. https://doi.org/10.1093/schbul/8.2.267.
8. Cavanna, Andrea E., and Stefano Seri. "Tourette's Syndrome." *BMJ (Clinical Research Ed.)* 347 (August 20, 2013): f4964. https://doi.org/10.1136/bmj.f4964.
9. Lin, Wei-De, Fuu-Jen Tsai, and I.-Ching Chou. "Current Understanding of the Genetics of Tourette Syndrome." *Biomedical Journal* 45, no. 2 (April 2022): 271–79. https://doi.org/10.1016/j.bj.2022.01.008.
10. Kurlan, R., P. G. Como, B. Miller, D. Palumbo, C. Deeley, E. M. Andresen, S. Eapen, and M. P. McDermott. "The Behavioral Spectrum of Tic Disorders: A Community-Based Study." *Neurology* 59, no. 3 (August 13, 2002): 414–20. https://doi.org/10.1212/wnl.59.3.414.
11. Ünal, Dilek, and Devrim Akdemir. "[Neurobiology of Tourette Syndrome]." *Turk Psikiyatri Dergisi = Turkish Journal of Psychiatry* 27, no. 4 (2016): 275–85.
12. Chandiwana, S. K. "Spatial Heterogeneity in Patterns of Human Schistosomisis Infection in the Zimbabwean Highveld." *The Central African Journal of Medicine* 34, no. 9 (September 1988): 212–21.
13. Hartmann, Andreas, Per Andrén, Cyril Atkinson-Clement, Virginie Czernecki, Cécile Delorme, Nanette Marinette Debes, Natalia Szejko, Keisuke Ueda, and Kevin Black. "Tourette Syndrome Research Highlights from 2021." *F1000Research* 11 (2022): 716. https://doi.org/10.12688/f1000research.122708.2.
14. Shavitt, Roseli Gedanke, Ana Gabriela Hounie, Maria Conceição Rosário Campos, and Eurípedes C. Miguel. "Tourette's Syndrome." *The Psychiatric Clinics of North America* 29, no. 2 (June 2006): 471–86. https://doi.org/10.1016/j.psc.2006.02.005.

15. Hartmann, Andreas, Cyril Atkinson-Clement, Christel Depienne, and Kevin Black. “Tourette Syndrome Research Highlights from 2020.” *F1000Research* 11 (2022): 45. https://doi.org/10.12688/f1000research.75628.2.
16. Hoekstra, Pieter J., Andrea Dietrich, Mark J. Edwards, Ishraga Elamin, and Davide Martino. “Environmental Factors in Tourette Syndrome.” *Neuroscience and Biobehavioral Reviews* 37, no. 6 (July 2013): 1040–49. https://doi.org/10.1016/j.neubiorev.2012.10.010.
17. Burd, Larry, Roger D. Freeman, Marilyn G. Klug, and Jacob Kerbeshian. “Tourette Syndrome and Learning Disabilities.” *BMC Pediatrics* 5 (September 1, 2005): 34. https://doi.org/10.1186/1471-2431-5-34.
18. Albin R. Neurobiology of basal ganglia and TS: neurotransmitters and neurochemistry overview. Presented at: 4th International Scientific Symposium on Tourette Syndrome; June 25-27, 2004; Cleveland, Ohio.
19. Woods, D. W., T. S. Watson, E. Wolfe, M. P. Twohig, and P. C. Friman. “Analyzing the Influence of Tic-Related Talk on Vocal and Motor Tics in Children with Tourette’s Syndrome.” *Journal of Applied Behavior Analysis* 34, no. 3 (2001): 353–56. https://doi.org/10.1901/jaba.2001.34-353.
20. Meidinger, Amy L., Raymond G. Miltenberger, Michael Himle, Matthew Omvig, Casey Trainor, and Ross Crosby. “An Investigation of Tic Suppression and the Rebound Effect in Tourette’s Disorder.” *Behavior Modification* 29, no. 5 (September 2005): 716–45. https://doi.org/10.1177/0145445505279262.
21. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed., (DSM-5). Washington, DC: American Psychiatric Publishing; 2013.
22. Singer, Harvey S. “Tourette’s Syndrome: From Behaviour to Biology.” *The Lancet. Neurology* 4, no. 3 (March 2005): 149–59. https://doi.org/10.1016/S1474-4422(05)01012-4.
23. Block MH. Presentation at: 4th International Scientific Symposium on Tourette Syndrome. June 25-27, 2004; Cleveland, OH.
24. Bockner S. Gilles de la Tourette"s disease. J Ment Sci. 1959 Oct. 105:1078-81.
25. Kurlan R, Trinidad KS. Treatment of tics. In: Kurlan R, ed. Treatment of Movement Disorders. Philadelphia, PA: JB Lippincott. 1995: 365-406.
26. McCracken JT, Suddath R, Chang S, Thakur S, Piacentini J. Effectiveness and tolerability of open label olanzapine in children and adolescents with Tourette syndrome. J Child Adolesc Psychopharmacol. 2008 Oct. 18(5):501-8.
27. Müller-Vahl, Kirsten R. “Treatment of Tourette Syndrome with Cannabinoids.” *Behavioural Neurology* 27, no. 1 (2013): 119–24. https://doi.org/10.3233/BEN-120276.
28. Kurlan, R. “Tourette Syndrome. Treatment of Tics.” *Neurologic Clinics* 15, no. 2 (May 1997): 403–9. https://doi.org/10.1016/s0733-8619(05)70321-2.
29. Kurlan, Roger M. “Treatment of Tourette Syndrome.” *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics* 11, no. 1 (January 2014): 161–65. https://doi.org/10.1007/s13311-013-0215-4.
30. Liu, Shijie, Ying Li, and Yonghua Cui. “Review of Habit Reversal Training for Tic Disorders.” *Pediatric Investigation* 4, no. 2 (June 2020): 127–32. https://doi.org/10.1002/ped4.12190.
31. Casagrande, Sara C. B., Rubens G. Cury, Eduardo J. L. Alho, and Erich Talamoni Fonoff. “Deep Brain Stimulation in Tourette’s Syndrome: Evidence to Date.” *Neuropsychiatric Disease and Treatment* 15 (2019): 1061–75. https://doi.org/10.2147/NDT.S139368.
32. “Deep Brain Stimulation.” Accessed September 25, 2023. https://tourette.org/research-medical/deep-brain-stimulation/.
33. Curtis, Adrienne, Carl E. Clarke, and Hugh E. Rickards. “Cannabinoids for Tourette’s Syndrome.” *The Cochrane Database of Systematic Reviews* 2009, no. 4 (October 7, 2009): CD006565. https://doi.org/10.1002/14651858.CD006565.pub2.
34. Müller-Vahl, K. R., H. Kolbe, U. Schneider, and H. M. Emrich. “Cannabinoids: Possible Role in Pathophysiology and Therapy of Gilles de La Tourette Syndrome.” *Acta Psychiatrica Scandinavica* 98, no. 6 (December 1998): 502–6. https://doi.org/10.1111/j.1600-0447.1998.tb10127.x.
35. Mogwitz, Sabine, Judith Buse, Stefan Ehrlich, and Veit Roessner. “Clinical Pharmacology of Dopamine-Modulating Agents in Tourette’s Syndrome.” *International Review of Neurobiology* 112 (2013): 281–349. https://doi.org/10.1016/B978-0-12-411546-0.00010-X.
36. Eddy, Clare M., Hugh E. Rickards, and Andrea E. Cavanna. “Treatment Strategies for Tics in Tourette Syndrome.” *Therapeutic Advances in Neurological Disorders* 4, no. 1 (January 2011): 25–45. https://doi.org/10.1177/1756285610390261.
37. Eddy CM, Rickards HE, Cavanna AE. Treatment strategies for tics in Tourette syndrome. Ther Adv Neurol Disord. 2011 Jan;4(1):25-45. doi: 10.1177/1756285610390261. PMID: 21339906; PMCID: PMC30369

Topic: Dissociative Amnesia.

Authors: Manar Lotfy, Nada Talal, Niveen Sherif, Rovan Emad.

Editor: Menna Marwan.

Reviewer: Ethar Hazaimeh.

Keywords: Amnesia, dissociative amnesia, controversial psychiatric disorders, DSM-5, post-traumatic amnesia, and memory loss.

Overview

Dissociative amnesia is among the most ambiguous and controversial psychiatric disorders. It is characterized by retrieval blockade of episodic autobiographical memories arising in the context of psychological trauma (whether known or not), with no evidence of brain injury on structural imaging. Patients experience an interruption of self. The definition of dissociative amnesia was given in the 2017 French International Classification of Diseases and Related Health Problems (CIM10) as "a disorder characterized by a retrospective gap in the memory of important personal information, generally of a traumatic or stressful nature; The individual experiences significant memory loss beyond typical forgetfulness, unrelated to substance use or medical conditions." [1][2]

Dissociative amnesia can be classified as localized (lack of memory for a period), selective (lack of memory for specific parts of an event) or generalized (lack of memory for the life history and identity). The differential diagnosis of dissociative amnesia includes substance use disorder, malingering, cognitive disorder, and neurological conditions like seizure disorders and transient global amnesia. [3]

The disorder is quite diverse, as symptoms and disease progression can differ significantly. Dissociative amnesia is primarily retrograde, particularly in the domain of episodic-autobiographical memory. It is uncommon to experience anterograde dissociative amnesia without significant retrograde memory impairment. Functional neuroimaging studies of dissociative amnesia with prevailing retrograde memory impairments display adjustments within the network that sub-serve autobiographical memory. Currently, there are no evidence-based treatments available for dissociative amnesia, and there is no established framework for its rehabilitation. [2]

Epidemiology

The occurrence of dissociative amnesia varies among different countries and populations. Epidemiological studies on dissociative amnesia have been conducted in over 16 countries. However, due to differences in terminologies, case definitions, assessment methods, sample size, and selection criteria, accurate estimates of the prevalence of dissociative amnesia and fugue are hindered. Prevalence studies have shown rates of dissociative amnesia ranging from 0.2% to 7.3%. Additionally, the prevalence of dissociative amnesia is similar for both males and females.[2]

Etiology and Risk Factors

Developmental stressful childhood events such as abuse, emotional neglect, boundary violations, and boundary violations are the etiological components that result in dissociative identity disorder (DID). Familial, societal, and cultural elements may give rise to trauma, and/or they may influence the expression of DID. Memory and the construction of self-identity are cognitive processes that appear disrupted in DID and are linked to its etiology. [4]

Premorbid risk factors for the development of dissociative amnesic conditions involve genetic vulnerabilities for dissociation, biological biasing towards increased sensitivity to stress, early age, early onset of trauma, impairments in emotional processing, traits of decreased cognitive flexibility, and repressive cognitive style, which may be partly culturally shaped. [5]

Types

Dissociative amnesia can cause several memory disturbances, according to the DSM-5:

1. Localized amnesia (the most common type): failure to recall events that occurred within a specific time.
2. Selective amnesia: recalls some but not all aspects of a specific time or traumatic event.
3. Systematized amnesia refers to the phenomenon of selective memory loss for a specific category of information.
4. Continuous amnesia: a condition where an individual experiences memory loss for every new event as it occurs.
5. Generalized amnesia (rare): sudden loss of memory for one's entire life. [6]

Signs and Symptoms

The primary symptom is severe memory loss that cannot be explained by a medical condition. Patients are unable to recall information about themselves, events, or people in their lives, particularly during a traumatic period. Dissociative amnesia can be

associated with a specific time, such as intense combat, or it can be a complete loss of memory about self. It may occasionally entail travel or a confused wandering away from life (dissociative fugue). Amnesia usually occurs suddenly and can last minutes, hours, months, or even years. [7]

Most cases of dissociative amnesia are brief. Memories frequently return abruptly and completely. Memory recovery may be triggered by something in the person's surroundings or in therapy. Furthermore, people suffering from medical amnesia are distressed by their memory loss, while most people suffering from dissociative amnesia appear to be unconcerned about their amnesia. [8]

Diagnosis

According to DSM-5 diagnostic criteria, dissociative amnesia is diagnosed clinically if the following DSM-5-TR criteria are met:

- Predominant disturbance of one or more episodes of an inability to recall important personal information, commonly of a traumatic or stressful nature, that is extensive to be by ordinary forgetfulness.
- The disturbance does not occur during dissociative identity disorder, posttraumatic stress disorder (PTSD), acute stress disorder, or somatization disorder and is not due to the direct physiological effects of a substance or of neurological or other general medical conditions.
- Symptoms seriously disrupt social or occupational functioning or cause significant distress. [9][10]

Treatment

Successful treatments include psychotherapies that help patients process traumatic memories and manage dissociative states. Techniques such as hypnosis have proven their worth, along with the selective use of antianxiety and antidepressant medications for comorbid conditions. Identification as well as modulation of dissociative symptoms, coupled with management of related posttraumatic syndromes, have been shown to be effective treatments. [11]

Prognosis

The clinical course is self-limited, and the short-term prognosis is positive. Memory commonly recovers fully within days, but mild residual impairment can sometimes persist for weeks. Minimum is known about the long-term prognosis. Recurrent

episodes of dissipative amnesia are uncommon but can certainly occur through the years. [12]

References

1. Thomas-Antérion C. (2017). Dissociative amnesia: Disproportionate retrograde amnesia, stressful experiences and neurological circumstances. *Revue neurologique*, *173*(7-8), 516–520. https://doi.org/10.1016/j.neurol.2017.07.007
2. Staniloiu, A., & Markowitsch, H. J. (2014). Dissociative amnesia. *The lancet. Psychiatry*, *1*(3), 226–241. https://doi.org/10.1016/S2215-0366(14)70279-2
3. Hafizi, S., & Afolabi, B. (2021). Generalized Dissociative Amnesia Versus Transient Global Amnesia. *The primary care companion for CNS disorders*, *23*(2), 20l02631. https://doi.org/10.4088/PCC.20l02631
4. Vedat Şar, Martin J Dorahy & Christa Krüger (2017) Revisiting the etiological aspects of dissociative identity disorder: a biopsychosocial perspective, Psychology Research and Behavior Management, 10: 137-146, DOI: 10.2147/PRBM.S113743
5. Staniloiu, A., & Markowitsch, H. J. (2014). High prevalence of dissociative amnesia and related disorders in immigrated people. In L. T. B. Jackson, D. Meiring, F. J. R. Van de Vijver, E. S. Idemoudia, & W. K. Gabrenya Jr. (Eds.), Toward sustainable development through nurturing diversity: Proceedings from the 21st International Congress of the International Association for Cross-Cultural Psychology. https://scholarworks.gvsu.edu/iaccp_papers/134/
6. Hosein, M., & Treisman, G. (n.d.). Dissociative amnesia: Johns Hopkins Psychiatry Guide. Retrieved April 6, 2023, from https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_Psychiatry_Guide/787157/all/Dissociative_Amnesia
7. Dissociative amnesia: Symptoms, causes, Management & Treatment. (n.d.). Retrieved April 6, 2023, from https://my.clevelandclinic.org/health/diseases/9789-dissociative-amnesia
8. Staniloiu, A., & Markowitsch, H. J. (2014). Dissociative amnesia. The lancet. Psychiatry, 1(3), 226–241. https://doi.org/10.1016/S2215-0366(14)70279-2
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. Washington, DC: APA Press; 2013. 519-33.
10. Dissociative disorders. (2022, December 13). Retrieved April 6, 2023, from https://www.mayoclinic.org/diseases-conditions/dissociative-disorders/symptoms-causes/syc-20355215
11. Maldonado, J. R., Butler, L. D., & Spiegel, D. (2002). Treatments for dissociative disorders. In P. E. Nathan & J. M. Gorman (Eds.), A guide to treatments that work (pp. 463–496). Oxford University Press. https://doi.org/10.1093/med:psych/9780199342211.001.0001
12. Arena, J. E., & Rabinstein, A. A. (2015). Transient global amnesia. Mayo Clinic proceedings, 90(2), 264–272. https://doi.org/10.1016/j.mayocp.2014.12.001

Article Title: Medication-induced Akathisia.

Author: Mouns Saed Radaideh.

Editors: Ihda Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: akathisia, antipsychotics, motor restlessness, dopamine D2 receptors, medication-induced

Overview

Akathisia is a quite common and distressing movement disorder that can be associated with antipsychotic drug use. It is characterized by subjective (inner restlessness) and aim (excessive movements) components. Akathisia may have a negative impact on clinical outcomes and even lead to treatment discontinuation. (1)

Diagnosing akathisia is sometimes hard as it can be confusing - A mild degree of akathisia could be misattributed to psychotic agitation, resulting in further escalation of the offending drug. On the other hand, it can co-occur or be caused by other psychiatric and organic conditions (including acute psychosis, comorbid affective disorders, drug withdrawal states, insomnia, and delirium), as well as other psychotropic medication, most commonly antidepressants. (2)

Propranolol, a non-selective beta-adrenergic receptor antagonist, is the first-line treatment for antipsychotic-induced akathisia (AIA). (3)

History & Epidemiology of Akathisia.

Akathisia is a term derived from the Greek for ‘inability to sit’. Refers to a neuropsychiatric syndrome characterized by subjective and objective psychomotor restlessness. Although recognized soon after the use of antipsychotic medication. (4) Historically, the dominant symptom of akathisia is disorientation. Haskoves, who described the syndrome in 1901, concluded that the illness was hysterical. Bing classified akathisia as a "psychosis" characterized by a "morbid fear of sitting," but explained it in another chapter to overcome the muscle stiffness of Parkinson's disease. Oppenheim described akathisia as a form of neurosis, "usually a form of a phobia". (5) Wilson chose it “hysterical” in one chapter of his classic textbook and described the syndrome in association with Parkinson's disease in a later chapter. (5) The incidence of the disease among people using antipsychotic drugs ranges from 5-50% depending on the duration of treatment and the drug used. (6)

Pathogenesis and etiology

Akathisia was initially classified as part of the extrapyramidal syndrome (EPS) induced by antipsychotic drugs, but some evidence suggests that akathisia is distinct from other EPS manifestations. (6) The mechanism is the inhibition of dopaminergic neurotransmission in the nigrostriatal pathway for acute events, while tardive dyskinesia has been attributed to D2 receptor upregulation and subsequent hypersensitivity to dopamine following prolonged exposure to D2 antagonists. Patients are characteristically indifferent to EPS and the presentation is more distressing to observers of the movement disorders than to those experiencing them. (6)

Akathisia is classified according to the time range of symptoms development. Acute akathisia occurs within a few days to weeks of the beginning of treatment or increasing the dose of antipsychotic medication. If akathisia develops later, it is considered subacute or chronic. (7) Chronic akathisia is when akathisia has been present for several months. In contrast, tardive akathisia occurs later (1-3 months) during treatment with antipsychotics, and it may even appear after antipsychotic discontinuation or dosage reduction. Tardive akathisia is reduced by increasing the antipsychotic dose, but it may also persist for months to years after the antipsychotic is discontinued. (7) Despite that akathisia can occur due to antipsychotic drug withdrawal, it can also occur with illicit substance intoxication and withdrawal states. The syndrome is most seen with the use of cocaine, methamphetamine, MDMA, ecstasy, and GHB. Alcohol and opioid withdrawal can give rise to anxious, restless states which are like akathisia. (8)

The neurotransmitters mostly associated with akathisia are gamma-aminobutyric acid (GABA) and serotonin. GABA (via GABAA receptor interactions) produces an influence on dopamine-dependent signaling, thus, increasing or reducing activity. With a distinctive distribution pattern, serotonin is also associated with motor regulation through serotonin receptors found in several cortical areas as well as the striatum. More specifically, serotonin manages dopaminergic motor function in the Nigro-striatal system. (7)

Clinical presentation and complications

The presentation of akathisia is different from restless leg syndrome (RLS), though the pathophysiological foundation may be similar. Patients with RLS complain of an intolerable sensation in the legs and an insurmountable urge to move them. It is worse during the night and the pain associated with it is primarily due to its disruptive effect on sleep. Patients may have a history of drug abuse, as RLS is commonly present in the post-acute withdrawal syndrome of many illicit drugs. It is also associated with iron deficiency. (6)

When akathisia is mild to moderate in severity, the lower extremities are involved, usually from the hips to ankles, and the movements take the form of shifting positions while standing and moving the feet while sitting. (9) The predilection to affect primarily the lower extremities is often helpful in differentiating akathisia from other antipsychotic-induced side effects that tend to affect other body parts. With increasing severity, however, akathisia can involve the entire body, resulting in near-unceasing writhing and rocking movements often accompanied by jumping around, running, and occasionally flinging oneself out of a chair or a bed. (9) Patients typically show other evidence of mild or early extrapyramidal dysfunction such as decreases in facial expression (despite complaints of extremely subjective distress), a rapid shuffling gait with a lack of accessory movements, decreased blink rate, and a positive glabellar reflex. A mild intention tremor and cogwheel rigidity can also be present. Mild rigidity can best be drawn out by recruitment. Movement rating scales are important instruments for adequate identification. (10)

Diagnosis

The clinical diagnosis of akathisia may be complicated because the intensity can vary according to the case and the degree of arousal. It has to be differentiated from psychotic agitation and anxiety, substance abuse or withdrawal syndromes, some somatic illnesses (for example, hyperthyroidism, hyponatremia), or neurologic disorders (for example, Parkinson’s disease, restless legs syndrome) The Barnes Akathisia Rating Scale (BARS), a 4-item scale. with good validity and reliability, recommended to diagnose akathisia, as well as to monitor its severity. (11)

The patients with akathisia would experience a desire to move, an awareness that they could not keep their legs still, or a compulsion to move which was often particularly referable to the legs. (12) Many patients complained that the condition was least tolerable when they were required to stand still, for example when lining up for meals or medication on the ward, waiting at the supermarket checkout, or standing in the kitchen while cooking. These symptoms are the subjective diagnostic criteria for akathisia included in the item 'awareness of restlessness' on the scale. (12)

The BARS rate the observable movements on a separate Objective item, with severity points attached with descriptions of the nature of the movements and the proportion of time they are exhibited. (13)

After assessing the objective and subjective (awareness of restlessness and distress related to restlessness) components of BARS, the assessor will systematically gain information on the intensity of the feelings of restlessness, the level of associated distress, and the type and frequency of fidgety, restless movements. This allows for an overall measure of severity to be made using the Global item. It was expected that the Global item score, incorporating all these elements of the condition, would provide a

better reflection of overall severity than a sum of the other items, and would be relevant for most research and clinical purposes. (13) The Global item score allows for prevalence or incidence estimates: using accepted definitions of akathisia, the diagnostic threshold score on the Global item is 2 (i.e., a score of 2 or more indicates the presence of akathisia) (Barnes, 1989). (13)

Barnes Akathisia Rating Scale	**Prince Henry Hospital Akathisia Rating Scale**
OBJECTIVE (rated 0-3)	OBJECTIVE (each rated 0-3)
0. Normal - occasional fidgetiness	1. Sitting
1. Characteristic movements - present less than half the time	1. Semipurposeful/purposeless leg/feet movements
2. As above: present for at least half the time	2. Semipurposeful hand/arm movements
3. Constant during the time observed	3. Shifting body position in chair
	4. Inability to remain seated
SUBJECTIVE	
Awareness of restlessness (0-3)	2. Standing
0. Absence of inner restlessness	1. Purposeless/semi-purposeless leg/feet movements
1. Non-specific inner restlessness	2. Shifting weight and/or walking-on-the-spot
2. Awareness	3. Inability to remain standing (walking/pacing)
3. Awareness of intense compulsion	
2. Standing	
Distress related to restlessness (0-3)	SUBJECTIVE (each rated 0-3)
0. None	1. Feelings of restless, especially in legs

1. Mild 2. Moderate 3. Severe	2. Inability to keep legs still 3. Inability to remain still, standing or sitting
Global clinical assessment of akathisia (ratings 0-5) (anchor definitions provided) 0. Absent 1. Questionable 2. Mild (anchor definitions provided) 3. Moderate 4. Marked	Global rating Absent: 0 Mild: 1 Moderate: 2 Severe: 3

Table 1: Standardized recording of akathisia: two scales derived from a single source.[14]

DSM 5 diagnostic criteria for drug-induced akathisia

Here are the DSM-5 criteria for drug-induced akathisia:

- Restlessness or the need to move frequently, which is usually accompanied by an unpleasant subjective sensation (e.g., crawling, creeping, pulling, itching, tingling, burning, or aching) in the lower limbs. (15)
- restlessness is caused by antipsychotic or other dopamine-receptor-blocking agents (e.g., metoclopramide). (15)
- The restlessness is not due to a medical condition (e.g., parkinsonism, dystonia, chorea, or tics) or akathisia caused by another medication. (15)
- restlessness is not better accounted for by another mental disorder (e.g., anxiety disorder, obsessive-compulsive disorder, or attention-deficit/hyperactivity disorder). (15)

Treatment and Prognosis

Sadly, the actual evidence base for treatments of akathisia is very small, and many of the recommendations are based on clinician experiences, case reports, and reports from studies of drugs where akathisia was not a primary concern. (9) First, the cause of the akathisia should be identified, and initial treatment aimed at that cause. Since the most of patients with akathisia developed it secondary to psychotropic medications, the initial recommendation is, if possible, to reduce or switch medication. (9)

For treatment, anticholinergic drugs such as benztropine, biperiden, and benzhexol were most used in the past. In fact, some investigators considered a response to an anticholinergic drug as diagnostic for acute akathisia. (16) Other studies have shown that only some patients respond, and often partially, and this response may relate to the presence of Parkinsonian side effects. Some favor benzhexol over other drugs when they do use them, but research evidence for this is lacking. (16,17)

The doses commonly used in the treatment are 2 to 6 mg/day of benztropine, or the equivalent, although higher doses may sometimes be necessary. Benzodiazepines, especially diazepam, lorazepam, and clonazepam, have been used again with partial success, as have other sedative drugs such as barbiturates and diphenhydramine. (16)

In the last few years, adrenergic drugs have received a lot of attention. (18) Several studies have shown that small doses (20 to 60 mg/day) of propanol can produce a significant improvement that usually occurs within a few hours. (19) Most studies of propranolol have been uncontrolled, but all have been positive, and a recent double-blind cross-over study has supported this conclusion. (19) Others have reported benefits with selective beta-1 antagonists (20) and even with peripherally acting beta-adrenergic antagonists, (21) but these results have not been consistent; propranolol is at present the preferred drug. Clonidine is also reported to be successful. (22)

Rarely, dopamine agonists like bromocriptine and amantadine have been tried. (23) Finally, piracetam, (24) buspirone, and opiates have been suggested to be of benefit in case reports of more severe akathisia. (23)

A slower infusion of metoclopramide decreases the rate of akathisia. A double-blind clinical trial of patients aged 18 years and older who were to receive intravenous metoclopramide for treating nausea, vomiting, or headache was eligible. Patients were excluded if they were taking medications that might mimic or mask akathisia, had a movement disorder, or renal insufficiency, or were unable or unwilling to consent. In conclusion, a slower infusion of metoclopramide reduces the incidence of akathisia. (28)

Risk factors

Although acute antipsychotic-induced akathisia is often thought of in association with schizophrenia, it appears that patients with mood disorders, particularly bipolar disorder, may be at higher risk. (9)

Other risk factors may include exaggerated dose or rapid dose increase, traumatic brain injury, cancer, and iron deficiency. (9) No proven evidence of risk is associated with age, gender, or ethnic background. (25) Chronic or tardive akathisia may be related to advanced age and female gender, just as is tardive dyskinesia. (26)

Patients in palliative care units may face several neuropsychiatric syndromes that include delirium, agitation, and other behavioral disturbances due to types of neurological and neuropsychiatric conditions. In addition, they also develop nausea and other general medication disturbances. (27)

Conclusion.

It is important to raise awareness about akathisia and its symptoms, as well as to advocate for more research into effective treatments. By doing so, we can help those who suffer from this condition and improve their quality of life.

References

1. Demyttenaere K, Detraux J, Racagni G, Vansteelandt K. Medication-Induced Akathisia with Newly Approved Antipsychotics in Patients with a Severe Mental Illness: A Systematic Review and Meta-Analysis. CNS Drugs. 2019 Jun;33(6):549–66.
2. Kalniunas A, Chakrabarti I, Mandalia R, Munjiza J, Pappa S. The Relationship Between Antipsychotic-Induced Akathisia and Suicidal Behaviour: A Systematic Review. Neuropsychiatr Dis Treat. 2021;17:3489–97.
3. Poyurovsky M, Weizman A. Treatment of Antipsychotic-Induced Akathisia: Role of Serotonin 5-HT(2a) Receptor Antagonists. Drugs. 2020 Jun;80(9):871–82.
4. Pringsheim T, Gardner D, Addington D, Martino D, Morgante F, Ricciardi L, et al. The Assessment and Treatment of Antipsychotic-Induced Akathisia. Can J Psychiatry. 2018 Nov;63(11):719–29.
5. Van Putten T. The many faces of akathisia. Compr Psychiatry. 1975;16(1):43–7.
6. Zareifopoulos N, Katsaraki M, Stratos P, Villiotou V, Skaltsa M, Dimitriou A, et al. Pathophysiology and management of Akathisia 70 years after the introduction of the chlorpromazine, the first antipsychotic. Eur Rev Med Pharmacol Sci. 2021 Jan;25(14):4746–56.
7. Salem H, Nagpal C, Pigott T, Teixeira AL. Revisiting Antipsychotic-induced Akathisia: Current Issues and Prospective Challenges. Curr Neuropharmacol. 2017;15(5):789–98.
8. Thippaiah SM, Fargason RE, Birur B. Struggling to find Effective Pharmacologic Options for Akathisia? B-CALM! Psychopharmacol Bull. 2021 Jun;51(3):72–8.
9. Lohr JB, Eidt CA, Abdulrazzaq Alfaraj A, Soliman MA. The clinical challenges of akathisia. CNS Spectr. 2015 Dec;20 Suppl 1:1–6.
10. Brown P. Review: drug-induced akathisia in medical and surgical patients. Int J Psychiatry Med. 1988;18(1):1–15.
11. Sienaert P, van Harten P, Rhebergen D. The psychopharmacology of catatonia, neuroleptic malignant syndrome, akathisia, tardive dyskinesia, and dystonia. Handb Clin Neurol. 2019;165:415–28.
12. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989 May;154:672–6.
13. Barnes TRE. The Barnes Akathisia Rating Scale--revisited. J Psychopharmacol. 2003 Dec;17(4):365–70.

14. Owens DGC. An overview of some standardised recording instruments [Internet]. A Guide to the Extrapyramidal Side-Effects of Antipsychotic Drugs. Cambridge University Press; 2014. p. 276–94. Available from: https://www.cambridge.org/core/product/identifier/9781139149112%23c02286-10-1/type/book_part
15. DSM-5-TR Classification. In: Diagnostic and Statistical Manual of Mental Disorders [Internet]. American Psychiatric Association Publishing; 2022. (DSM Library). Available from: https://doi.org/10.1176/appi.books.9780890425787.x00_Diagnostic_Classification
16. Sachdev P, Longragan C. The present status of akathisia. J Nerv Ment Dis. 1991 Jul;179(7):381–91.
17. Chue P, Agyapong V, Abba-Aji A. Antipsychotic Drugs. Side Eff Drugs Annu. 2018;40:99–119.
18. Adler LA, Angrist B, Reiter S, Rotrosen J. Neuroleptic-induced akathisia: a review. Psychopharmacology (Berl). 1989;97(1):1–11.
19. Adler L, Angrist B, Peselow E, Corwin J, Maslansky R, Rotrosen J. A controlled assessment of propranolol in the treatment of neuroleptic-induced akathisia. Br J Psychiatry. 1986 Jul;149:42–5.
20. Dupuis B, Catteau J, Dumon JP, Libert C, Petit H. Comparison of propranolol, sotalol, and betaxolol in the treatment of neuroleptic-induced akathisia. Am J Psychiatry. 1987 Jun;144(6):802–5.
21. Ratey JJ, Sorgi P, Polakoff S. Nadolol as a treatment for akathisia. Am J Psychiatry. 1985 May;142(5):640–2.
22. Adler LA, Angrist B, Peselow E, Reitano J, Rotrosen J. Clonidine in neuroleptic-induced akathisia. Am J Psychiatry. 1987 Feb;144(2):235–6.
23. Blaisdell GD. Akathisia: a comprehensive review and treatment summary. Pharmacopsychiatry. 1994 Jul;27(4):139–46.
24. Fehr C, Dahmen N, Klawe C, Eicke M, Szegedi A. Piracetam in the treatment of tardive dyskinesia and akathisia: a case report. Vol. 21, Journal of clinical psychopharmacology. United States; 2001. p. 248–9.
25. Chong SA, Mythily, Remington G. Clinical characteristics and associated factors in antipsychotic-induced akathisia of Asian patients with schizophrenia. Schizophr Res. 2003 Jan;59(1):67–71.
26. Sachdev P. The epidemiology of drug-induced akathisia: Part II. Chronic, tardive, and withdrawal akathisias. Schizophr Bull. 1995;21(3):451–61.
27. Kumar R, Sachdev PS. Akathisia and second-generation antipsychotic drugs. Curr Opin Psychiatry. 2009 May;22(3):293–9.
28. Regan LA, Hoffman RS, Nelson LS. Slower infusion of metoclopramide decreases the rate of akathisia. Am J Emerg Med. 2009 May;27(4):475–80.

Article Topic: Delusional Disorder.

Author: Ghina Mohamad Kaskas.

Editor: Ihdaa Mahmoud Bani Khalaf, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: Delusional disorder, delusions, antipsychotics, paranoid psychosis.

Overview

Delusional disorder (DD) is a condition in which a person has monothematic delusions for more than a month. [4] This disorder has multiple names, including paranoia, paranoid condition, paranoid reaction, paraphrenia, paranoid state, paranoid psychosis, and paranoid disorder. [6] The first comprehensive psychopathological description of paranoia was described by Esquirol in 1838 as partial delirium, which, in the end, was named partial psychosis. [10] After that, Kraeplin separated paranoia (precursor of DD) from his dementia praecox category (later named Schizophrenia). [10] He believed that paranoia had an endogenous cause. [5] Paranoia/paranoid psychosis was then renamed by Winokur in 1977 as Delusional disorder. [6]

Sérieux and Capgras postulated a hypertrophy of attention in which the individual focuses on issues to the exclusion of other issues. [2] Kauffman investigated this in 1981 with people with delusions, finding true experiences at the root of delusion-like experiences. [2]

Epidemiology

This condition is underreported so the frequency in the population is not known. It usually presents the psychiatric facilities only when the person becomes litigious or criminal. [10] The estimated lifetime prevalence for DD is 0.2% in the general population and around 2-3% in patients with other psychotic disorders. [7] It affects both genders equally. [7] Persecutory DD is the most common type of DD. [4]

Clinical presentation and complications

Since delusions are the main symptom of delusional disorder, we need to clearly define them. According to DSM-V TR delusion is defined as:

Fixed beliefs that are not amenable to change even with the presence of conflicting evidence. Their content may include a variety of themes (e.g., somatic, referential, persecutory, religious, grandiose). [14]

Individuals present with delusions of a specific theme for more than one month, and they are usually uncooperative with treatment and annoyingly talkative during therapy sessions [2]. They will try to offer evidence to support their belief and get the doctor convinced [2]. They will argue anything presented against them through appeals to coincidence, misunderstanding, or alternative interpretations of facts [2]. An important feature of DD patients is that their personality is intact, and the delusions are encapsulated [2]. DD patients cannot have symptoms of thought alteration, passivity, and negativity [1].

A patient with DD is mostly characterized by:[10]

- An egocentric, narcissistic, self-overrated arrogance.
- A suspicious and negative attitude toward the outside world, which is perceived as hostility, causes the patient to isolate him/herself.
- A propensity for misinterpretations and misjudgments.
- A diminished ability for social adjustment and flexibility because of the points mentioned above.

Diagnosis

According to DSM-V, the diagnostic criteria are as follows:[14]

A. Presence of one (or more) delusions with a duration of 1 month or longer.

B. Criterion A for schizophrenia is never met.

Note that hallucinations, if present, are not prominent and are related to the delusional theme (e.g., the sensation of being infested with insects associated with delusions of infestation).

C. Apart from the impact of the delusion(s) or its ramifications, behavior is not bizarre or odd and functioning is not impaired.

D. If manic or major depressive episodes have occurred, these have been briefing in comparison to the duration of the delusional periods.

E. The disturbance is not due to the physiological effects of a substance or another medical condition and is not better explained by another mental disorder, such as obsessive-compulsive disorder or body dysmorphic disorder.

Specify whether:

- **Erotomaniac type:** This subtype applies when the central theme of the delusion is that another person is in love with the individual.
- **Grandiose type:** This subtype applies when the central theme of the delusion is the conviction of having some great (but unrecognized) insight or talent or having made some important discovery.
- **Jealous type:** This subtype applies when the central theme of the individual's delusion is that her or his spouse or lover is unfaithful.
- **Persecutory type:** This subtype applies when the central theme of the delusion involves the individual's belief that he or she is being conspired against, spied on, cheated, followed, drugged or poisoned, harassed, maliciously maligned, or obstructed in the pursuit of long-term goals.
- **Somatic type:** This subtype applies when the central theme of the delusion involves sensations or bodily functions.
- **Mixed type:** This subtype applies when there is no one delusional theme that predominates.
- **Unspecified type:** This subtype applies when the dominant delusional belief cannot be determined or is not described in the specific types (e.g., referential delusions without a prominent grandiose or persecutory component).

Specify if:

With bizarre content: Delusions are deemed bizarre if they are implausible, not understandable, and not derived from ordinary life experiences (e.g., an individual's belief that a stranger has removed his or her internal organs and replaced them with someone else's organs without leaving any wounds or scars).

Specify if:

The following course specifiers are only to be used after a 1-year duration of the disorder:

The first episode, currently in acute episode: The first manifestation of the disorder meets the defining diagnostic symptom and time criteria. An acute episode is a period in which the symptom criteria are fulfilled.

The first episode, currently in partial remission: Partial remission is a period during which an improvement after a previous episode is conserved and the defining criteria of the disorder are partially fulfilled only.

The first episode, currently in full remission: Full remission is a period after an earlier episode in which there are no disorder-specific symptoms are present.

Multiple episodes, currently in an acute episode.

Multiple episodes, currently in partial remission. Multiple episodes, currently in full remission.

Continuous:

Symptoms fulfilling the disorder's diagnostic symptom criteria remain for most of the illness course, with sub-threshold symptom periods being very brief compared to the overall course.

Unspecified

Specify current severity:

Severity is rated by a quantitative assessment of the primary symptoms of psychosis, including hallucinations, delusions, disorganized speech, abnormal psychomotor behavior, and negative symptoms. Each of these symptoms may be rated for its current severity (most severe in the last 7 days) on a 5-point scale ranging from 0 (not present) to 4 (present and severe).

Note: Diagnosis of the delusional disorder can be made without using this severity specifier.

Differential diagnosis:

- **Obsessive-compulsive and other related disorders** [14]: when a person with obsessive-compulsive disorder is totally persuaded that her or his obsessive-compulsive disorder beliefs are true then the diagnosis of obsessive-compulsive disorder, with absent insight / delusional beliefs specifier, should be given rather than a diagnosis of delusional disorder. Similarly, if an individual with body dysmorphic disorder is completely convinced that her or his body dysmorphic disorder beliefs are true, then the diagnosis of body dysmorphic disorder, with absent insight / delusional beliefs specifier, should be given rather than a diagnosis of delusional disorder.

- **Major neurocognitive disorder, delirium, psychotic disorder due to another medical condition, and substance/medication-induced psychotic disorder [**14]**:** Individuals with these disorders may present with symptoms that suggest delusional disorder. For example, simple persecutory delusions in the context of a major neurocognitive disorder would be diagnosed as a major neurocognitive disorder, with behavioral disturbance. A substance / medication-induced psychotic disorder cross-sectionally may be identical in

symptomatology to delusional disorder but can be distinguished by the chronological relationship of substance use to the onset and remission of delusional beliefs.

- **Schizophreniform disorder and Schizophrenia [**14]**:** Delusional disorder can be distinguished from schizophreniform disorder and schizophrenia by the absence of the other characteristic symptoms of the active phase of schizophrenia.

- **Bipolar and depressive disorders and schizoaffective disorders [**14]**:** These disorders may be differentiated from delusional disorders by the temporal relationship between delusions and mood disturbance and by the severity of the mood symptoms. If delusions occur exclusively during mood episodes, the diagnosis is a depressive or bipolar disorder with psychotic features. Mood symptoms that meet the full criteria for a mood episode can be superimposed on the delusional disorder. The delusional disorder can be diagnosed only if the total duration of all mood episodes remains brief compared to the total duration of the delusional disturbance. If not, then a diagnosis of other specified or unspecified schizophrenia spectrum and other psychotic disorders accompanied by other specified depressive disorder, unspecified depressive disorder, other specified bipolar and related disorder, or an unspecified bipolar and related disorder is appropriate.

Treatment and management

Pharmacological treatment

When it comes to treatment, there are no clear guidelines for the pharmacological treatment of Delusional disorder [8]. The most commonly used treatment is antipsychotics, mostly first-generation antipsychotics and second-generation antipsychotics [8]. Antipsychotics achieved a 33.6% good response in the treatment of DD [8]. second-generation antipsychotics were less effective than first-generation antipsychotics [8]. There is a high degree of heterogeneity in variables such as response rate, treatment, follow-up period length, and response criteria [8].

The response is greater in hospitalized patients [8]. second-generation antipsychotics are safer and more proper for DD as they have a wider coverage of affective and negative psychopathology [8]. The good response rate for SGAs was higher for inpatients rather than outpatients [8].

First-generation antipsychotics:[8]

- Pimozide was the most used drug, and it showed a similar response in all types of DD.
- Somatic DD responded better to pimozide than to other APS [8]
- Pimozide increases the risk of arrhythmia because it largely increases the QT interval on ECG. This is why it is no longer the first-choice treatment.
- Pimozide good response rate of 48.6%.
- Haloperidol good response rate of 32.3%.

Second-generation antipsychotics:

- Only a few case reports have documented the effectiveness of SGAs in DD [7].
- Risperidone good response of 34.3% [8].
- Olanzapine good response of 33.7% [8].

Aripiprazole:[7]

- This is a third-generation antipsychotic with partial D2 agonist properties, which differentiates it from SGAs.
- It showed a good response in only 33.6% of patients.
- It was used on patients who previously received treatment with FGAs and SGAs but either showed no response or were unable to tolerate the side effects.
- Improvement was reported in around 5-6 weeks with the dose used is 11.1 mg/day.
- It is mostly used as monotherapy but sometimes combined with antidepressants.
- A combination of aripiprazole with antidepressants was highly effective in the somatic DD.
- It is effective in DD cases because it modulates dopamine and serotonin signaling.

Treatment of Decisional disorder with antipsychotics is effective in 94% of patients regardless of the used medication [2].

Cognitive behavioral therapy (CBT) [2]

- CBT is the only psychological therapy with evidence of effectiveness. It resulted in a greater reduction in effect relating to belief, the intensity of conviction, and positive action on belief subscales of the Maudsley Assessment of Delusions schedule.
- CBT did not abolish delusions.
- It is intensive and may not be cost-effective.

Risk factors [5]

- **Low socioeconomic status.**
- **Older age.**

  - In women with premenopausal onset, erotomaniac themes predominated [4].
  - Somatic and jealousy delusions were more common in postmenopausal-onset women [4].

- **Family history of psychiatric disease** especially:

  - Schizophrenia > Almost 9% of patients had a positive family history of schizophrenia [11]
  - Paranoid personality disorder [11]
  - Premorbid tendency to jealousy [11]

- **Sensory defect (deafness).**
- **Exposure to stressful life events.**

  - The delusional disorder usually develops under variable levels of psychological stress. Vulnerable patients will develop delusion-like responses to the stress so they can be the ones controlling it [9].

- **Men:**[12]

  - A younger onset of disease.
  - More schizoid premorbid personality features.
  - More likely to have the diagnosis changed to schizophrenia or schizoaffective disorder.

- **Women:**[12]

  - Poorer initial social functioning.
  - Better engagement with therapeutic interventions helped to regain functioning.
  - More likely to receive medication but less likely for the disorder to remit.

Prognosis

Third of the patients were found to reach remission [10]. It is usually better when the duration of the delusion is short before seeking help and when precipitating factors have been present during the development of DD [10]. Acute and subacute turn out to have favorable outcomes [10]. The diagnostic stability of DD is moderate (around 60%) in long-term follow-up studies. The diagnosis would later be changed to schizophrenia in

20% of cases [10]. Delusions usually tend to weaken with time, but a small group of patients will still have the intensity of delusions for years [10]. The course of the disease is highly variable, going from rapid and full recovery to a chronic condition [7]. Psychiatric comorbidity rates ranged from 46.5% to 64.8%, considered high, with mood disorders being the most frequent [5].

Recent updates

Researchers conducted a combined functional and structural imaging study in a sample of delusional disorder (DD) patients to determine if DD is associated with structural and functional imaging changes and to what extent. They performed structured imaging with both modulated and unmodulated analysis. They also performed cognitive task fMRI and resting-state functional connectivity analysis. Results were compared between DD patients, schizophrenics, and controls. Structured imaging revealed a significant reduction of cortical thickness. The unmodulated analysis revealed a decline in the bilateral insula/middle temporal gyrus and the cortical grey matter in the medial frontal/anterior cingulate cortex. In addition, it showed a decrease in scattered distributed small clusters. The modulated analysis did not show any significant difference between patients and controls. Cognitive task fMRI revealed a significant cluster of failure of deactivation in the anterior/medial frontal cingulate cortex. Resting-state functional connectivity (fcMRI) demonstrated that DD patients showed a significant decline in resting-state connectivity in the bilateral insula. Structured imaging and cognitive task fMRI results in DD patients are a bit similar to Schizophrenia, or at least they are both present but to a different extent. The reduction in resting-state connectivity has fewer clear parallels with schizophrenia while the failure of deactivation is now considered a well-replicated finding in schizophrenia

Recommendations

This paper highlighted the most valuable information about delusional disorder. However, future researchers could further investigate the genetic basis of DD and the brain's structural and functional changes as this would help understand the disease more. We should raise awareness campaigns to educate the community about DD and encourage seeking professional help.

References

[1] A.E. Farmer, P. Mcguffin, I.I. Gottesman, Searching for the Split in Schizophrenia: A Twin Study Perspective, n.d.
[2] C.F. Fear, Recent developments in the management of delusional disorders, Advances in Psychiatric Treatment. 19 (2013) 212–220.
[3] A. González-Rodríguez, O. Molina-Andreu, V. Navarro Odriozola, C. Gastó Ferrer, R. Penadés, R. Catalán, Suicidal Ideation and Suicidal Behaviour in Delusional Disorder: A Clinical Overview, Psychiatry J. 2014 (2014) 1–8.

[4] A. González-Rodríguez, M. v. Seeman, E. Izquierdo, M. Natividad, A. Guàrdia, E. Román, J.A. Monreal, Delusional Disorder in Old Age: A Hypothesis-Driven Review of Recent Work Focusing on Epidemiology, Clinical Aspects, and Outcomes, Int J Environ Res Public Health. 19 (2022).
[5] I. Ibanez-Casas, J.A. Cervilla, Neuropsychological research in delusional disorder: A comprehensive review, Psychopathology. 45 (2012) 78–95.
[6] K.S. Kendler, Demography of Paranoid Psychosis (Delusional Disorder) A Review and Comparison with Schizophrenia and Affective Illness, n.d.
[7] A. Miola, B. Salvati, F. Sambataro, T. Toffanin, Aripiprazole for the treatment of delusional disorders: A systematic review, Gen Hosp Psychiatry. 66 (2020) 34–43.
[8] J.E. Muñoz-Negro, F.J. Gómez-Sierra, V. Peralta, A. González-Rodríguez, J.A. Cervilla, A systematic review of studies with clinician-rated scales on the pharmacological treatment of delusional disorder, Int Clin Psychopharmacol. (2020) 129–136.
[9] A.J. Muzyk, E.J. Christopher, J.P. Gagliardi, D.A. Kahn, Use of aripiprazole in a patient with multiple sclerosis presenting with paranoid psychosis, J Psychiatr Pract. 16 (2010) 420–424.
[10] S. Opjordsmoen, Delusional disorder as a partial psychosis, Schizophr Bull. 40 (2014) 244–247.
[11] E. de Portugal, N. González, J.M. Haro, J. Autonell, J.A. Cervilla, A descriptive case-register study of delusional disorder, European Psychiatry. 23 (2008) 125–133.
[12] E. de Portugal, N. González, V. Miriam, J.M. Haro, J. Usall, J.A. Cervilla, Gender differences in delusional disorder: Evidence from an outpatient sample, Psychiatry Res. 177 (2010) 235–239.
[13] V. Vicens, J. Radua, R. Salvador, M. Anguera-Camós, E.J. Canales-Rodríguez, S. Sarró, T. Maristany, P.J. McKenna, E. Pomarol-Clotet, Structural and functional brain changes in delusional disorder, British Journal of Psychiatry. 208 (2016) 153–159.
[14] DIAGNOSTIC AND STATISTICAL MANUAL OF DSM-5 ™, n.d.

Article topic: Medication-induced acute dystonia.

Author: Zaid Shakhatreh.

Editor: Ihda Mahmoud Bani Khalaf.

Reviewer: Ethar Hazaimeh.

Keywords: medication-induced acute dystonia, dystonia, muscle contractions, movement disorder, drug-induced, antipsychotic, extrapyramidal symptoms, EPS.

Overview

Medication-induced acute dystonia is a movement disorder characterized by uncontrollable, repetitive motions of the body and is frequently observed in patients receiving drugs that modulate dopamine and other neurotransmitters in the brain such as antipsychotics,[1] antiemetics, antidepressants, and anticonvulsants. [2] It is characterized by involuntary muscle contractions that can cause abnormal and often repetitive movements, postures, or both,[3] usually occurring in the face, neck, or limbs, that can result in twisting or repetitive movements.[4]

The term dystonia was introduced by Hermann Oppenheim in 1911,[5] but references to this disorder can be traced back to ancient times. Some statues, sculptures, paintings, and literary works may depict people with dystonia-like features.[6] However, for a long time, dystonia was considered a psychogenic or hysterical condition, influenced by Freudian theories and the lack of clear neuropathology. It was only in the late 20th century that dystonia was recognized as an organic disease.[6,7] Dystonia's classification system is now informed by neurogenetics, with over 20 genetically defined subtypes and many more inherited or acquired conditions that include dystonia as a feature. However, some historical tensions remain unresolved, such as the role of psychological factors in both organic and functional dystonia. Advances in neuroimaging and cognitive neuroscience have challenged the dualistic mind-brain models and suggested more inclusive biopsychosocial approaches to dystonia. [6]

Pathogenesis and Etiology

The exact pathophysiology of drug-induced dystonia is not fully understood, but it is thought to be related to a disruption of the balance between dopamine and acetylcholine in the basal ganglia.[8] Dopamine is a neurotransmitter that plays a critical role in regulating motor function, while acetylcholine is another neurotransmitter that opposes

dopamine and helps to control muscle contractions. When dopamine receptors are blocked by medication, the balance between dopamine and acetylcholine is disrupted, leading to involuntary muscle contractions and spasms characteristic of dystonia.[8]

Antipsychotic and antidepressant drugs are the most common medications that induce acute dystonia.[9,10] However, some antiemetics can also cross the blood-brain barrier and affect dopamine receptors in other parts of the brain, causing dystonic reactions.[11] Some drugs are more likely to cause dystonic reactions than others. For example, high-potency neuroleptics such as haloperidol and fluphenazine have a higher risk than low-potency neuroleptics such as chlorpromazine and thioridazine.[12–14] The risk also increases with higher doses, intravenous or intramuscular administration, rapid titration, and longer duration of treatment.[13] Moreover, some individuals are more prone to develop dystonic reactions than others. For instance, young males, patients with a history of substance abuse or psychiatric disorders, and patients with genetic mutations in dopamine-related genes have a higher susceptibility.[15,16,17]

Some medical conditions or drugs can increase the risk of dystonic reactions by altering the levels or activity of dopamine or other neurotransmitters in the brain. For example, dehydration, hypocalcemia, hypomagnesemia, hypokalemia, stroke, traumatic brain injury, Parkinson's disease, Huntington's disease, Wilson's disease, antihistamines, anticonvulsants, antimalarials, cocaine, caffeine, oral contraceptives.[18–22]

Epidemiology

The epidemiology of drug-induced dystonia is not well established, as different studies have used different definitions, methods, and populations to estimate its prevalence and incidence. However, some general trends can be seen based on the available literature. Drug-induced dystonia is more common in young males, especially those with a history of substance abuse(cocaine/alcohol) or psychiatric disorders.[2,17,23] Its likelihood is higher in children and declines with advancing age. [24]

Antipsychotics can cause acute dystonia in 2-3% of patients who receive them, usually within the first 48 hours of taking the drug.[25] The frequency of acute dystonia reactions can range from 2.8% to 25% depending on the type of antipsychotic being used.[23,26]

The prevalence of drug-induced dystonia varies depending on the type and dose of the drug, the duration of exposure, and the presence of risk factors. Therefore, the prevalence varies widely from 2% to 90%. [2]

Clinical Presentation and Complications

Acute dystonia can occur within minutes to hours of taking a single dose of a dopamine-blocking drug or within 24 to 96 hours of starting or increasing the dose of such a drug.[12] Some dystonic movements last several seconds/minutes but others can last for weeks/months. This can lead to permanent bone deformity and impairment in function.[22]

The clinical presentation and signs and symptoms of drug-induced dystonia vary depending on the affected body region and the severity of the condition. Some of the common symptoms and signs are:

- **Oculogyric** crisis: an involuntary upward or lateral deviation of the eyes, causing difficulty in seeing and blinking. It can be accompanied by facial grimacing, tongue protrusion, and neck extension.[27]
- **Torticollis**: a condition where the neck muscles contract and cause the head to tilt or twist to one side. It can cause pain, stiffness, difficulty in moving the head, swallowing problems, and cosmetic concerns.[22]
- **Trismus**: a spasm of the jaw muscles, limiting the opening or closing of the mouth.[28]
- **Laryngeal dystonia**: a condition where the vocal cords spasm and cause difficulty in speaking or breathing. It can cause hoarseness, strained or breathy voice, choking sensation, coughing, or respiratory distress.[17]
- **Opisthotonus**: contraction of the back muscles that cause the body to arch backward.[17]
- **Tremor**.[22]

Drug-induced dystonia can have various complications that affect the quality of life and health of the patients. Some of these complications are:

- **Rhabdomyolysis**: A syndrome characterized by muscle necrosis and the leakage of intracellular muscle constituents into the circulation, which can impair renal function.[29] Rhabdomyolysis can occur as a rare complication of drug-induced dystonia,[30] especially if prolonged dystonia is present. It can cause muscle pain, weakness, dark urine, fever, nausea, vomiting, etc. It can lead to kidney failure if not treated promptly.[29]
- **Dystonic storm:** This is a life-threatening condition where severe and generalized dystonia occurs along with fever, sweating, tachycardia, hypertension, etc. Dystonic storms can occur as a rare complication of drug-induced dystonia, especially in patients with primary known dystonia (e.g., DYT1 dystonia). It can be triggered by infection or medication adjustment in some cases. It can cause respiratory failure, cardiac arrest, or death if not treated urgently.[31]

- **Extrapyramidal symptoms (EPS):** These are a spectrum of movement disorders that arise from the disruption of the basal ganglia, a brain region

involved in motor control. Drug-induced dystonia can be considered a subset of extrapyramidal symptoms that share a common pathophysiology and etiology. EPS includes dystonia, akathisia (restlessness), parkinsonism (slowness and stiffness), and tardive dyskinesia (involuntary movements of the face and limbs). EPS can interfere with social functioning, communication, motor tasks, and activities of daily living. They can also cause psychological distress and poor adherence to treatment.[32]

Diagnosis and workup

The diagnosis of drug-induced dystonia is based on the history of exposure to a likely causative medication, and the clinical features of the movement disorder, by the observation of the type and pattern of abnormal movements and postures, which requires expert neurological assessment.[33]

The first diagnostic criteria were proposed by Herz,[34] who suggested that dystonic movements and postures are the hallmark phenomenology of dystonia. They form the main physical signs and are complemented by three other physical signs: gestes antagonists ("sensory tricks"), mirror dystonia, and overflow dystonia. Fahn observed that dystonic movements are often mistaken for other types of involuntary movements, and they can vary in speed and regularity.[35] Sometimes, they can appear as tremors alone, without any other hints of dystonia. This can make it hard to recognize dystonia in patients who only have tremors. [36] The exact criteria for diagnosing dystonia in different parts of the body are not clear yet, and some cases may go unnoticed. Focal dystonia syndromes lack specific diagnostic criteria; hence, only general criteria are currently available.[33]

Neuroimaging and lab tests may be helpful to rule out other causes of dystonia, such as structural lesions, metabolic disorders, or genetic conditions, especially when dystonia is combined with other neurological features.[37] A recent review summarized more than 100 different disorders where dystonia may be combined with other features.[38]

Some examples of neuroimaging and lab tests that may be used in drug-induced dystonia are:

- MRI or CT scan to look for any brain lesions or degenerative conditions.[33]
- Blood or urine tests to measure the levels of the drug or its metabolites, or to check for any signs of toxicity, such as liver or kidney dysfunction, or electrolyte imbalance.[33,39]
- Genetic tests to screen for any mutations that may predispose to dystonia, such as variants in the DRD2 gene that encodes the dopamine D2 receptor.[33]
- Electromyography (EMG). This test measures the electrical activity within muscles.[33,39]

A characteristic and almost unique feature of dystonic movements is the presence of sensory tricks or gestes antagonists. These are actions or stimuli that temporarily stop the muscle spasms. For instance, some people with cervical dystonia (torticollis) can touch their chin or face to relieve their neck contractions. Some people with oro-lingual dystonia can put a finger on the lips or an object in the mouth to ease their mouth spasms. Sensory tricks may involve changes in the brain's sensory feedback or motor planning mechanisms.[22]

DSM-5 criteria for medication-induced acute dystonia

The DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria for medication-induced acute dystonia is as follows[40]:

1- The condition involves involuntary and sustained muscle contractions that affect different parts of the body, such as:

- The eyes, causing them to roll upward or sideways (oculogyric crisis)
- The head and neck, causing them to twist or tilt in abnormal positions (torticollis or retrocollis)
- The limbs or trunk, causing them to bend or arch in painful ways

2-The condition develops within a few days of starting or increasing the dose of a medication that affects the brain and movement (such as a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms.

Differential diagnosis

Drug-induced acute dystonia reaction may be challenging to distinguish from other conditions, these include Huntington's disease, Wilson's disease, Parkinson's disease, conversion disorder, tetanus, focal seizure, strychnine poisoning, hypocalcemia, anticholinergic toxicity, meningitis, neuroleptic malignant syndrome, stroke, temporomandibular joint dislocation, mandibular fracture, orbital fracture, and clonus.[13,32,41]

Treatment and management

Discontinuation or reduction of the causative drug: This is an important step in managing medication-induced acute dystonia. involves gradually stopping or reducing the dose of the offending medication, under the guidance of a doctor. If the medication is essential for the patient's mental health, a different class of antipsychotics, called atypical neuroleptics, may be used instead. These drugs have a lower risk of causing dystonia.[47]

Both pharmacological and non-pharmacological treatments have proven effective for drug-induced dystonia, The following are some of the available treatment methods:

Anticholinergic drugs: These are the most effective medications for dystonia, according to clinical evidence and expert opinion.[42] Anticholinergic drugs can help relax the muscles and reduce the spasms caused by dystonia. Examples of anticholinergic drugs that are commonly used include benztropine, trihexyphenidyl, biperiden, and procyclidine. These drugs are usually given orally or intramuscularly as soon as possible after the onset of symptoms. They may cause side effects such as dry mouth, blurred vision, constipation, urinary retention, confusion, and sedation.[37]

Benzodiazepines: They enhance the activity of gamma-aminobutyric acid (GABA), a neurotransmitter that inhibits nerve impulses in the brain. Benzodiazepines can help calm the nervous system and reduce anxiety and agitation associated with dystonia. Some benzodiazepines that are used for dystonia are diazepam, lorazepam, clonazepam, and alprazolam. These drugs are usually given orally or intravenously as an adjunct to anticholinergic drugs. They may cause side effects such as drowsiness, dizziness, memory impairment, dependence, and withdrawal symptoms.[37]

Diphenhydramine: This is an antihistamine drug that inhibits histamine receptors and prevents allergic reactions. Diphenhydramine also has anticholinergic properties and can help relieve dystonic symptoms. It is usually given intravenously or intramuscularly as an alternative to anticholinergic drugs.[43,44]

Intrathecal baclofen is a form of treatment that involves delivering baclofen, a muscle relaxant drug, directly into the spinal fluid around the brain and spinal cord.[37,45]

Levodopa: This is a medication that is used to treat Parkinson's disease and some forms of dopa-responsive dystonia. Levodopa is converted into dopamine, a neurotransmitter that regulates movement, in the brain. Levodopa can help improve dystonic symptoms in some patients with drug-induced acute dystonia, especially if it occurs as a side effect of antipsychotic drugs or other drugs that affect the dopamine system in the brain.[42,46]

Botulinum toxin injections: Botulinum toxin works by blocking the release of acetylcholine at the neuromuscular junctions, thereby paralyzing the muscles. Botulinum toxin can help reduce dystonic spasms and improve function and appearance in focal or segmental dystonia. It may cause side effects such as pain, bruising, swelling, weakness, infection, and antibody formation.[33]

Speech therapy: a form of therapy that involves exercises and techniques to improve speech production and communication skills. Speech therapy can help people with dystonia affecting their oral muscles to speak more clearly and fluently.[32]

Physical therapy: This is a form of therapy that involves exercises and stretches to improve muscle strength, flexibility, coordination, and posture. Physical therapy can help prevent muscle stiffness and contractures caused by dystonia. It can also help improve mobility and function in daily activities.[33]

Psychotherapy: therapy that involves talking to a mental health professional to address emotional and psychological issues related to dystonia. Psychotherapy can help people with dystonia cope with stress, anxiety, depression, low self-esteem, social isolation, and stigma.[3]

Surgery is not a common treatment for drug-induced dystonia, but it can be considered for some patients who do not respond to other treatments.[42] Surgery for dystonia usually involves deep brain stimulation (DBS), which is a procedure that involves implanting electrodes in specific areas of the brain and connecting them to a battery-operated device that delivers electrical impulses to modulate the abnormal brain activity that causes dystonia.[33,42,45]

Prophylaxis

Anticholinergics should be maintained after the resolution of dystonia as a prophylactic measure against recurrence, in conjunction with antipsychotics. The typical protocol involves co-administering an anticholinergic with the antipsychotic for 4 to 7 days, followed by a slow tapering of the anticholinergic dose. The presence of other acute extrapyramidal adverse effects, such as parkinsonism, may warrant a longer duration of anticholinergic therapy.[2] Long-term anticholinergics in schizophrenia patients on antipsychotics may have detrimental effects on cognitive function and quality of life.[48] Therefore, current guidelines generally discourage the preventive or long-term use of anticholinergics in this population.[48] A meta-analysis showed that diphenhydramine prophylaxis reduces extrapyramidal symptoms in patients receiving antiemetic as a bolus, but not as an infusion; hence, this meta-analysis suggested that the optimal strategy would be to give the antiemetic as an infusion without anticholinergic prophylaxis.[32]

Prognosis and effect on life

The prognosis and long-term effects of medication-induced acute dystonia depend on several factors, such as the type, dose, and duration of the offending drug, the age and genetic susceptibility of the patient, and the presence of other neurological or psychiatric conditions. In general, Dystonic reactions are rarely life-threatening,[2] The adverse effects often cause distress for patients and families, but it usually responds well to treatment.[13]

The impact of medication-induced acute dystonia on quality of life is variable and depends on the severity, frequency, and psychological and social consequences. Some patients may experience anxiety and fear, as well as embarrassment or stigma, which may eventually lead to depression due to their dystonic symptoms.[22,45] They may also have difficulties with daily activities, work, education, or interpersonal relationships.[22] Therefore, it is important to provide adequate education and support to these patients and their caregivers.[49]

Conclusion

Medication-induced acute dystonia is a serious and distressing condition that affects many patients who use antipsychotic drugs. This field faces many challenges and limitations, such as the lack of standardized criteria, guidelines, and protocols, the variability in clinical presentation and response to treatment, and the potential for misdiagnosis and adverse outcomes. Future research should explore the genetic and environmental factors that influence the susceptibility and severity of dystonia, evaluate the efficacy and safety of available drugs that can prevent or treat this condition, and improve the awareness, education, and care of patients who suffer from this condition. This topic is important and deserves more understanding and recognition.

References

1. Cornett EM, Novitch M, Kaye AD, Kata V, Kaye AM. Medication-induced tardive dyskinesia: a review and update. *Ochsner Journal*. 2017;17(2):162-174.
2. van Harten PN, Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. *Bmj*. 1999;319(7210):623-626.
3. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Movement disorders*. 2013;28(7):863-873.
4. Dystonia | National Institute of Neurological Disorders and Stroke. Accessed March 11, 2023. https://www.ninds.nih.gov/health-information/disorders/dystonia
5. De Pablo-Fernandez E, Warner TT. Dystonia. *Br Med Bull*. 2017;123(1):91-102.
6. Newby RE, Thorpe DE, Kempster PA, Alty JE. A history of dystonia: ancient to modern. *Mov Disord Clin Pract*. 2017;4(4):478-485.
7. Balint B, Mencacci NE, Valente EM, et al. Dystonia. *Nat Rev Dis Primers*. 2018;4(1):25.
8. D'Souza RS, Hooten WM. Extrapyramidal symptoms. In: *StatPearls [Internet]*. StatPearls Publishing; 2022.
9. Loonen AJM, Ivanova SA. Neurobiological mechanisms associated with antipsychotic drug-induced dystonia. *Journal of Psychopharmacology*. 2021;35(1):3-14.
10. Uğurlu GK, Önen S, Bayındırlı D, Çayköylü A. Acute dystonia after using single dose duloxetine: case report. *Psychiatry Investig*. 2013;10(1):95.
11. Park HW, Kwak JR, Lee JS. Clinical characteristics of acute drug-induced dystonia in pediatric patients. *Clin Exp Emerg Med*. 2017;4(3):133.
12. Dystonia Medical Research Foundation Canada. Drug Induced Dystonia.
13. J Michael Kowalski. Medication-Induced Dystonic Reactions Clinical Presentation. Published June 27, 2022. Accessed April 26, 2023. https://emedicine.medscape.com/article/814632-clinical#showall
14. Bosanac P, Hollander Y, Castle D. The comparative efficacy of intramuscular antipsychotics for the management of acute agitation. *Australasian Psychiatry*. 2013;21(6):554-562.
15. Spina E, Sturiale V, Valvo S, et al. Prevalence of acute dystonic reactions associated with neuroleptic treatment with and without anticholinergic prophylaxis. *Int Clin Psychopharmacol*. Published online 1993.
16. Wider C, Melquist S, Hauf M, et al. Study of a Swiss dopa-responsive dystonia family with a deletion in GCH1: redefining DYT14 as DYT5. *Neurology*. 2008;70(16 Part 2):1377-1383.
17. Wongveerasin P, Othong R, Pinchumponsang A, Hungspruke W, Jongjaroenwit P. Clinical Presentation and Management of Acute Dystonia from Drug Abuse or Misuse in Adolescents and Young Adults: A Retrospective Cohort Study in Bangkok, Thailand. *Emerg Med Int*. 2023;2023.

18. Paul SA, Mondal GP, Bhattacharyya R, et al. Clinical spectrum of movement disorders in neurology inpatients in a tertiary care centre. *J Neurosci Rural Pract*. 2021;12(03):581-585.
19. Macerollo A, Edwards MJ, Huang HC, et al. Peripheral trauma and risk of dystonia: What are the evidence and potential co-risk factors from a population insurance database? *PLoS One*. 2019;14(5): e0216772.
20. Lennox H Huang. Dehydration: Background, Pathophysiology, Etiology. Published December 7, 2018. Accessed April 26, 2023. https://emedicine.medscape.com/article/906999-overview#showall
21. Snaith A, Wade D. Dystonia. *BMJ Clin Evid*. 2014;2014.
22. Pana A, Saggu BM. Dystonia. Published online 2017.
23. Tural Hesapcioglu S, Ceylan MF, Kandemir G, Kasak M, Sen CP, Correll CU. Frequency and correlates of acute dystonic reactions after antipsychotic initiation in 441 children and adolescents. *J Child Adolesc Psychopharmacol*. 2020;30(6):366-375.
24. İncecik F, Hergüner MÖ, Özcan K, Altunbasak S. Albendazole-induced dystonic reaction: a case report. *Turk J Pediatr*. 2011;53(6):709.
25. Young SL, Taylor M, Lawrie SM. "First do no harm." A systematic review of the prevalence and management of antipsychotic adverse effects. *Journal of Psychopharmacology*. 2015;29(4):353-362.
26. Yamamoto N, Inada T. Dystonia Secondary to Use of Antipsychotic Agents. *DYSTONIA–THE MANY FACETS*. Published online 2012:55.
27. Schneider SA, Udani V, Sankhla CS, Bhatia KP. Recurrent acute dystonic reaction and oculogyric crisis despite withdrawal of dopamine receptor blocking drugs. *Movement disorders*. 2009;24(8):1226-1229.
28. Batla A. Dystonia: A review. *Neurol India*. 2018;66(7):48.
29. Cabral BMI, Edding SN, Portocarrero JP, Lerma E V. Rhabdomyolysis. *Disease-a-Month*. 2020;66(8):101015.
30. Allena N, Doppalapudi S, Khanal S, Tank S, Nasr R. Acute Dystonia with Rhabdomyolysis Induced by Paliperidone Palmitate: A Rare Adverse Effect. *Cureus*. 2022;14(9).
31. Termsarasab P, Frucht SJ. Dystonic storm: a practical clinical and video review. *J Clin Mov Disord*. 2017;4(1):1-8.
32. D'Souza RS, Hooten WM. Extrapyramidal symptoms. In: *StatPearls [Internet]*. StatPearls Publishing; 2022.
33. Albanese A, Di Giovanni M, Lalli S. Dystonia: diagnosis and management. *Eur J Neurol*. 2019;26(1):5-17.
34. Herz E. Dystonia: I. Historical review; analysis of dystonic symptoms and physiologic mechanisms involved. *Arch Neurol Psychiatry*. 1944;51(4):305-318.
35. Fahn S. The varied clinical expressions of dystonia. *Neurol Clin*. 1984;2(3):541-554.
36. Albanese A, Del Sorbo F. Dystonia and tremor: the clinical syndromes with isolated tremor. *Tremor and Other Hyperkinetic Movements*. 2016;6.
37. Jinnah HA, Factor SA. Diagnosis and treatment of dystonia. *Neurol Clin*. 2015;33(1):77-100.
38. Fung VSC, Jinnah HA, Bhatia K, Vidailhet M. Assessment of patients with isolated or combined dystonia: an update on dystonia syndromes. *Movement Disorders*. 2013;28(7):889-898.
39. Dystonia - Diagnosis and treatment - Mayo Clinic. Accessed April 27, 2023. https://www.mayoclinic.org/diseases-conditions/dystonia/diagnosis-treatment/drc-20350484
40. Edition F. Diagnostic and statistical manual of mental disorders. *Am Psychiatric Assoc*. 2013;21(21):591-643.
41. Lewis K, O'Day CS. Dystonic reactions. In: *StatPearls [Internet]*. StatPearls Publishing; 2022.
42. Bledsoe IO, Viser AC, San Luciano M. Treatment of Dystonia: Medications, Neurotoxins, Neuromodulation, and Rehabilitation. *Neurotherapeutics*. 2020;17(4):1622. doi:10.1007/S13311-020-00944-0
43. Digby G, Jalini S, Taylor S. Medication-induced acute dystonic reaction: the challenge of diagnosing movement disorders in the intensive care unit. *BMJ Case Rep*. 2015;2015. doi:10.1136/BCR-2014-207215
44. Marano M, Biase L di, Salomone G, Santo A Di, Montiroli A, Lazzaro V Di. The Clinical Course of a Drug-induced Acute Dystonic Reaction in the Emergency Room. *Tremor and Other Hyperkinetic Movements*. 2016;6(0):436. doi:10.7916/D87P8ZS1
45. Cloud LJ, Jinnah HA. Treatment strategies for dystonia. *Expert Opin Pharmacother*. 2010;11(1):5. doi:10.1517/14656560903426171
46. Pandey S, Srivanitchapoom P. Levodopa-induced Dyskinesia: Clinical Features, Pathophysiology, and Medical Management. *Ann Indian Acad Neurol*. 2017;20(3):190. doi:10.4103/AIAN.AIAN_239_17
47. Kamin J, Manwani S, Hughes D. Emergency psychiatry: extrapyramidal side effects in the psychiatric emergency service. *Psychiatr Serv*. 2000;51(3):287-289. doi:10.1176/APPI.PS.51.3.287
48. Benefits and limits of anticholinergic use in schizophrenia: focusing on its effect on cognitive function - PubMed. Accessed April 28, 2023. https://pubmed.ncbi.nlm.nih.gov/24102938/
49. Dystonia | National Institute of Neurological Disorders and Stroke. Accessed April 28, 2023. https://www.ninds.nih.gov/health-information/disorders/dystonia

Article topic: Genito-pelvic pain/penetration disorder (GPP/PD).

Author: Batool AlQadri.

Editor: Ihda Mahmoud Bani Khalaf.

Reviewer: Ethar Hazaimeh.

Keywords: Female sexual disorders, Pelvic pain, Vaginismus, Dyspareunia, libido.

Introduction

Genitopelvic pain/penetration disorder (GPP/PD) was recently added to the DSM-5 criteria in 2013, to include the previously named female sexual disorders “vaginismus” and “dyspareunia”. This disorder might be explained by patients as “pain or difficulty during intercourse”, clinical assessment of this complaint includes medical history, sexual history, and occasionally a physical examination.

This article addresses the fact that GPP/PD is multifactorial, explains these factors’ role in contributing to it, clarifies the psychiatric and biological analysis of the disorder, shows its key signs and symptoms along with suggesting multiple methods of treatment which include non-medical, medical, and surgical options.

Overview

Genitopelvic pain/penetration disorder (GPP/PD) is a sexual disorder in females due to multiple psychological, biological, and social etiologies. It’s considered a broad category that includes both vaginismus and dyspareunia.[1]

Vaginismus is defined as recurrent or persistent involuntary spasms of the vagina’s outer muscles which prevent penetrative sex, vaginismus is further classified as primary; which means that penetration has never occurred before, and secondary; meaning that penetration has been possible before. It also can be global under whatever circumstances or situational under specific ones. [2]

Dyspareunia on the other hand is defined as pain just before, during, or after sexual intercourse leading to decreased interest and orgasmic pleasure in sexual behavior. [3]

Etiology

GPP/PD is a complex disorder and not purely psychological, it must be viewed from other perspectives too including biology social relationships, and background. [4]

The biological perspective states that mast cell activation and hypersensitization in the long-term lead to the proliferation of nociceptors which eventually lead to increased sensitivity to the painful stimuli -which is also known as hyperalgesia. [21] In addition, genital infections, decreased vaginal lubrication and mechanical trauma are all important risk factors contributing to GPP/PD.[4] The psychological perspective mainly points to the fact that the accompanying depression and anxiety symptoms in most of cases can lead to GPP/PD.[4]

Epidemiology

Unfortunately, GPP/PD is under-researched worldwide due to the social stigma arising from cultural and religious beliefs concerning female sexual disorders and the patients' embarrassment of discussing their sensitive symptoms with the health providers leading to misdiagnosing and mistreating of those disorders. [20,22] Studies show that there is a relationship between GPP/PD and sexual abuse, although not physical abuse. [23]

Around 14-34% of premenopausal women are affected, their pain is eight times more accidental than chronic and usually associated with comorbidities such as endometriosis, irritable bowel syndrome (IBS), fibromyalgia, and postictal cystitis. Furthermore, psychiatric conditions such as childhood trauma, dissociative symptoms, and inadequate sexual education have been reported among patients.[5,6,7] Studies regarding racial differences in patients are rare although some show that black women are 2.15 times more affected than white women.[8]

Symptoms

- Pain or fear of pain upon vaginal penetration - of a penis or any other object like a tampon or even a speculum during gynecological physical exam - is the defining symptom of the disorder. [11]

This pain is reduced in intensity if the patient has strong beliefs that she can overcome it, in addition to the pivotal role of her partner by avoiding over-focusing on the issue but promoting adaptive coping techniques with her pain, leading to a higher level of satisfaction in her sexual relationship. [24]

The woman herself should have thorough acknowledgment of the female's anatomy, physiology, sexual education, also understanding of any previous sexual experiences especially if any abuse or feelings of shame are involved. [12]

On the other hand, the pain is intensified when the patient anticipates it, she will enter a vicious cycle of more and more pain during any attempts of vaginal penetration and her vaginal mucosa will be more prone to abrasions, tears, and inflammation due to the feedback inhibition of both the mental and physical sexual arousal, thus decreasing vaginal lubrication, vulvar congestion, pelvic muscle relaxation, and sexual pleasure. [9]

- Decreased Libido (sexual desire).
- Anorgasmia (difficulty in reaching an orgasm).
- Decreased arousal: lack of somatic responses, lack of excitement and lack of vaginal and clitoral enlargement.
- Hispareunia: male partner pain after intercourse usually after female reconstructive surgery.[10]

Signs

Genital examination is essential in diagnosing GPP/PD, although it can be difficult due to pain and discomfort, the following might be noticed during the exam:

- Vaginal Dryness.
- Pelvic mass tenderness during bimanual exam.
- Vaginal agglutination: fusion of vaginal walls above hymen.
- Reduced or increased sensitivity during Q tip touch test.
- Vulval gaping or non-coaptation at rest.[10]

DSM-5 Diagnostic Criteria

Persistent or recurrent difficulties with 1 or more of the following:

1. Vaginal penetration during intercourse.
2. Marked vulvovaginal or pelvic pain during intercourse or penetration attempts.
3. Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as a result of vaginal penetration.
4. Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration.

To be diagnosed with GPP/PD, one of the aforementioned requirements must be met, together with clinically substantial discomfort that affects the sexual life quality of the patient, is not explained by any other medical disorder, and has persisted for at least six months. [11]

Before Diagnosing a patient with GPP/PD, physicians should look for and treat medical causes of genital pain, including [20]

- Infections: Pelvic inflammatory disease, sexually transmitted infections, vaginal candidiasis.
- Dermatological conditions: lichen planus, skin allergy (e.g., to semen)
- Pelvic neoplasms.
- Structural causes: Endometriosis, Leiomyoma, imperforated hymen, vaginal agenesis.
- Hormonal disorders: oophorectomy, menopause, hyperprolactinemia, anorexia.

Treatment

An essential point to be considered in treating GPP/PD patients is that it's individualized, which means that each patient should be assessed thoroughly by a physician before deciding her specific treatment plan starting from the least to the most invasive methods: [20]

First: Non-pharmacological

1. Female sexual education: it is greatly helpful for the patient to study her body anatomy, physiology, and sexual cycle; this will help her to understand what to expect from her partner during sexual intercourse.
2. Lifestyle modification: such as management of mood disorders, adequate physical exercise, and avoiding douches and irritants.[12]
3. Weight loss and focusing on low oxalate diets such as fruits, vegetables, and proteins.
4. Bibliotherapy: which involves reading creative books and stories and watching educational videos is proved to reduce the patients' anxiety.[13]
5. Pelvic muscle exercise: this is achieved by gradually lowering anxiety related to penetration by increasing awareness of the pelvic muscles, enhancing relaxing techniques, restoring tone, and delivering stretching stimuli at the introitus.
6. Psychotherapy:

- Cognitive Behavioral Therapy (CBT): emphasizes on treating and dealing with the patient's thoughts that negatively impact her sexual pleasure.
- Mindfulness Therapy: it teaches the patient how to be fully relaxed in the moment without having any unwanted automated responses.

Those two psychological methods are used, and studies show that they are equally beneficial.[14]

Second: Pharmacological

1. Topical therapies on the vaginal area: such as essential arousal oil, vulvar non-hormonal soothing cream, and prostaglandin E1 analogues to dilate genital blood vessels. [15]
2. Antidepressants: Tricyclic antidepressants and Bupropion specifically showed improvement in sexual desire in women with and without depression.[16]
3. Vaginal estrogen: especially if the patient has vaginal atrophy and dyspareunia.[16]
4. Exogenous testosterone in postmenopausal women increases their desire, but patients should be warned that is not always available in all countries, also it is not FDA-approved and not fully studied to show its exact benefits and side effects in the long term.[16]
5. Selective estrogen receptor modulator: Ospemifene acts as an estrogen receptor agonist/antagonist in selective tissues, and helps in decreasing dyspareunia, especially in postmenopausal women. [17]
6. Botox injections: works on the nociceptors to create temporary localized muscular paralysis that lasts for three to six months, making it a good option for women who struggle with painful pelvic floor hyperactivity.[18]

Third: Surgical methods

1. Pelvic reconstructive surgery for genital prolapses and urinary incontinence patients.[19]
2. Vulvar vestibulectomy: the removal of the vestibular mucosa is the most invasive procedure, so it is the most prone to complications and the last one to be tried.[20]

Conclusion

Genitopelvic pain/penetration disorder (GPP/PD) is a female sexual disorder that includes both vaginismus which is defined as persistent involuntary spasms of the vagina's outer muscles and dyspareunia which is defined as pain before, during, or after sexual intercourse. The disorder is multifactorial; with psychological, biological, and social factors in its background, its prevalence varies among women with other co-existing medical disorders and there are some racial differences.

Patients usually present with pain upon penetration, decreased libido, and anorgasmia. Upon examination vaginal dryness, tenderness, and abnormal Q tip sensation test. Treatment is individualized and usually starts from the least invasive methods including lifestyle modification, psychotherapy, and pharmacological options to the most invasive methods like surgical ones.

References

- Berenguer-Soler, M., Navarro-Sánchez, A., Compañ-Rosique, A., Luri-Prieto, P., Navarro-Ortiz, R., Gómez-Pérez, L., Pérez-Tomás, C., Font-Juliá, E., Gil-Guillén, V. F., Cortés-Castell, E., Navarro-Cremades, F., Montejo, A. L., Arroyo-Sebastián, M. del Á., & Pérez-Jover, V. (2022). Genito pelvic pain/penetration disorder (GPPPD) in Spanish women—clinical approach in primary health care: Review and meta-analysis. *Journal of Clinical Medicine*, *11*(9), 2340. https://doi.org/10.3390/jcm11092340
- McEvoy, M., McElvaney, R., & Glover, R. (2021). Understanding vaginismus: a biopsychosocial perspective. *Sexual and Relationship Therapy: Journal of the British Association for Sexual and Relationship Therapy*, 1–22. https://doi.org/10.1080/14681994.2021.2007233
- Heim, L. J. (2001). Evaluation and differential diagnosis of dyspareunia. *American Family Physician*, *63*(8), 1535–1545. https://www.aafp.org/pubs/afp/issues/2001/0415/p1535.html
- Graziottin, A., & Gambini, D. (2017). Evaluation of Genito-pelvic pain/penetration disorder. In *The Textbook of Clinical Sexual Medicine (*pp. 289–304). Springer International Publishing.
- Bachmann, G., Cheng, R.-F. J., & Rovner, E. (2007). Vulvovaginal Complaints. In R. A. Lobo (Ed.), *Treatment of the Postmenopausal Woman (*pp. 263–269). Elsevier.
- Dias-Amaral, A., & Marques-Pinto, A. (2018). Female Genito-pelvic pain/penetration disorder: Review of the related factors and overall approach. *Revista Brasileira de Ginecologia e Obstetricia: Revista Da Federacao Brasileira Das Sociedades de Ginecologia e Obstetricia*, *40*(12), 787–793. https://doi.org/10.1055/s-0038-1675805
- Ozen, B., Özdemir, Y. O., & Bestepe, E. E. (2018). Childhood trauma and dissociation among women with genito-pelvic pain/penetration disorder. *Neuropsychiatric Disease and Treatment*, *14*, 641–646. https://doi.org/10.2147/ndt.s151920
- Azim, K. A., Happel-Parkins, A., Moses, A., & Haardoerfer, R. (2023). Racialized differences across experiences and measurements of pain in genitopelvic pain/penetration disorder. *The Journal of Sexual Medicine*, *20*(2), 224–228. https://doi.org/10.1093/jsxmed/qdac028
- Journal, M. (n.d.). *Genito-pelvic pain/ penetration disorder (GPPPD): An overview of current terminology, etiology, and treatment UNIVERSITY OF OTTAWA JOURNAL OF MEDICINE*. Uojm.Ca. Retrieved August 14, 2023, from http://en.uojm.ca/uploads/1/1/5/8/11584834/uojm_fall_2017.pdf#page=48
- Bo, K., Frawley, H. C., Haylen, B. T., Abramov, Y., Almeida, F. G., Berghmans, B., Bortolini, M., Dumoulin, C., Gomes, M., McClurg, D., Meijlink, J., Shelly, E., Trabuco, E., Walker, C., & Wells, A. (2017). An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the conservative and nonpharmacological management of female pelvic floor dysfunction. *International Urogynecology Journal*, *28*(2), 191–213. https://doi.org/10.1007/s00192-016-3123-4
- American Psychiatric Association. Genito-pelvic pain/penetration disorder. (2013). In *Diagnostic and Statistical Manual of Mental Disorders (*pp. 437–440). American Psychiatric Association.
- Perez, S., Brown, C., & Binik, Y. M. (2016). Vaginismus: When Genito-pelvic pain/penetration disorder makes intercourse seem impossible. In *Management of Sexual Dysfunction in Men and Women (*pp. 273–285). Springer New York.
- Balzer, A. M., & Mintz, L. B. (2015). Comparing two books and establishing probably efficacious treatment for low sexual desire. *Journal of Counseling Psychology*, *62*(2), 321–328. https://doi.org/10.1037/cou0000067
- Brotto, L. A., Bergeron, S., Zdaniuk, B., Driscoll, M., Grabovac, A., Sadownik, L. A., Smith, K. B., & Basson, R. (2019). A comparison of mindfulness-based cognitive therapy vs cognitive behavioral therapy for the treatment of provoked vestibulodynia in a hospital clinic setting. *The Journal of Sexual Medicine*, *16*(6), 909–923. https://doi.org/10.1016/j.jsxm.2019.04.002
- Islam, A., Mitchel, J., Rosen, R., Phillips, N., Ayers, C., Ferguson, D., & Yeager, J. (2001). Topical alprostadil in the treatment of Female Sexual Arousal Disorder: a pilot study. *Journal of Sex & Marital Therapy*, *27*(5), 531–540. https://doi.org/10.1080/713846804
- Kingsberg, S. A., & Woodard, T. (2015). Female sexual dysfunction: Focus on low desire. *Obstetrics and Gynecology*, *125*(2), 477–486. https://doi.org/10.1097/aog.0000000000000620
- Wurz, G. T., Kao, C.-J., & DeGregorio, M. W. (2014). Safety and efficacy of ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy due to menopause. *Clinical Interventions in Aging*, *9*, 1939–1950. https://doi.org/10.2147/CIA.S73753
- Zoorob D, South M, Karram M, et al. A pilot randomized trial of levator injections versus physical therapy for treatment of pelvic floor myalgia and sexual pain. Int Urogynecol J. 2015;26:845–852.
- . Rogers RG, Kammerer-Doak D, Darrow A, et al. Does sexual function change after surgery for stress urinary incontinence and/or pelvic organ prolapse? A multicenter prospective study. Am J Obstet Gynecol. 2006;195:e1–e4
- Goldstein AT, Pukall CF, Brown C, Bergerson S, Stein A, Kellogg-Spadt S. Vulvodynia: assessment and treatment. J Sex Med 2016;13(4):572-90.

- Graziottin, A., Skaper, S. D., & Fusco, M. (2014). Mast cells in cronich infammation, pelvic pain and depression in women. *Gynecol Endocrinol*, *30*(7), 472–477.
- Pukall, C. F., Goldstein, A. T., & Bergerson, S. (2016). Vulvodynia: defnition, prevalence, impact, and pathophysiological factors. *J Sex Med*, *13*(3), 291–304.
- Tetik, S., & Yalçınkaya Alkar, Ö. (2021). Vaginismus, dyspareunia and abuse history: A systematic review and meta-analysis. *The Journal of Sexual Medicine*, *18*(9), 1555–1570. https://doi.org/10.1016/j.jsxm.2021.07.004
- Rosen, N. O., Bergeron, S., & Glowacka, M. (2012). Harmful or helpful: perceived solicitous and facilitative partner responses are diferentially associated with pain and sexual satisfaction in women with provoked vestibulodynia. *J Sex Med*, *9*(9), 2351–2360.

Article topic: Panic Disorder.

Authors: Harith Al-Azzawi, Ghadeer Al-Qaq.

Editor: Fadlullah M. F. Al-Saleem.

Reviewer: Philip J. Sweidan.

Keywords: Antidepressants, CBT, Cognitive Behavior Therapy, Panic Attack, Panic Disorder.

Abstract

Panic disorder is a prevalent mental illness that affects up to 5% of the population at some time in their lives. It is frequently debilitating, especially when accompanied by agoraphobia, and is associated with significant functional morbidity and worse quality of life.[1] The condition is also expensive for people and society, as seen by higher healthcare utilization, absenteeism, and decreased workplace productivity. Some medical conditions (for example, asthma) are frequently associated with panic disorder, and some lifestyle variables (for example, smoking) enhance the risk for the disorder, although the causative pathways are yet unknown. There are additional genetic and early experience susceptibility factors, although their exact nature and pathophysiological processes are unclear. Despite an incomplete, but growing, understanding of the etiology, considerable evidence supports the use of various successful therapies (For example, pharmaceutical, cognitive-behavioral). The adaption and diffusion of these therapies to the frontlines of medical care should be top priorities for the public health community.[2]

Overview

According to the DSM-5, panic disorder is recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak level within minutes.[1]

It is a common mental disorder that affects up to 5% of the population at a point in life. It can be disabling especially when complicated by agoraphobia, which is associated with substantial functional morbidity and reduced life quality. This disorder is costly for individuals and society, as shown by increased use of health care, absenteeism, and reduced workplace productivity. [2]

Etiology

The exact cause of panic disorder has not been determined, although some factors can play a role in this disorder such as family history, drug abuse, brain abnormalities, and stress are some of the factors that can trigger panic attack episodes attributed to this disorder. [4]

Pathogenesis

The central nervous system's neurotransmitters and peptides appear to have a vital influence on physical symptoms.[4] Brain imaging studies have revealed distinct alterations in certain geographic locations, such as the limbic and frontal regions, including enhanced flow and receptor activity. The amygdala is thought to be the primary source of malfunction.[5] Medical sickness and panic disorder are highly connected from a pathophysiological and psychological standpoint. Two basic theories try to explain why patients are more prone to panic episodes. The first hypothesis proposes that vulnerable patients lack the neurochemical mechanisms that would usually regulate serotonin and that this elevated serotonin produces changes in the autonomic nervous system's fear network model. [5]

Presentation and Diagnosis

Panic disorder is characterized by episodic, unexpected attacks that occur with no obvious trigger, although many patients with this disorder have expected panic attacks, to occur in response to a known trigger. The most common physical symptom occurring with panic attacks is palpitations. [3]

Below are 13 symptoms in which four or more occur combined and they are [3]:

- Accelerated heart rate.
- Shaking or trembling.
- Shortness of breath.
- The feeling of choking.
- Chest pain and discomfort.
- Abdominal distress
- Feeling light-headed, dizzy, unsteady, or faint.
- A sensation of chills or heat.
- Paresthesias (tingling or numbness).
- Depersonalization (being detached from oneself) or derealization (feelings of unreality).
- Losing control.

- Fear of death.

The frequency of panic attacks varies widely. There may be moderately frequent attacks; for months at a time, or short bursts of more frequent attacks separated by weeks or months without any attacks or with less frequent attacks over many years. In terms of severity, individuals with panic disorder may have both full-symptom attacks, which include four or more symptoms, and limited-symptom attacks, which include fewer than four symptoms. The type and number of symptoms differ from one panic attack to the other. However, more than one unexpected full-symptom panic attack is necessary for the diagnosis. [1]

Risk factors

Symptoms of the disorder often start late in teens or in early adulthood and affect women more than men. Many factors may increase the risk of developing panic attacks or panic disorder including: [14]

- Familial history of panic attacks or disorder
- Major life stress, such as a loved one's death or critical illness
- A traumatic occurrence, such as sexual assault or a serious automobile accident
- Significant life events, such as a divorce or the birth of a child
- Smoking or excessive caffeine use
- A history of physical or sexual abuse as a child

Prognosis

Panic disorder is a chronic condition with a wide range of symptoms. In more than 85 percent of instances, proper pharmacologic therapy and cognitive-behavioral therapy (CBT), either alone or in combination, are beneficial. Patients with good premorbid functioning and symptoms that last for a brief time have a better prognosis. 10-20% of people continue to experience large symptoms.

Overall, the long-term prognosis for panic disorder is favorable, with over 65 percent of patients experiencing remission within six months. However, as discussed under History, trigger factors can cause panic attacks; several of these triggers have been linked to poor outcomes, including severe illness at the time of the initial assessment, high interpersonal sensitivity, low social class, separation from a parent due to death when young, divorce, and single status. [11]

Patients with panic disorder have a significantly increased incidence of coronary artery disease. Panic can cause myocardial ischemia in patients with coronary artery disease.

Reduced heart rate variability and increased QT interval variability may theoretically raise the risk of sudden death. [14]

Individuals with panic disorder have a suicide rate that is many times greater than the overall population. [14]

Treatment

In general, panic disorder can be treated effectively with pharmacological and psychological treatments, like cognitive-behavioral therapy and mindfulness interventions. [6]

Although pharmacological treatments are proven to be potent in panic disorder therapy, their potential side effects can be obstacles to binding to treatment and the long-term maintenance of achieved treatment goals. So, providing effective psychological interventions is important for this disorder either as a supportive or stand-alone treatment. However, the availability of treatment places is limited to conventional face-to-face mental health centers. [7]

Various effective medications are available for treating this disorder, but results have been unsatisfactory in some patients, suggesting the effectiveness of expanding the array of anti-panic medications and improving the quality of response to currently recommended treatments. [8]

Treatment choices are listed below:

- ## Antidepressants

Antidepressant medications have proved to reduce panic attack severity, eliminate attacks, and improve the overall life quality measures in patients with panic disorder. [8]

Two recent meta-analyses [10],[11] found that TCAs (tricyclic antidepressants) and SSRIs (selective serotonin reuptake inhibitors) are effective equally in reducing the number and severity of the attacks. The choice of antidepressant medication should be based on the patient's choices according to side effect profiles. MAO inhibitors (Monoamine oxidase inhibitors) also are effective in the treatment of panic disorders, but their use is limited due to safety concerns. [9]

Benzodiazepines have been proven to be useful in the treatment of various forms of anxiety for decades. These anxiety expressions have recently been separated into categories and diseases, such as generalized anxiety disorder and panic disorder. [7] The use and efficacy of benzodiazepine receptor agonists in individuals with these different diagnoses have been explored by researchers. Clinical research on generalized anxiety

disorder and panic disorder typically shows that benzodiazepine agonists have similar efficacy, while true comparison studies with two or three medications are rare. The differences in side effects, pharmacokinetics, and withdrawal reactions for benzodiazepines require more research. Concerns regarding benzodiazepine reliance, whether justified or not, and cessation effects have prompted researchers to look for novel benzodiazepines that do not have these issues. This study addresses recent breakthroughs in research on novel benzodiazepine compounds and reviews the efficacy and comparative studies of benzodiazepines that are already accessible. [13]

Along with drug therapy for panic disorder, neuromodulation techniques including TMS (Transcranial Magnetic stimulation) are used in panic disorder with varying results. [10]

- ## Cognitive Behavior Therapy

Cognitive behavior therapy (CBT) includes many techniques, for instance, exposure in vivo, applied relaxation, panic management, exposure through imagery, breathing retraining, and cognitive restructuring. Meta-analyses encourage the efficacy of CBT in relieving panic symptoms and overall disability.

It is uncertain if cognitive treatment (e.g., detecting mistaken feelings, educating patients about panic episodes) or behavior therapy is more important in CBT (e.g., breathing exercises, exposure, relaxation). However, in patients with panic disorder, particularly in patients with agoraphobia, the efficacy of exposure approaches alone, in which the patient repeatedly meets the anxiety-provoking stimulus through visualization or in vivo, is well documented. Referral to an expert exposure therapist is suggested whenever possible. [9]

Some panic disorder sufferers, especially men, self-medicate with alcohol, which interferes with therapy. In a single trial of people with alcohol addiction with panic disorder, adding CBT to an alcohol treatment program had no more effect on reducing panic symptoms than alcohol therapy alone. [9]

Prevention

There is no guarantee that panic episodes or panic disorders will not occur. However, these suggestions might be useful:

- To prevent panic attacks from getting worse or becoming more common, seek treatment as soon as possible.
- To avoid relapses or worsening panic attack symptoms, stick to your treatment plan.

- Maintain a regular physical activity regimen, which may help to reduce anxiety. [15]

Conclusion

Panic disorder is a common condition with an unclear origin. To begin adequate therapy, the disease must be detected early.[14] There are two methods of therapy that are indicated. One or both are chosen based on the patient's desire and the intensity of the panic attack. CBT is typically the first-line treatment for panic disorder, followed by at least a year of antidepressant medication. Patients suffering from this disease should be provided counseling to help them overcome their concerns. It is vital to consult a psychologist regularly to ensure that the panic attack is under control.[15]

References

[1] Diagnostic and statistical manual of mental disorders: DSM-5, American Psychiatric Publishing, Washington, D.C., 2013.

[2] P.P. Roy-Byrne, M.G. Craske, M.B. Stein, Panic disorder, Lancet. 368 (2006) 1023–1032. https://doi.org/10.1016/S0140-6736(06)69418-X.

[3] A.B. Locke, N. Kirst, C.G. Shultz, Diagnosis and management of generalized anxiety disorder and panic disorder in adults, Am. Fam. Physician. 91 (2015) 617–624. https://pubmed.ncbi.nlm.nih.gov/25955736/ (accessed October 12, 2022).

[4] A.H. Friedlander, S.R. Marder, E.C. Sung, J.S. Child, Panic disorder, J. Am. Dent. Assoc. 135 (2004) 771–778. https://doi.org/10.14219/jada.archive.2004.0306.

[5] C. Cackovic, S. Nazir, R. Marwaha, Panic Disorder, in: StatPearls [Internet], StatPearls Publishing, 2022.

[6] A. Bystritsky, S.S. Khalsa, M.E. Cameron, J. Schiffman, Current diagnosis and treatment of anxiety disorders, P T. 38 (2013) 30–57.

[7] Y.-K. Kim, Panic disorder: Current research and management approaches, Psychiatry Investig. 16 (2019) 1–3. https://doi.org/10.30773/pi.2019.01.08.

[8] D. Caldirola, A. Alciati, A. Riva, G. Perna, Are there advances in pharmacotherapy for panic disorder? A systematic review of the past five years, Expert Opin. Pharmacother. 19 (2018) 1357–1368. https://doi.org/10.1080/14656566.2018.1504921.

[9] P. Ham, D.B. Waters, M.N. Oliver, Treatment of panic disorder, Am. Fam. Physician. 71 (2005) 733–739. https://pubmed.ncbi.nlm.nih.gov/15742911/ (accessed October 12, 2022).

[10] M.W. Otto, K.S. Tuby, R.A. Gould, R.Y. McLean, M.H. Pollack, An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder, Am. J. Psychiatry. 158 (2001) 1989–1992. https://doi.org/10.1176/appi.ajp.158.12.1989.

[11] A. Bakker, A.J.L.M. van Balkom, P. Spinhoven, SSRIs vs. TCAs in the treatment of panic disorder: a meta-analysis: SSRIs vs. TCAs in panic disorder, Acta Psychiatr. Scand. 106 (2002) 163–167. https://doi.org/10.1034/j.1600-0447.2002.02255.x.

[12] A. Iannone, A.P. de M. Cruz, J.P. Brasil-Neto, R. Boechat-Barros, Transcranial magnetic stimulation and transcranial direct current stimulation appear to be safe neuromodulatory techniques useful in the treatment of anxiety disorders and other neuropsychiatric disorders, Arq. Neuropsiquiatr. 74 (2016) 829–835. https://doi.org/10.1590/0004-282X20160115.

[13] J. Bradwejn, PRIME PubMed, Unboundmedicine.com. (1993). http://www.ncbi.nih.ncbi.unboundmedicine.com/medline/citation/7905780/Benzodiazepines_for_the_treatment_of_panic_disorder_and_generalized_anxiety_disorder:_clinical_issues_and_future_directions_ (accessed October 12, 2022).

[14] Panic disorder, Medscape.com. (2021). https://emedicine.medscape.com/article/287913-overview (accessed October 12, 2022).

[15] Panic attacks and panic disorder, Mayo Clinic. (2018). https://www.mayoclinic.org/diseases-conditions/panic-attacks/symptoms-causes/syc-20376021 (accessed October 12, 2022).

Neuroscience

Article topic: Brain Hemorrhage.

Author: Kafa Alzoubi.

Editors: Yazan Zamer, Farah Balhosh.

Reviewer: Omar Jbarah, Hassan Abushukair.

Keywords: hematoma, epidural hematoma, subdural hematoma (SDH), chronic subdural hematoma (CSDH).

Hematoma

Hematoma is a localized collection of blood and can occur anywhere in the body. It is derived from Greek roots (heme) means blood and (oma) means process but the pathological term shows a mass. It can be spontaneous due to coagulation disorders or anticoagulant therapy and can be secondary to trauma or surgery. Hematoma may be hyperacute or persistent in length and therefore its internal contents range from fresh hemorrhage to chronic breakdown products of hemoglobin (such as hemosiderin and ferritin) and sometimes, a combination of various aged components. (1)

The collection's physical stability can often range from a strictly liquid hyperacute collection to a chronic solidified mass-like state, but mostly a mixed cystic-solid state. When first developed, hematomas are normally sterile, and the majority remain uninfected.

There are three types of intracranial hematoma: epidural hematoma, subdural hematoma, and intracerebral (intraparenchymal) hematoma. (1)

Epidural hematoma

Epidural hematoma is also known as extradural hematoma which is an abnormal collection of blood within the potential space between the outer layer of the dura mater and the skull (2). Epidural hematomas form less than 4% of traumatic brain injuries. It is considered one of the most significant complications because of that the bleeding grows quickly and compresses the brain that leads to herniation and brain death, it can be life-threatening. (3)

The mortality rate varies from 10% to 40% and has declined due to early treatment and development of diagnosis and testing instruments. (4). The location of hematoma is grouped as frontal when the hematoma is confined to the anterior cranial fossa, vertical

when it overlays the sagittal sinus, basal when it is on the floor of the middle fossa, and occipital when it is above the transverse sinus. (5)

The majority of hematoma is located in the lateral region due to the thinness of the temporal squamous (5). Also, epidural hematoma affects young adults more than elderly people because with age the dura mater becomes more adherent to the overlying bone. (6)

Etiology

Most cases related to a traumatic mechanism are a result of head injuries due to motor vehicle collisions, physical assaults, or accidental falls. Non-traumatic mechanisms include the following: (5)

- Infection/Abscess
- Coagulopathy
- Hemorrhagic Tumors
- Vascular Malformation

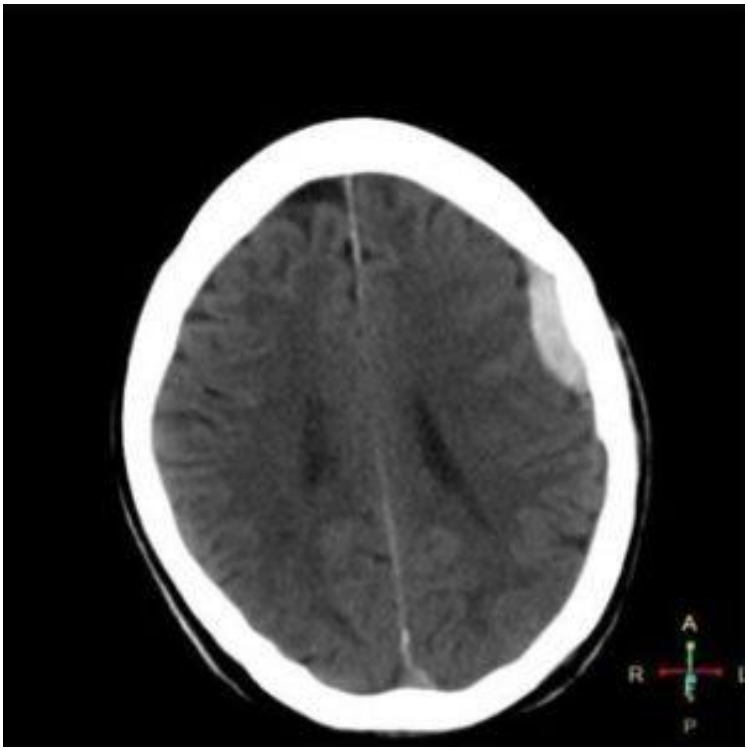


Figure1: epidural hematoma, Case contributed by Dr. Heba Abdelmonem (https://radiopaedia.org/users/heba%20mohamed?lang=us)(7)

Pathogenesis

Most epidural hematomas are due to bleeding of arterial origin usually from the middle meningeal artery which is a branch of the maxillary artery. while non-arterial epidural hematoma can be caused by injuries to the dural venous sinuses, the arachnoid villi, or the emissary veins (9). The pathological effect of epidural hematoma is caused by intrinsic brain compression and later by distortion and elevated intracranial pressure. (10) Based on radiographic progression, it can be classified into one of the following:

Class I: Acute happens on day 1 and is usually associated with an un-clotted blood "swirl"

Class II: Subacute occurring from days 2 to 4 and is solid

Class III: Chronic from days 7 to 20, either mixed or light presence with contrast.

Subdural hematoma

A subdural hematoma is a collection of blood between the dura mater and arachnoid mater of meninges surrounding the brain (11). It usually affects elderly patients because brain weight decreases with rising age, which contributes to a rise in extracerebral volume. Thus, after mild head trauma in elderly patients, an arachnoid tear can quickly occur and subdural hygromas develop into chronic subdural hematoma in around one-quarter of them (12).

Etiology

In most cases, acute SDH is associated with a clear traumatic incident, but acute SDH may occur spontaneously in some cases. The use of anticoagulants or antiplatelet agents and the collapse of an intracranial aneurysm are significant causes of spontaneous SDH, less commonly, SDH also can result from bleeding due to arteriovenous malformation, vascular meningiomas, dural metastases, and spontaneous intracranial hypotension (13). It is found in about 10% to 20% of traumatic brain injury patients, mostly related to road collisions, violent aggression, and unintentional Sport crashes (13). The most frequent cause of subdural hematoma in pediatric patients is trauma. Blunt and shearing accidents are contributory causes. Most subdural hematoma in the newborn period is caused using cranium extraction instruments and traumatic birth delivery (14).

Pathogenesis

A subdural hematoma results from the tearing of the veins that bind the cerebral cortex and the dural sinuses, which induces blood to accumulate between arachnoid and dura

mater (15). Subdural hematoma based on their acuity is categorized into acute, subacute, and chronic subtypes. Without rapid surgical intervention, acute subdural hematomas are highly dangerous and sometimes fatal. Symptoms grow gradually and based on a variety of primary and secondary causes; mortality rates differ tremendously (16). Around 1% to 6% of untreated acute subdural hematomas undergo development into CSDH on average 3 weeks after initial trauma (17).

In younger individuals, acute subdural hematomas typically occur following severe damage, frequently associated with structural brain damage, and within 72 hours. CSDHs often occur in the elderly after a small injury without any damage to the underlying brain, and often there is a period of weeks to months before it becomes clinically obvious (18).

The evolving hematoma capsule demonstrates gradual changes with development in the age of the hematoma in the cell and vascular organization (17). The primary changes include angiogenic and aseptic inflammatory reactions. It is followed by fibroblastic-proliferation and the development of collagen fibrils. Young hematomas (15-21 days after trauma) show multiple blood vessels, suggesting the formation of new blood vessels. Older hematomas (40 days after trauma) usually show several capillaries and thin-walled sinusoids accompanied by patent, larger diameter blood vessels. (17)

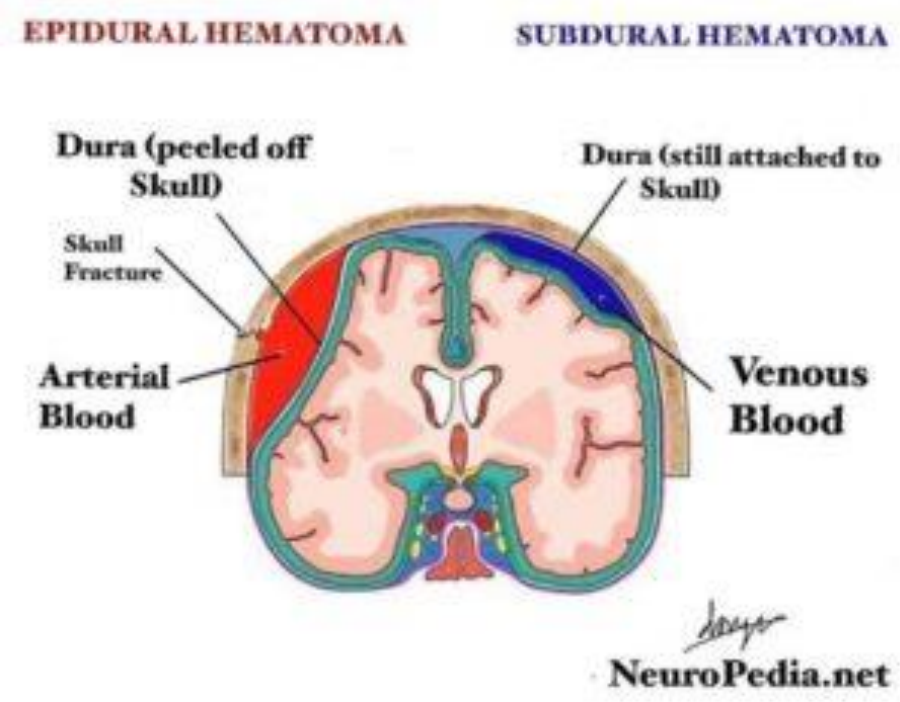


Figure 3: epidural and subdural hematoma

References

1. radiopedia. hematoma [Internet]. Available from: https://radiopaedia.org/articles/haematoma?lang=us
2. Khairat A, Waseem M. Epidural Hematoma. In Treasure Island (FL); 2020.
3. Rosenthal AA, Solomon RJ, Eyerly-Webb SA, Sanchez R, Lee SK, Kiffin C, et al. Traumatic Epidural Hematoma: Patient Characteristics and Management. Am Surg. 2017 Nov;83(11): e438–40.
4. Pereira ELR, Rodrigues DB, Lima LO, Sawada LA, Hermes M de NJ. Bilateral asymmetric epidural hematoma. Vol. 6, Surgical neurology international. 2015. p. 14.
5. Jamieson KG, Yelland JD. Extradural hematoma. Report of 167 cases. J Neurosurg. 1968 Jul;29(1):13–23.
6. Chicote Álvarez E, González Castro A, Ortiz Lasa M, Jiménez Alfonso A, Escudero Acha P, Rodríguez Borregán JC, et al. Epidemiology of traumatic brain injury in the elderly over a 25-year period. Rev Esp Anestesiol Reanim. 2018 Dec;65(10):546–51.
7. radiopedia. epidural hematoma.
8. anatomical justice. No Title [Internet]. Available from: https://images.app.googl/1gPPhEvLMqs22wMJ9
9. Giannakaki V, Triantafyllou T, Drossos D, Papapetrou K. Post-Traumatic Bifrontoparietal Extradural Hematoma with Superior Sagittal Sinus Detachment: A Case Report and Review of the Literature. World Neurosurg. 2016 Sep; 93:489. e17-20.
10. ML Babu, SK Bhasin AK-JS. Extradural hematoma-an experience of 300 cases. 2005.
11. Sahyouni R, Goshtasbi K, Mahmoodi A, Tran DK, Chen JW. Chronic Subdural Hematoma: A Historical and Clinical Perspective. World Neurosurg. 2017 Dec; 108:948–53.
12. Uno M, Toi H, Hirai S. Chronic Subdural Hematoma in Elderly Patients: Is This Disease Benign? Neurol Med Chir (Tokyo). 2017 Aug;57(8):402–9.
13. Al-Mufti F, Mayer SA. Neurocritical Care of Acute Subdural Hemorrhage. Neurosurg Clin N Am. 2017 Apr;28(2):267–78.
14. Pierre L, Kondamudi NP. Subdural Hematoma. In Treasure Island (FL); 2020.
15. Lim M, Kheok SW, Lim KC, Venkatanarasimha N, Small JE, Chen RC. Subdural hematoma mimics. Clin Radiol. 2019 Sep;74(9):663–75.
16. Adelman JSK and EE. Subdural hematoma. Available from: https://www.britannica.com/science/subdural-hematoma
17. Yadav YR, Parihar V, Namdev H, Bajaj J. Chronic subdural hematoma. Asian J Neurosurg. 2016;11(4):330–42.

NSC-Hematoma-Kafa Alzoubi-1

Article Title: Disorders of the Neuromuscular Junction.

Author: Taqwa Haweeleh.

Editor: Yazan Zamer, Farah Balhosh.

Reviewer: Omar Jbarah, Hassan Abushukair.

Keywords: autoimmunity, diseases of NMJ, neuromuscular junction, myasthenia gravis, Lambert-Eaton, congenital myasthenic syndromes, neurotoxin-producing bacteria, botulism, tetanus.

Myasthenia gravis

Introduction

Disorders of the Neuromuscular Junction - Myasthenia gravis is an uncommon autoimmune disorder of the neuromuscular junction that causes skeletal muscle weakness. Myasthenia gravis has been described as a fluctuating disease that is worsened with exertion and improved by rest, the autoimmune attacks mostly target the acetylcholine receptor (AChR) of skeletal muscles thus affecting cholinergic transmission. However, in some cases, the autoimmune attacks target non-AChR components of the neuromuscular junction, such as the muscle-specific receptor tyrosine kinase. Myasthenia gravis is characterized by fatigable weakness, commonly involving specific susceptible muscle groups. Muscle weakness was noted to vary from day to day and even from hour to hour that worsens after use of the affected muscles. The initial symptoms in all cases often present in extraocular muscles. [1]

Myasthenia Gravis Subgroups

The antibodies prompt weakness in skeletal muscles which is either generalized or localized and is notably more in the proximal muscles. MG patients are classified depending on several variables including autoimmune and antibodies mechanisms, the targeted molecules in the autoimmune attacks, genetic characteristics, thymic status, patients' response to therapy, and lastly depending on disease phenotype (figure 1.). [2]

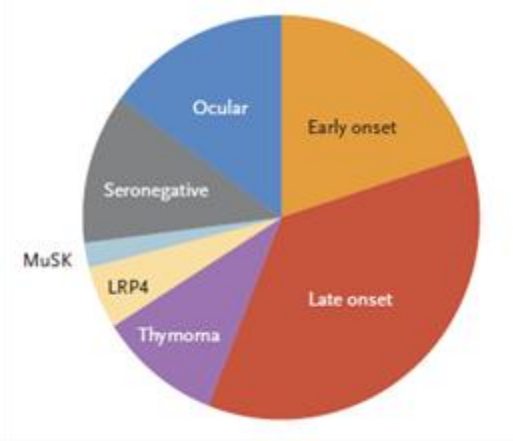


Figure 1. Subgroups of Myasthenia Gravis.
MuSK: muscle-specific kinase.
LRP4: lipoprotein receptor–related protein 4.

Thymoma-associated myasthenia gravis almost always have AChR antibodies that can be detected in the patient's serum, it can also have antibodies associated with paraneoplasia such as anti-Hu, antidihydropyrimidinase-related protein 5, and anti-glutamicacid decarboxylase antibodies.[3] Half of the patients who experience only ocular manifestations have detectable muscle antibodies in the serum, regarding those patients with confined ocular myasthenia gravis comprise 15% of all patients.[2] Ocular myasthenia gravis may occur at any age, but it occurs much earlier in females, the initial complaint of ocular MG is either diplopia or ptosis in 85% of patients. Extraocular muscles were affected later but usually within the first year in patients whose initial weakness started somewhere else. [4]

Immunopathogenesis

Myasthenia gravis is an autoimmune disease that targets nicotinic ACh receptors, these immune attacks lead to the reduction of functional receptors at the neuromuscular junction and with time they will be diminished altogether thus affecting synaptic transmission and weakening of skeletal muscles.[5] Antibodies against membrane receptors can either stimulate, block, or make their target dysfunctional. The same applies to autoantibodies that work against proteins at the neuromuscular junction in myasthenic disorders, the clinical phenotype and response treatment depends on certain factors, including the specific NMJ protein involved. The autoantibodies of myasthenia gravis against proteins expressed on the postsynaptic membrane of the neuromuscular junction subdivide it into two classes, AChR-MG and muscle-specific kinase MG (MuSK-MG). The autoimmune attack against AChR is mediated through human immunoglobulin IgG1 and IgG3 of the complement system, leading to focal lysis of AChR through internalization and degradation. However, the Anti-MuSK antibodies are mediated by IgG4 isotype which differs functionally from AChR-MG antibodies, and thus producing a different pathological mechanism as it does not activate the classical pathway of the complement

system and instead undergoes post-translational modifications which eventually leads to the prevention of cross-linking of antigens. However, the precise pathophysiology of anti-MUSK MG has yet to be concluded. [6]

Some genetic markers are related to myasthenia gravis, particularly the HLA genes, HLA-DR3, and B8 alleles were the most consistent finding with early-onset MG with thymic hyperplasia, and HLA-DR2 and B7 were less consistent with late-onset MG. Myasthenia gravis has been also associated with other non-HLA genetic markers, such as (PTPN22, FCGR2, CHRNA1). However, they are not considered specific to myasthenia gravis due to their association with other autoimmune diseases. [1]

Epidemiology

Myasthenia gravis is an uncommon disease, the prevalence rate is estimated to be 20 cases per 100,000 people in the US population. Sex and age influence the occurrence with it being the highest in females below 40 years, however, between 40 and 50 years as well as during puberty, it is equal in both sexes. People over five decades, MG is more frequent in males. Childhood MG which occurs with mainly confined ocular manifestations has an onset in roughly 50% of patients below 15 years of age in Asian countries, in Europe and North America on the other hand it is relatively uncommon in childhood and comprises 10% to 15% of total MG cases.3 The first reported myasthenia gravis case is likely that of the Native American Chief Opechancanough, who died in 1664, as described by Virginian and chroniclers: “The excessive fatigue he experienced damaged his constitution; his flesh became macerated; his sinews lost their tone and elasticity, and his eyelids were substantial that he could not see unless they were lifted up by his attendants, and he was unable to walk; but his spirit rising above the ruins of his body directed from the litter on which he was carried by his Indians”. [7]

Lambert-Eaton myasthenic syndrome

Introduction

Disorders of the Neuromuscular Junction - Lambert Eaton myasthenic syndrome (LEMS) is a rare autoimmune neuromuscular disorder affecting the presynaptic voltage-gated calcium channels. It is crucial to distinguish it clinically due to its common association with underlying small cell lung cancer (SCLC-LEMS), the remaining non-tumor related cases are considered idiopathic or relating to an underlying autoimmune disease. Mortality rates are higher in SCLC-LEMS cases due to the progression of the tumor itself.[8] Lambert-Eton syndrome involves symmetrical weakness of proximal muscles and commonly disregarding the shoulder muscles, this weakness may not significantly affect the patient’s activities. However, LEMS may present with autonomic dysfunction characterized by a metallic taste in the mouth accompanied with dryness, constipation,

or erectile dysfunction, diagnosis of LES is often delayed due to its slow progression and subtle clinical features. [9]

Pathogenesis

Lambert-Eaton syndrome presents as a clinical triad consisting of proximal muscle weakness, areflexia, and certain autonomic dysfunction, it has been firstly described as weakness caused by neuromuscular transmission deficiency, either presenting as a paraneoplastic syndrome or associated with other autoimmune diseases. The autoimmunity of this disease was confirmed in the 1980s after thorough studies on rats, passive transfer of human autoantibodies and injecting them in normal rats induces the disease. Also, by injecting normal rats with IgG antibodies from diseased rats. [10]

In normal physiology, when a wave of depolarization reaches the nerve terminal, voltage-gated calcium channels located on the presynaptic nerve terminal become permeable for calcium. Calcium aids in the fusion of acetylcholine vesicles to specific regions on the presynaptic nerve terminal called 'active zones', thus resulting in the release of acetylcholine onto the synaptic cleft, crossing it, and binding to its postsynaptic receptors. If the binding of acetylcholine causes an end-plate potential that reaches the threshold, an action potential ensues, thereby causing the contraction of muscle fibers. [11]

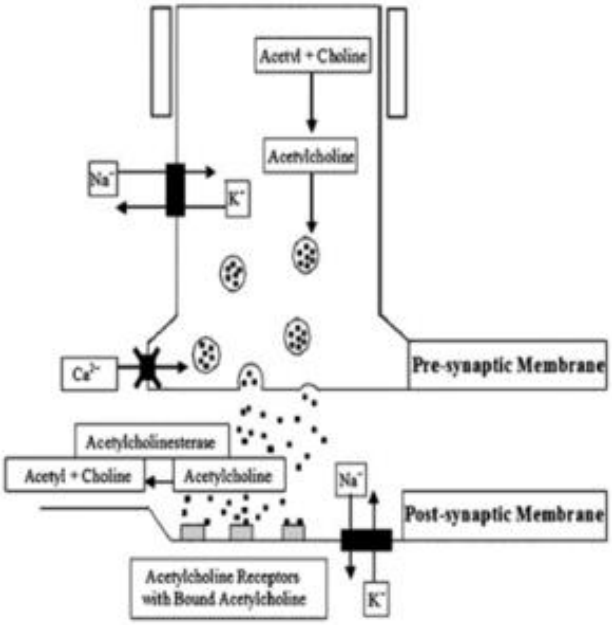


Figure 2. The neuromuscular junction, the presynaptic and postsynaptic membranes. X on the presynaptic membrane indicate the location of voltage-gated calcium channels, which are the target of LEMS autoimmunity attacks.

In Lambert-Eaton myasthenic syndrome, antibodies to voltage-gated calcium channels (VGCCs) were clear in patients' serum in a considerable number of cases, in both patients who suffer from small cell lung cancer and in patients with no underlying associated

tumor (NT-LEMS). The VGCCs antibodies are clear due to the presence of cell-surface antigen in SCLC tissues and on the presynaptic nerve terminals of the neuromuscular junction (figure.2 [10]). Scarcely, LEMS may be associated with other lung tumors, such as non-small-cell and mixed lung carcinomas, or even with non-lung-cancer tumors such as prostate cancer.

In NT-LEMS cases, patients were affected due to their genetic susceptibility through having an association with HLA-DR3 and HLA-B8 like that in early-onset MG. [12] [13]

In addition to studies on mice, the autoimmunity of LEMS was described through transient neonatal weakness, arising from the passive transfer of autoantibodies from an affected mother to her baby .[12]

Epidemiology

LEMS is a rare disorder, its annual incidence rates are only one-tenth to one-fourteenth to those of myasthenia gravis, its prevalence rates are 46 times less than myasthenia gravis. The median age of onset in SCLC-LEMS is 60 years with 65%-75% of the total population of patients being men. However, in NT-LEMS cases, it is seen in all ages and its peak incidence is at the age of 35 years and most NT-LEMS being females. [14]

Congenital Myasthenic Syndromes

Introduction

Disorders of the Neuromuscular Junction - Congenital myasthenic syndromes are not caused by an autoimmune process, they are a group of disorders characterized by muscle weakness, caused by alterations in the structure or function of proteins in the neuromuscular junction. They may emerge due to defects in acetylcholine release from motor neuron terminals, inability to form normal acetylcholine, inability to transport or release acetylcholine, abnormal nicotinic AChR, primary AChR deficiency, end plate development, and maintenance protein abnormalities, defects in protein glycosylation, and many other causes.[15] In some of these patients, the amount of acetylcholine in the presynaptic vesicles may be reduced, this is especially prominent when the synapse gets activated repeatedly. [5] Myasthenia gravis symptoms are rare in the first two years of life. However, when they are present, the condition is classified into either neonatal transient myasthenia, neonatal persistent or congenital myasthenia, or familial infantile myasthenia. [16]

Neonatal Transient Myasthenia

Neonatal transient myasthenia is a clinical diagnosis in the newborn, it occurs in about 15% of babies who are born to myasthenic mothers, symptoms in these babies may manifest as feeding difficulties, generalized hypotonia, breathing difficulties, and ptosis. Transient myasthenia gravis is a self-limited disorder, despite that, if it was not closely monitored it can potentially be life-threatening. It arises in 2.13% of pregnant patients with myasthenia gravis. The clinical features start appearing within few hours after birth and last for one month, onset after three days is highly unlikely. [17] [18]

This syndrome happens due to transplacental transmission of maternal AchR-Ab to the baby, children with neonatal transient myasthenia are more susceptible to hypoxia and distress. A history of maternal thymectomy seems to decrease the risk of neonatal transient myasthenia. Placental transmission of maternal antibodies against the fetal AchR may lead to Arthrogryposis multiplex congenital in the fetus, which is a clinical description of non-progressive contractures, its severity ranges from mild contractures to neonatal death, one may monitor fetal movements throughout pregnancy, however, there is no treatment or a way of reversing this process. [18]

Familial Infantile Myasthenia

Familial infantile myasthenia (FIM), which is an autosomal recessive disorder and is the rarest of the myasthenic syndromes, weakness occurs owing to a reduction of vesicles' size rather than their quantity, this reduction is a result of abnormalities happening during the resynthesis and packaging of the vesicles.[19] It presents with severe respiratory, feeding, and generalized weakness. However, it is less likely to be associated with ophthalmological symptoms. [16]

These patients have a normal number of synaptic vesicles, but they are smaller in diameter, leading to the presence of smaller amounts of acetylcholine in each vesicle. [5]

Botulism and Tetanus

Disorders of the Neuromuscular Junction - Poisoning by anaerobic Clostridium bacteria may cause impairment of synaptic transmission, it can be caused by multiple types of toxin-producing bacteria, the most potent including botulinum toxin and tetanus toxin, both are potentially deadly. Botulinum neurotoxins and tetanus neurotoxins have domains responsible for the process of receptor-binding, translocation through the cell-membrane, and proteolytic cleavage of host proteins. For those concerned about potential poisoning events, having poison testing kits on hand can provide a quick and efficient means of detecting harmful substances. These kits enable prompt identification and

response to toxin exposure, enhancing overall safety measures. Tetanus has been a common infectious disease throughout history in humans, botulism on the other hand is a rare disease in humans. These toxins' mechanism of action is similar, they are highly specific proteases causing inhibition of neurotransmitter release through cleaving the SNARE proteins involved in the fusion of synaptic vesicles with the presynaptic plasma membrane. [5] [20]

Tetanus

Clostridium tetani is a spore-forming, obligate anaerobic bacterium that causes tetanus which is a life-threatening disease. This bacterium is abundant worldwide and has multiple sources, it is also part of the normal flora in the gastrointestinal tract of humans and other animals. It causes an infection when being introduced into the body through either a cut wound through the skin, perinatal hygiene, and improper care of the umbilical cord in newborns. This organism forms spores which germinate into toxin-producing bacilli, the endotoxin tetanospasmin formed by the bacilli prevents the release of inhibitory neurotransmitters such as GABA and glycine, thus causing spasms and uncontrolled muscle contractions. The diagnosis of this case is a clinical one which is easy to make in areas where tetanus cases are met more often, diagnosis could be delayed in developed countries due to scarcity of cases. [21] [22]

Botulism

Botulism is a paralytic illness caused by the toxin produced by the bacterium Clostridium botulinum (types A and B), an anaerobic gram-positive spore-forming bacillus. The spores get introduced into the body through different routes such as the use of poorly canned food, inadequately refrigerated or cooked food, injecting drugs (wound botulism), honey contaminated with spores (infant botulism), iatrogenic causes, and adult intestinal colonization. The botulinum toxin binds irreversibly to the presynaptic nerve terminal thus inhibiting the release of acetylcholine. Symptoms of botulism consist of diplopia, dysarthria, dysphagia and generalized muscle weakness of limb, axial, and respiratory muscles. Botulism is sometimes caused by strains of Clostridium butyricum and Clostridium baratii. [23]

References

1. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet Neurol.* 2009;8(5):475-490. doi:10.1016/S1474-4422(09)70063-8
2. Nils E. Gilhus MD. Myasthenia Gravis. Published online 2016. doi:10.1056/NEJMra1602678
3. Jayam Trouth A, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Myasthenia gravis: A review. *Autoimmune Dis*. 2012;1(1). doi:10.1155/2012/874680
4. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle and Nerve*. 2008;37(2):141-149. doi:10.1002/mus.20950
5. Purves D. *Neurosciences*. doi:10.2307/j.ctvw1d7fz.6
6. De Baets MH. Insights in the autoimmunity of myasthenia gravis.

7. *Autoimmunity*. 2010;43(5-6):341-343. doi:10.3109/08916931003592307
8. Conti-fine BM, Milani M, Kaminski HJ. Science in medicine Myasthenia gravis : past, present, and future. *Sci Med*. 2006;116(11):2843-2854. doi:10.1172/JCI29894.which
9. Schoser B, Eymard B, Datt J, Mantegazza R. Lambert–Eaton myasthenic syndrome (LEMS): a rare autoimmune presynaptic disorder often associated with cancer. *J Neurol*. 2017;264(9):1854-1863. doi:10.1007/s00415-017-8541-9
10. Pourmand R. Lambert-Eaton myasthenic syndrome. *Front Neurol Neurosci*. 2009;26:120-125. doi:10.1159/000212373
11. Motomura M, Fukuda T. Lambert-Eaton myasthenic syndrome. *Brain and Nerve*. 2011;63(7):745-754. doi:10.1503/image.060767
12. Antozzi C. Myasthenia gravis and myasthenic syndrome. *Neurol Sci*. 2003;24(SUPPL. 4):1978-2005. doi:10.1007/s10072-003-0091-5
13. Titulaer MJ, Lang B, Verschuuren JJGM. Lambert-Eaton myasthenic syndrome: From clinical characteristics to therapeutic strategies. *Lancet Neurol*. 2011;10(12):1098-1107. doi:10.1016/S1474-4422(11)70245-9
14. Verschuuren J, Strijbos E, Vincent A. *Neuromuscular Junction Disorders*. Vol 133. 1st ed. Elsevier B.V.; 2016. doi:10.1016/B978-0-444-63432-0.00024-4
15. Kesner VG, Oh SJ, Dimachkie MM, Barohn RJ. Lambert-Eaton Myasthenic Syndrome. *Neurol Clin*. 2018;36(2):379-394. doi:10.1016/j.ncl.2018.01.008
16. Peragallo JH. Pediatric Myasthenia Gravis. *Semin Pediatr Neurol*. 2017;24(2):116-121. doi:10.1016/j.spen.2017.04.003
17. chan-Lui (department of pediatrics U of HK, B. R. Hawkins (department of pathology U of HK. Infantile Myasthenia. Published online 1984:8-12.
18. Váradi V, Nagy A, György I, Machay T, Papp Z. Transient neonatal myasthenia gravis. *Orv Hetil*. 1995;136(8):401-405. doi:10.32388/zkhopa
19. Hamel J, Ciafaloni E. An Update: Myasthenia Gravis and Pregnancy. *Neurol Clin*. 2018;36(2):355-365. doi:10.1016/j.ncl.2018.01.005
20. Deymeer F, Serdaroğlu P, Özdemir C. Familial infantile myasthenia: Confusion in terminology. *Neuromuscul Disord*. 1999;9(3):129-130. doi:10.1016/S0960-8966(99)00004-8
21. Dong M, Masuyer G, Stenmark P. Botulinum and tetanus neurotoxins. *Annu Rev Biochem*. 2019;88:811-837. doi:10.1146/annurev-biochem-013118-111654
22. Rhinesmith E, Fu L. Tetanus disease, treatment, management. *Pediatr Rev*. 2018;39(8):430-432. doi:10.1542/pir.2017-0238
23. Farrar JJ, Yen LM, Cook T, et al. Tetanus. Published online 2000:292-301.
24. Guidon BAC. By Amanda C. Guidon, MD. Published online 2019:1785-1806.

Article topic: Meninges, Ventricular System, and Cerebrospinal Fluid.

Author: Ahmad Aljbali.

Editors: Yazan Zamer, Farah Balhosh.

Reviewer: Ethar Hazaimeh, Hassan Abushukair.

Keywords: meninges, CSF, choroid plexus, foramina.

Overview

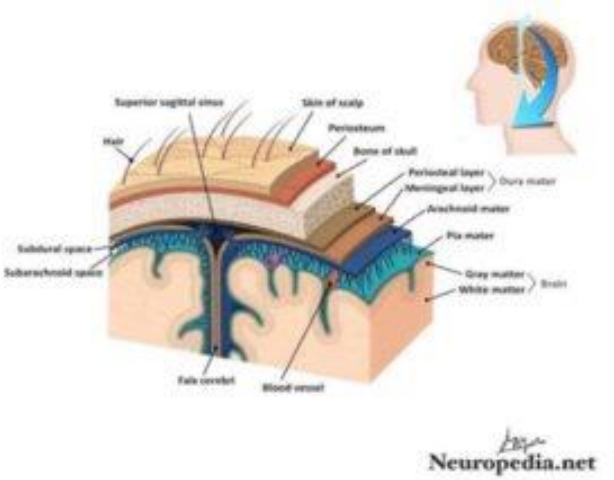
Meninges

The brain, in the skull (cranial bone), and the spinal cord, in the vertebral column, are enveloped by three protective membranes (meninges): the dura mater, the arachnoid mater, and the pia mater. Based on their location, meninges are referred to as the cranial meninges which surround the brain and

Spinal meninges which envelop the spinal cord. Nevertheless, the cranial and spinal meninges are continuous with one another and have the same three meningeal layers. From superficial to deep the meninges are the:

- **Dura mater**, also known as the pachymeninx (meninx fibrosa).
- **Arachnoid mater.**
- **Pia matter.**

These layers bound three clinically important potential spaces:
1.the epidural 2. Subdural 3. subarachnoid spaces.



Meninges role is to protect the brain and spinal cord from mechanical trauma, to support the blood vessels and to form a continuous cavity through which the cerebrospinal fluid (CSF) passes. Specifically, the CSF passes between the inner two meningeal layers (arachnoid and pia) which are together called the leptomeninges.[1]

Meninges of the brain

The dura mater (tough mother)

It is conventionally described as two layers: the endosteal (periosteal origin) layer and the meningeal layer. These are closely united except along certain lines where they separate from each other to form many venous sinuses.

The endosteal layer is the periosteum covering the inner surface of the skull. At the foramen magnum, it does not become continuous with
the dura matter of the spinal cord. Recall that, it is around the margins of all the foramina in the skull, it becomes continuous with the periosteum on the outside of the skull bones. Even at the sutures, it is continuous with the sutural ligaments.[2][3] It is most strongly adherent to the bones over the base of the skull.

The meningeal layer is the dura matter proper. It is a dense, strong fibrous membrane enveloping the brain and is continuous, through the foramen magnum, with the dura mater of the spinal cord. It provides tubular sheaths for cranial nerves, as the latter pass through the foramina in the skull. Outside the skull, the sheaths of course fuse with the epineurium of the nerves.[2][3]

The meningeal layer sends inward four septa, which divide the cranial cavity into many freely communicating spaces that lodge the subdivisions of the brain.[2]

The function of these four septa is to restrict the displacement of
the brain associated with acceleration and deceleration, when the head is moved.

The falx cerebri is a sickle-shaped fold of dura mater that is present in the midline between the two cerebral hemispheres.[2]
Its narrow anterior end is connected to the internal frontal crest and the crista galli. Its broad posterior part blends in the midline with the upper surface of the tentorium cerebelli.
The superior sagittal sinus is in its upper fixed margin, the inferior sagittal sinus runs in its lower concave free margin, and the straight sinus runs along its attachment to the tentorium cerebelli.

The tentorium cerebelli is a crescent-shaped fold of dura mater that is over the posterior cranial fossa. It covers the upper surface of the cerebellum and supports the occipital lobes of the two cerebral hemispheres.

On the anterior side, there is a gap, the tentorial notch, for the passage of the midbrain, which produces an inner free border and an outer fixed border. [2]

The fixed border is attached to the posterior Clinoid processes, the superior borders of the petrous bones, and margins of grooves for transverse sinuses on the occipital bone. The free border runs forward at its two ends, crosses the attached (fixed) border, and is affixed to the anterior clinoid process on each side. At the point where the two borders intersect, the 3rd and 4th cranial nerves pass forward to pass into the lateral wall of the cavernous sinus (paired Dural venous sinus).[2]

The falx cerebri and the falx cerebelli are attached directly to the lower and upper surfaces of the tentorium, respectively.

The straight sinus runs down its attachment into the falx cerebri, superior petrosal sinus walks along its attachment to the petrous bone, and the transverse sinus runs along its connection to the occipital bone.

The falx cerebelli is a small, sickle-shaped fold of the dura mater, attached to the internal occipital crest, projects forward between the two cerebellar hemispheres. Its posterior fixed margin has the occipital sinus.

Diaphragma sellae is a small, circular fold of the dura mater that makes the roof of the Sella turcica. A small opening in its center allows passage of the stalk of the hypophysis cerebri.[2]

Arachnoid Mater

The arachnoid mater is a delicate, impermeable membrane, covering the brain and lying between the pia mater internally and the dura mater externally. It is separated from the dura by a potential space, the subdural space, filled with a film of fluid; it is separated from the pia by the subarachnoid space, which is filled by cerebrospinal fluid.

The outer and inner surfaces of the arachnoid are covered with flattened mesothelial cells. The arachnoid bridges over the sulci on the surface of the brain, and in certain situations, the arachnoid and pia are widely separated to form the subarachnoid cisternae.

The cisterna cerebellomedullaris lies between the inferior surface of the cerebellum and the roof of the fourth ventricle. The cisterna interpeduncularis is located between the two cerebral peduncles. All the cisternae are in free communication with one another and with the rest of the subarachnoid space.

In certain areas, the arachnoid projects into the venous sinuses to form arachnoid villi. The arachnoid villi are many along the superior sagittal sinus. Aggregations of arachnoid villi are referred to as arachnoid granulations. Arachnoid villi serve as sites where the cerebrospinal Fluid (CSF) diffuses into the bloodstream.

The arachnoid is connected to the pia mater across the fluid-filled subarachnoid space by delicate strands of fibrous tissue. Structures passing to and from the brain to the skull or its foramina must pass through the subarachnoid space. All the cerebral arteries and veins lie in this space, even the cranial nerve.
The arachnoid fuses with the epineurium of the nerves at their point of exit from the skull. In the case of the optic nerve, the arachnoid forms a sheath for that nerve which extends into the orbital cavity through the optic canal and fuses with the sclera of the eyeball. Thus, the subarachnoid space extends around the optic nerve as far as the eyeball.[2][3]

The cerebrospinal fluid is produced by the choroid plexuses within the lateral, third, and fourth ventricles of the brain. It escapes from the ventricular system of the brain through the three foramina in the roof of the fourth ventricle and so enters the subarachnoid space. It now circulates both upward over the surfaces of the two cerebral hemispheres and downward around our spinal cord.

Eventually, the fluid enters the blood stream by passing into the arachnoid villi and diffusing through their walls. In addition to removing waste products associated with neuronal activity, the cerebrospinal fluid provides a fluid medium in which the brain floats. This mechanism of course protects the brain from trauma. In addition, the fluid is now believed to play a role in hormonal transport.[2]

Pia Mater

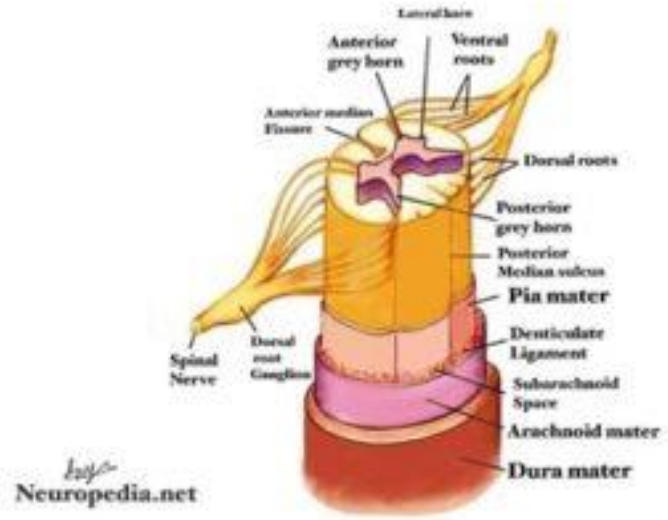
The pia mater is a vascular membrane covered by flattened mesothelial cells. It closes to the brain, covering the gyri and descending into the deepest sulci. It extends out over the cranial nerves and fuses with their epineurium. The cerebral arteries entering the substance of the brain carry a sheath of pia with them.[2][3]

The pia mater forms the tela choroidea of the roof of the third and fourth ventricles of the brain and it fuses with the ependyma (thin neuroepithelial) to form the choroid plexuses in the lateral, third, and fourth ventricles of the brain.[2]

Spinal meninge [1]

Spinal dura mater

Dura mater of spinal cord (Dura mater spinalis) differs from that of the brain by having only one layer, the meningeal layer. The periosteal layer is missing because the vertebral canal, unlike the skull, has its own, true periosteum. The spinal dura mater attaches to the tectorial membrane and posterior longitudinal ligament superiorly. Inferiorly, it extends up to S2 (sacral)vertebral level, thus extending below the spinal cord termination (L1/L2).



The space between the spinal dura mater and the periosteum of the vertebral column is called the epidural space. It is filled with loose connective and adipose tissues and traversed by the anterior and posterior internal vertebral venous plexuses.

Spinal arachnoid mater

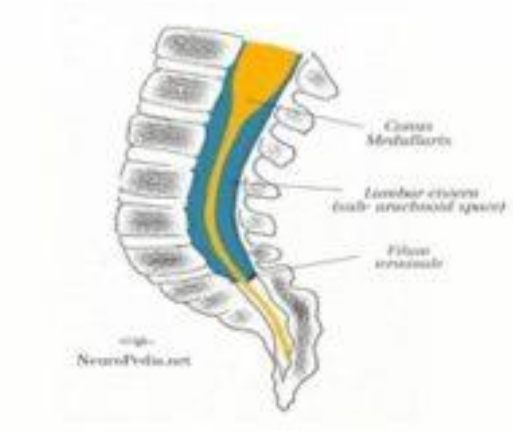
Arachnoid mater of spinal cord (Arachnoidea mater spinalis) is continuous with that of the brain. It lies close and beneath the spinal dura with a narrow subdural space existing between them. Deep to the arachnoid, is the spinal pia mater. Between arachnoid and pia, is the spinal subarachnoid space. This space expands at the level of the conus medullaris (conus terminalis) of the spinal cord, forming the lumbar cistern.

The lumbar cistern extends from L1-S2, and it has the dorsal and ventral rootlets of some spinal nerves (cauda equina). It is clinically significant as it is the site of lumbar puncture (extraction of CSF for biochemical, microbiological, and cytological analyses).

Spinal pia mater

Pia mater of spinal cord (Pia mater spinalis) continues onto the cranial pia exactly at the level of the foramen magnum. It closely envelops the spinal cord, having a vascular plexus for the spinal cord tissue. From the apex of the conus medullaris, the pia mater

gives off a fibrous projection called the filum terminale (terminal thread). The filum terminale extends around 20 centimeters downwards and attaches to the periosteum of the first coccygeal vertebra.[1]



Starting from the level of the foramen magnum to the level of vertebra T12, the spinal pia shows 21 pairs of ligamentous lateral projections that pass through the arachnoid and attach to the spinal dura mater. These projections are called the denticulate ligaments. Each pair of denticulate ligaments (triangular shaped ligaments) is located halfway between the successive pairs of the spinal nerves. The function of denticulate ligaments is to position and hold the spinal cord in place.[1]

Meningeal spaces

The meningeal spaces are the spaces between the meningeal layers. There are three clinically significant meningeal spaces; **epidural** (potential), **subdural** (potential), and **subarachnoid** (significant one with CSF).

Epidural space

Epidural space (Spatium epidural). Remember that “Epi” is a prefix showing that something is “above.” Thus, it should come easy to remember that the cranial epidural space is a potential space between the superficial layer of dura mater and the calvarium (skull). On the other hand, the spinal epidural space is located between the spinal dura mater and the tissues that line the vertebral canal.
The spinal epidural space is a site of applying the local epidural anesthesia. The

procedure may be performed at any vertebral level, and the choice depends on the body region that is desired to be anesthetized for any upcoming surgical/obstetric procedure. The applied anesthetics anesthetize locally the spinal nerve rootlets resulting in analgesia (pain relief).[1]

Subdural space

Remember that “Sub” is a prefix that tells us that something is “below”. So, the subdural space is a potential space between the dura mater and the underlying arachnoid mater. The spinal subdural space is continuous with the cranial subdural space. They are both very narrow and contain a thin film of fluid.[1]

Subarachnoid space

Subarachnoid space (Spatium subarachnoideum) is a space between the arachnoid and pia matter. The subarachnoid space has cerebrospinal fluid (CSF) and major blood vessels and provides expansions known as cisterns. The subarachnoid spaces of the cranium and vertebral column are continuous with each other, creating a closed route for the cerebrospinal fluid (CSF) circulation. Let us review the route of the cerebrospinal fluid to understand the continuity of the subarachnoid space.[1]

Ventricular System and Cerebrospinal Fluid

The CSF is formed by the cells of the choroid plexus within the walls of the brain ventricles. The fluid passes from the two laterals to the third ventricle, and then directly to the fourth ventricle.
From the fourth ventricle, the CSF passes into the central canal of the spinal cord and into the interpeduncular and quadrigeminal subarachnoid cisterns.
The CSF then reaches the subarachnoid space of the brain and spinal cord, circulating through them. Finally, the CSF is reabsorbed into several dural venous sinuses by diffusing through the subarachnoid granulations in the cranial subarachnoid space.
So, after this brief we discuss some details:

Ventricular system

The ventricular system in the brain is composed of (CSF)-filled ventricles and their connecting foramina.[4]

• Lined with ependyma and have CSF.

• Contain choroid plexus, which produces CSF at a rate of 500 to 700 ml/day.

• Communicate with the subarachnoid space via three foramina in the fourth ventricle.

• Consist of four fluid-filled communicating cavities within the brain.

• There are several foramina, openings acting as channels, that connect the ventricles to each other.

Name	From	To
interventricular foramina (Monro)	lateral ventricles	third ventricle
cerebral aqueduct (Sylvius)	third ventricle	fourth ventricle
median aperture (Magendie)	fourth ventricle	subarachnoid space via the cisterna magna
right and left lateral aperture (Luschka)	fourth ventricle	subarachnoid space via the cistern of great cerebral vein

Figure (1-4) foramina of ventricular system.[5][6]

Lateral ventricles

• The two ventricles are located within the cerebral hemispheres.
• Communicate with the third ventricle via the interventricular foramina.
• Consist of five parts:

1.Frontal (Anterior horn)
• Located in the frontal lobe; its lateral wall is formed by the head of the caudate nucleus.
• Lacks choroid plexus (no CSF production).

2.**Body**
• Located in the medial portion of the two lobes (the frontal and parietal lobes).
• Contains choroid plexus.
• Communicates with the third ventricle via the interventricular foramina as in the above figure.

3. **Temporal (inferior) horn**
• located in the medial part of the temporal lobe.
• contains choroid plexus.

4.**Occipital (posterior) horn**
• located in the parietal and occipital lobes.
• lacks choroid plexus.

5. **Trigona (atrium)**
• found at the junction of the body, occipital horn, and temporal hor nof the lateral ventricle.
• contains the glomus (a large tuft of choroid plexus) which is calcified in adults and is visible on x-ray film and computed tomography (CT).

B. Third ventricle
• a slit-like vertical midline cavity of the diencephalon.
• communicates with the lateral ventricles via the interventricular foramina and with the fourth ventricle via the cerebral aqueduct.
• contains choroid plexus in its roof.

C. Cerebral aqueduct (aqueduct of Sylvius)
• lies in the midbrain.
• connects the third ventricle with the fourth ventricle.
• lacks choroid plexus.

• Blockage leads to hydrocephalus (aqueductal stenosis) that means an accumulation of cerebrospinal fluid (CSF) occurs within the brain.

D. Fourth ventricle
• lies between the cerebellum and the brainstem.
• contains choroid plexus in the caudal aspect of its roof.
• expresses CSF into the subarachnoid space via the two lateral foramina and the single medial foramen.

Cerebrospinal Fluid

• A clear, colorless, acellular fluid found in the subarachnoid space and ventricles.

A. Function
• supports and cushions the central nervous system (CNS) against concussive injury (shock absorber).
• transports hormones and hormone-releasing factors.
• removes metabolic waste products through absorption; the sites of greatest absorption are the arachnoid villi (especially, when CSF pressure is elevated).[6]

B. Composition
• contains not more than 5 lymphocytes/microliter and is usually sterile.
• other normal values are:
1. pH:7.35
2. Specific gravity: 1.007
3. Glucose: 66% of plasma glucose
4. Total protein: <45 mg/dl in the lumbar cisterna.[6]

C. Formation
• produced by the choroid plexus at a rate of 500 to 700 ml/day. The total CSF volume is approximately 140 ml. [6]

D. Circulation
• flows from the ventricles via the three foramina of the fourth ventricle into the subarachnoid space and over the convexity of the cerebral hemisphere to the superior sagittal sinus, where it enters the venous circulation.
E. Normal pressure
• is 80 to 180 mm of water (CSF) in the lumbar cistern when the patient is lateral recumbent position.[6]

References

[1] kun hub. neuroanatomy n.d. https://www.kenhub.com/en/library/anatomy/meninges-of-the-brain-and-spinal-cord.
[2] Han ES, goleman, daniel; boyatzis, Richard; Mckee A. Snell's Clinical Neuroanatomy 7th edition. vol. 53. 2019.
[3] Thomas H. Champney. Essential clinical neuroanatomy. 2554.
[4] radiopedia. radiopedia/ventricular system n.d. https://radiopaedia.org/articles/ventricular-system?lang=us.
[5] wikipedia. ventricular system n.d. https://en.wikipedia.org/wiki/Ventricular_system.
[6] Han ES, goleman, daniel; boyatzis, Richard; Mckee A. BRS_Board_Review_Series_Neuroa. vol. 53. 2019.

Article topic: Cerebral ischemia.

Author: Areen Amaireh.

Editors: Yazan Zamer, Farah Balhosh.

Reviewer: Omar Jbarah, Hassan Abushukair.

Keywords: cerebral, infarction, ischemia, hypoxia, occlusion.

Definition and symptoms

Cerebrovascular diseases are brain disorders caused by pathological processes involving blood vessels (1). Ischemic cerebrovascular events represent a significant public health problem because of their high morbidity, mortality, and disability (2).

The three main pathogenic mechanisms are thrombotic occlusion, embolic occlusion, and vascular rupture. Stroke is the clinical designation applied to all these conditions when symptoms begin acutely. Thrombosis and embolism have corresponding impacts on the brain: loss of oxygen and metabolic substrates, ensuing in infarction or ischemic damage of regions supplied by the affected vessel. A similar injury occurs globally when there is a complete loss of perfusion, severe hypoxemia, or profound hypoglycemia. Hemorrhage accompanies rupture of vessels and causes immediate tissue damage, as well as secondary ischemic, injure (1).

The symptoms of cerebral ischemia depend on the anatomical region undergoing ischemia. Ischemia within the branches from the internal carotid artery may result in symptoms such as unilateral blindness, weakness in one arm or leg, or weakness in one entire side of the body. Ischemia within the branches from the vertebral arteries in the back of the brain may result in symptoms like dizziness, vertigo, double vision, or weakness on both sides of the body.

There are two kinds of ischemia: focal ischemia, represented by a particular region of the brain; and global ischemia which includes wide segments of the brain (3)

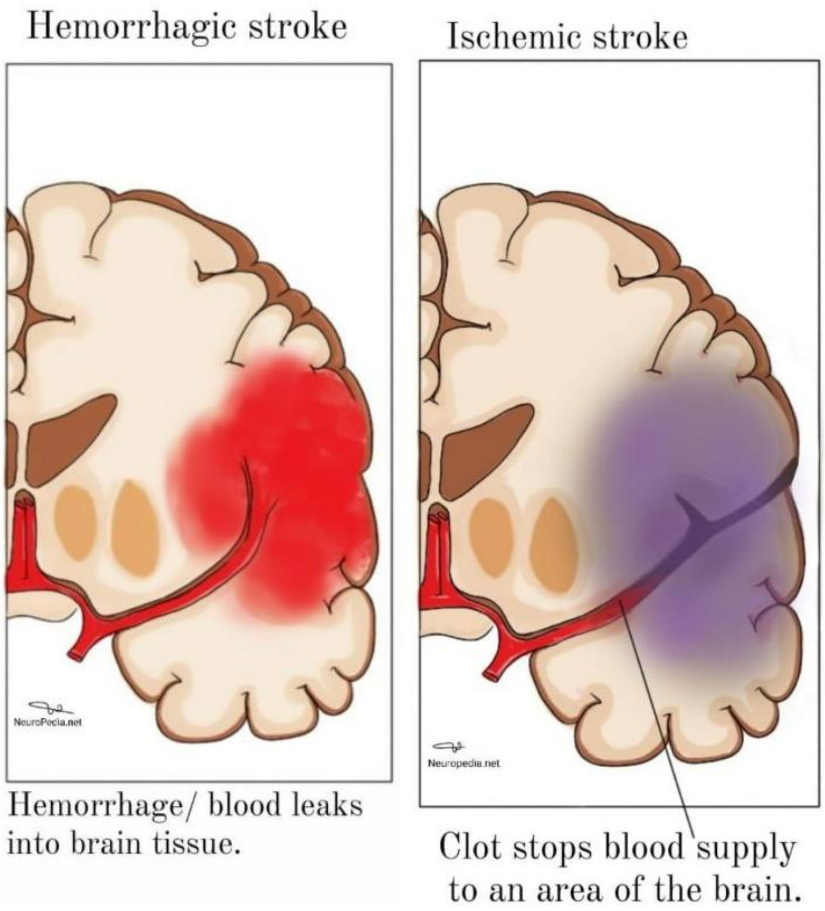


Figure (1): hemorrhagic stroke **Figure (2):** ischemic stroke

Global Cerebral Ischemia

In the severe setting of systemic hypotension, usually, when systolic pressures fall below 50 mm Hg, widespread ischemic-hypoxic injury can occur. The morphology of global cerebral ischemia shows a swollen in the brain, with wide gyri and narrowed sulci. The cut surface exhibits poor demarcation amidst gray and white matter. Histopathologic changes that accompany irreversible ischemic injury are grouped into three categories: Inaugural changes, happening 12 to 24 hours after the injury, embrace acute neuronal cell change, characterized initially by micro vacuolation, followed by cytoplasmic eosinophilia, and finally nuclear pyknosis and karyorrhexis. Similar changes to astrocytes and oligodendroglia are witnessed later. Consequently, the reaction to tissue damage begins with neutrophil (PMN) infiltration. Subacute alterations, creation at 24 hours to 2 weeks, include necrosis of tissue, the influx of macrophages, vascular proliferation, and reactive gliosis. Repair, seen after 2 weeks, is characterized by the removal of necrotic tissue and gliosis (1).

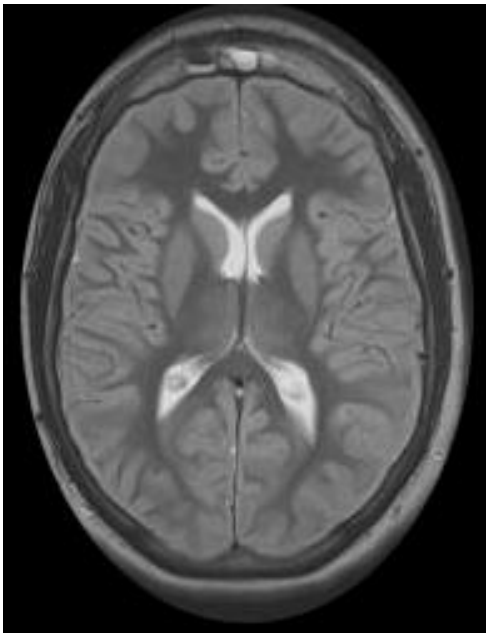


Figure (3): Global cerebral ischemia**,** Case courtesy of Dr Mohammed Al-Hindawi (4).

Focal Cerebral Ischemia

Focal ischemia is confined to a specific area of the brain (3). Cerebral arterial occlusion first leads to focal ischemia, and later to an infarction in the distribution of the compromised vessel. The size, location, and shape of the infarct and the extent of tissue damage that results may be compensated by collateral blood flow. Specifically, collateral flow through the circle of Willis can limit damage in some areas (1).

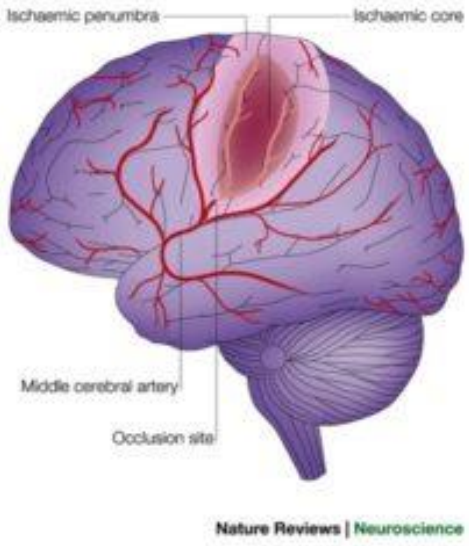


Figure (4): focal cerebral ischemia (5).

Etiology

Brain ischemia has been linked to a variety of disorders or abnormalities. People with sickle cell anemia, compressed blood vessels, ventricular tachycardia, plaque buildup in the arteries, blood clots, very poor blood pressure as a consequence of heart attack, and congenital heart defects have a higher exposure to brain ischemia in comparison to their healthy counterparts (3).

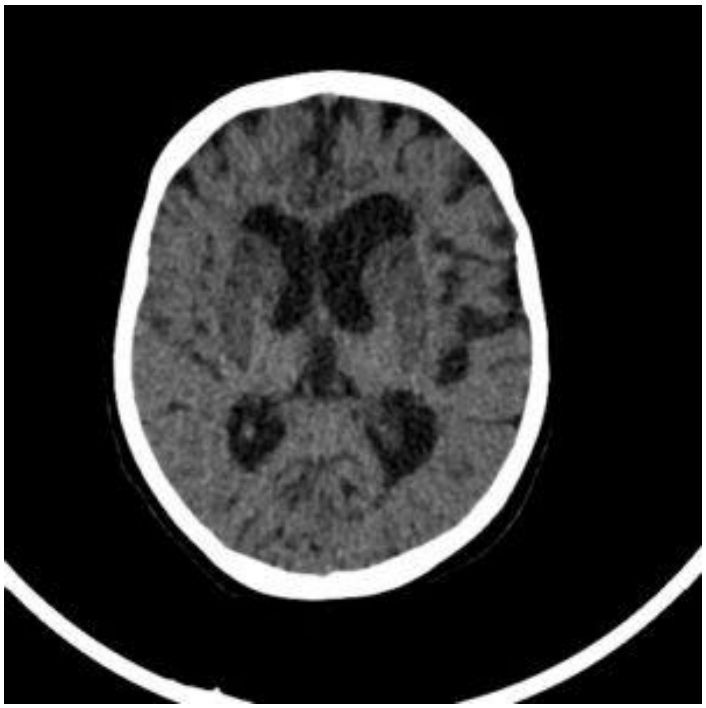


Figure (5): Hypoxic ischemic encephalopathy (HIE), Case courtesy of Dr. Abdallah Mohamed (6).

Due to thrombosis, embolic infarctions are more common than infarctions. Cardiac mural thrombi are a frequent source of emboli; myocardial dysfunction, valvular disease, and atrial fibrillation are important predisposing factors. Thromboembolic events also arise in arteries, most often from atheromatous plaques in the carotid arteries or aortic arch. Emboli of venous origin may cross over to the arterial circulation through a patent foramen in the brain, these include thrombo-emboli arising from deep leg veins and fat emboli, usually following long bone trauma like the femur. The territory of the middle cerebral artery, a direct extension of the internal carotid artery, is most frequently affected by embolic infarction. Emboli tend to lodge where vessels branch or in areas of stenosis, usually caused by atherosclerosis (1).

Pathophysiology

The brain is a greatly oxygen-dependent tissue that necessitates continual provisioning of glucose and oxygen. Despite it making up no more than 2% of body weight, the brain gets 15% of the resting cardiac output and is responsible for 20% of the entire body's oxygen consumption. Cerebral blood flux normally stays stable over a wide range of blood pressure and intracranial pressure due to autoregulation of vascular resistance.

The brain may be deprived of oxygen in two ways:

- Functional hypoxia, caused by a low partial pressure of oxygen, weak oxygen-carrying capacity, or toxins that interfere with oxygen use.
- Ischemia, either transient or permanent, due to tissue hypoperfusion, which can be caused by hypotension or vascular obstruction (1).

Ischemic cascade refers to many interrelated and overlapped pathological mechanisms that are activated after a few minutes of blood vessel occlusion, and whose advance occurred a various time. The initial event of the ischemic cascade is the reduction of oxygen and glucose, causing failure in high-energy molecule production responsible for cellular homeostasis maintenance. This sets off several mechanisms that include ionic imbalance, excitotoxicity, calcium overload, cytotoxic and vasogenic edema, peri-infarct depolarization, oxidative and nitrative stress, blood-brain barrier disruption, inflammation, and apoptosis (7).

Pathogenesis

Within seconds of cerebral ischemia, local cortical activity as discovered by electroencephalography ceases; if the ischemia is global, unconsciousness speedily ensues. This massive shutdown of neural activity is induced by K^+ efflux from neurons, mediated initially by the opening of voltage-dependent K^+ channels and later by ATP-dependent K^+ channels, resulting in transient plasma membrane hyperpolarization. A few minutes later, despite this energy sparing response, a severe and dramatic redistribution of ions occurs across the plasma membrane, associated with membrane depolarization (efflux of K^+ and influx of Na^+, Cl^-, and Ca^{2+}). This "anoxic depolarization" results in the excessive release of neurotransmitters especially glutamate, promoting a more spatial spread of cellular depolarization, depletion of energy stores, and advancement of harm cascades (8).

Obviously, lack of energy causes initially an electrical failure. If energy depletion lasts longer, the arrest of cellular functions and cell death takes place. However, animal trials and clinical studies display that there are other factors, like energy loss, that account for neuronal damage. Even sublethal hypoxic-ischemic encephalopathy can set in motion a series of toxic reactions that finish off injured neurons and kill additional ones that have not been damaged during the initial injury. Accordingly, following global ischemia, neurons do not die suddenly or all at once. In some cases, global ischemia leads to

bilateral, symmetric cerebral infarcts in the border zones amid major arterial territories. Rarely, hypoxic-ischemic encephalopathy involves the white matter, causing myelin damage and loss. Dismantling of damaged myelin results in vacuolization and a spongy appearance of the white matter in tissue parts. White matter damage is common in carbon monoxide (CO) poisoning but may occur in other forms of hypoxic-ischemic encephalopathy (9).

References

(1)Kumar, V. (n.d.). *Robbins basic pathology*. https://l.facebook.com/l.php?u=https%3A%2F%2Fdrive.google.com%2Ffile%2Fd%2F1766V9MOsir-f_OSDpfYKdKHWVHVby2Fv%2Fview%3Fusp%3Ddrivesdk%26fbclid%3DIwAR1wzJ_NdrU94tRxXgnmW9h-br8GcR2vpce_KR0vFHxdEQ15-heBgcaVlcM&h=AT0AHn9NNdDu913mmpGLHGF2NtUnV1xbZUEdPxoEaT6J6g4
(2) Signorelli, S. S., Platania, I., Tomasello, S. D., Mangiafico, M., Barcellona, G., Di Raimondo, D., & Gaudio, A. (2020). Insights from Experiences on Antiplatelet Drugs in Stroke Prevention: A Review. *International Journal of Environmental Research and Public Health*, *17*(16). https://doi.org/10.3390/ijerph17165840
(3)wikipedia. (n.d.). *brain ischemia*. https://en.wikipedia.org/wiki/Brain_ischemia#cite_note-4
(4)radiopaedia. (n.d.-a). *global cerebral ischemia*. https://radiopaedia.org/cases/global-cerebral-ischaemia
(5)ResearchGate. (n.d.). *focal cerebral ischemia*. https://www.researchgate.net/figure/Damage-after-focal-cerebral-ischaemiaFocal-ischaemia-can-be-induced-by-cerebral_fig4_11765847
(6)radiopaedia. (n.d.-b). *Hypoxic ischemic encephalopathy (HIE)*. https://radiopaedia.org/cases/hypoxic-ischemic-encephalopathy-hie-1?lang=us
(7)MartInez-Coria, H., Arrieta-Cruz, I., Cruz, M.-E., & López-Valdés, H. E. (2021). Physiopathology of ischemic stroke and its modulation using memantine: evidence from preclinical stroke. *Neural Regeneration Research*, *16*(3), 433–439. https://doi.org/10.4103/1673-5374.293129
(8)Lee, J. M., Grabb, M. C., Zipfel, G. J., & Choi, D. W. (2000). Brain tissue responses to ischemia. *The Journal of Clinical Investigation*, *106*(6), 723–731. https://doi.org/10.1172/JCI11003
(9)neuropathology. (2017). *CEREBRAL ISCHEMIA AND STROKE*. https://neuropathology-web.org/chapter2/chapter2aHIE.html

Article Topic: Alzheimer's Disease.

Author: Boshra Alajarma.

Editors: Yazan Zamer, Farah Balhosh.

Reviewer: Omar Jbarah, Hassan Abushukair.

Key Words: Alzheimer's disease, AD, Dementia, Amyloid Beta, Tau,

Neurodegenerative Diseases.

Introduction

Neurodegenerative diseases are marked by the progressive loss of neurons, typically affecting a combination of neurons with functional interconnections. Multiple disorders tend to involve particular neural systems and therefore have relatively stereotypic presenting signs and symptoms [1].

Example of Neurodegenerative diseases:

- Alzheimer's disease
- Spinocerebellar ataxia (SCA)
- Spinal muscular atrophy (SMA)
- Frontotemporal lobar degeneration
- Parkinson disease
- Huntington disease
- Amyotrophic lateral sclerosis (ALS)

Alzheimer's disease

A brain disorder that gives rise to issues with memory, thinking, and behavior. It causes dementia to develop, Specific neurons are affected, therefore losing their function.

Symptoms

1. Difficulty remembering things and some events

2. Forgetting family members' names

3. Repetitive questions

4. Short in attention spam

About 5.8 million people in the US, age 65 and older have Alzheimer's disease. Of those, 80% are 75 years old and older. Out of the approximately 50 million people worldwide with dementia, between 60% and 70% are estimated to have Alzheimer's disease. [2]

Reisberg Scale (global Deterioration Scale (GDS) for stage Alzheimer's disease, including seven stages: [3]

Stage 1: No cognitive decline

Stage 2: Vastly mild cognitive decline [age-associated memory impairment]

Stage 3: Mild cognitive decline [mild cognitive impairment]

Stage 4: Moderate cognitive decline

Stage 5: Moderately severe cognitive decline

Stage 6: Severe cognitive decline

Stage 7: Very severe cognitive decline

Pathogenesis [4]

The fundamental abnormality in AD is the accumulation of two proteins (Aβ and tau) in specific brain regions, in the forms of plaques, deposits of aggregated Aβ peptides in the neuropil, and tangles (aggregates of the microtubule-binding protein tau) that develop intracellularly and then persist extracellularly after neuronal death, respectively; these changes result in secondary effects including neuronal dysfunction, neuronal death, and inflammatory reactions.

Aβ production is the critical initiating incident for the development of AD. Amyloid precursor protein (APP) on chromosome-21 is cleaved by β-amyloid–converting enzyme (BACE), γ-secretase, α-secretase, and β-Secretase. After it is cleaved, it yields Aβ Monomer and Aβ Oligomers, which eventually propagate into large aggregates and fibrils located in plaques. Patients with Down syndrome have a higher risk for AD for they have an additional copy of chromosome-21. Apolipoprotein E (ApoE) has a vigorous impact on the likelihood of AD progression.

References

1 . [Robbins Basic Pathology 10th edition page 875, 876 ,877]
2. [Fisher Center for Alzheimer's Research Foundation. Clinical Stages of Alzheimer's. 2019. https://www.alzinfo.org/understand-alzheimers/clinical-stages-of-alzheimers/ Accessed March 13, 2019].

3. [Alzheimer Society Canada. Global Deterioration Scale. 2018. https://alzheimer.ca/en/Home/About-dementia/Alzheimer-s-disease/Stages-of-Alzheimer-s-disease/Global-Deterioration-Scale Accessed March 13, 2019.]
4.[The Global Deterioration Scale for Assessment of Primary Degenerative Dementia. 1983. https://www.fhca.org/members/qi/clinadmin/global.pdf Accessed March 13, 2019.
5.Daroff RB, et al. Alzheimer's disease and other dementias. In: Bradley's Neurology in Clinical Practice. 7th ed. Philadelphia, Pa.: Saunders Elsevier; 2016. https://www.clinicalkey.com. Accessed Nov. 23, 2020.]

Article Topic: Cerebral edema.

Author: Areen Amaireh.

Editor: Marah Bassam Akhdar.

Reviwer: Ethar Hazaimeh.

Keywords: Brain Edema, Swelling, Cerebral Edema, ICP.

Definition

Cerebral edema is the accumulation of extreme quantities of fluid within the brain parenchyma [1]. It can be caused by brain damage because of several potential reasons, such as ischemic or hemorrhagic strokes, brain traumas, infections, or tumors. Brain edema causes weakened nerve function, increased intracranial pressure (ICP), leading eventually to unconsciousness and herniation [3]. Cerebral edema could cause an irreversible injury [2]. The herniation results in direct stress on the brain tissue and compresses the vessels which leads to further ischemia and, later on, death [3].

The edematous brain is softer than a normal brain. It often appears to overfill the cranial cavity. In brain edema, the surfaces of the gyri are flattened due to compression of the expanding brain by the dura mater and the inner surface of the skull. Such changes result in a dangerous increase in intracranial pressure [1]. There are two types of brain edema [1]:

1-Vasogenic edema.

2-Cytotoxic edema.

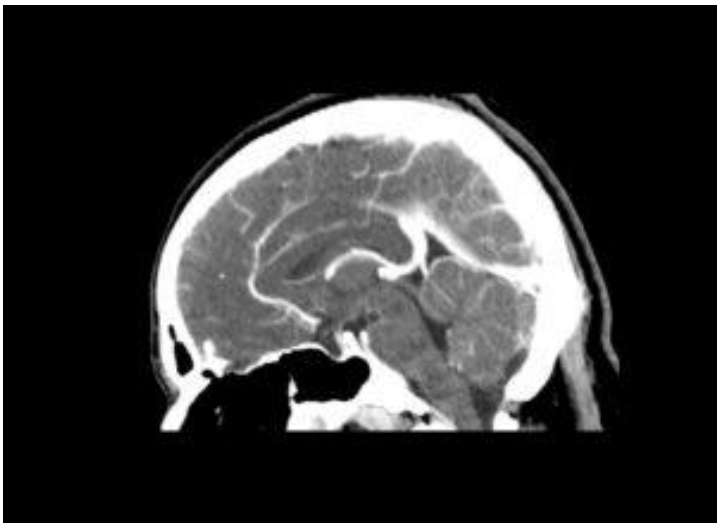


Figure (1): Cerebral edema Case courtesy of Dr Orsolya Lajos [4].

Vasogenic edema

Vasogenic edema occurs when the integrity of the normal blood-brain barrier (BBB) is disrupted [1]. This disruption involves the breakdown of the tight endothelial junctions comprising the blood-brain barrier following a physical disruption or a release of vasoactive compounds [5]. The blood-brain barrier is formed by astrocytes and pericytes joined together, along with adhesive proteins producing tight junctions [6]. As a result, intravascular proteins and fluid move from the vascular area into the extracellular compartment of the brain [5].

This type of edema can be localized in a specific area or generalized in a wider area [1]. Accumulation of extracellular fluid increases the brain volume and intracranial pressure (ICP) causing the symptoms of cerebral/brain edema [6].The white matter is greatly affected because of its reduced density with multiple unconnected parallel axonal tracts [5]. Vasogenic edema is seen extensively around brain tumors and cerebral abscesses. However, some vasogenic edema may be seen around maturing cerebral contusion and brain hemorrhage [7].

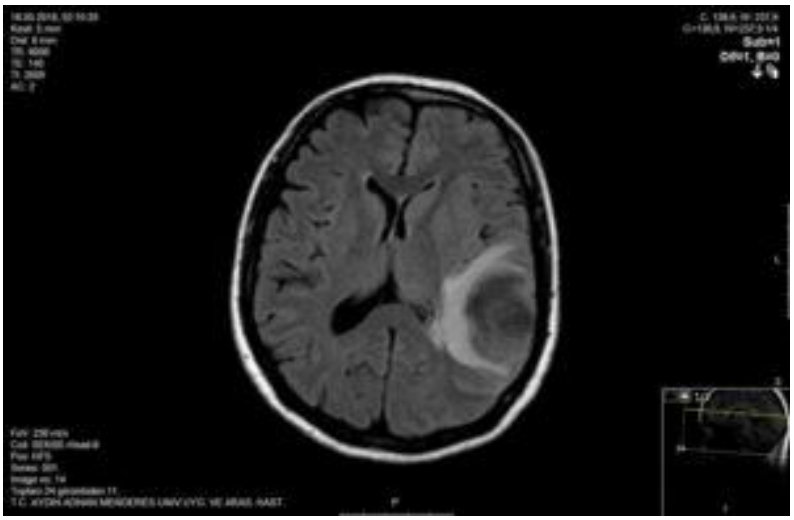


Figure (2): Intraparenchymal hematoma and vasogenic edema in the left parieto-occipital lobe [8].

Cytotoxic edema

Cytotoxic edema is an increase in intracellular fluid secondary to neuronal and glial cell damage. It might occur following generalized hypoxic or ischemic insult or exposure to specific toxins [1]. In other words, it is a type of brain edema that is most commonly seen in cerebral ischemia in which extracellular water passes into cells resulting in swelling [9].

Cytotoxic edema results from a disruption in adenosine triphosphate (ATP)-dependent transmembrane sodium-potassium and calcium pumps. It is usually caused by brain

ischemia or excitotoxic brain injury [5]. Attrition of energy sources reduces the activity of the sodium-potassium pump in the cell membrane leading to cellular retention of sodium ions [6]. This leads to intracellular accumulation of fluid in neurons, axons, glial cells, and myelin sheaths. The gray matter will be affected first due to its high metabolic activity and greater astrocyte density. Eventually, both the gray and white matters will be involved. There is an overall limitation of diffusion of water molecules across the cell membrane and within the cytoplasm. Initially, the blood-brain barrier (BBB) remains unchanged or intact and extracellular water does not increase. Nonetheless, intense or repeated insults overwhelm the transmembrane ion pumps which leads to cell death with the breakdown of the blood-brain barrier causing vasogenic edema [5]. Subsequent complications include neuronal apoptosis, atrophy, and gliosis [5]. However, the definitive consequence of cytotoxic edema is the oncotic death of neurons [6].

Etiology and Symptoms

Brain swelling is a life-threatening condition that develops because of an inflammatory reaction. Most frequently, this is the result of cerebral trauma, severe cerebral infarction, hemorrhages, abscess, tumor, allergy, sepsis, hypoxia, and other toxic or metabolic factors [10]. Symptoms of brain edema are nonspecific [5]. Additionally, its severity depends on the exact cause, but it is related to an acute increase in the pressure within the skull.

Increased pressure within the skull can lead to a compensatory elevation of blood pressure to preserve cerebral blood flow [6]. Symptoms of brain edema include Headache, nausea, loss of coordination, seizures, lethargy, memory loss, and reduced level of consciousness [11]. Also, symptoms are frequently accompanied by visual problems and vertigo [6].

Pathophysiology

For cerebral edema and swelling to occur, brain tissue must be supplied by an external fluid source [12]. The pathophysiology of cerebral edema/swelling at the cellular level is complex. Injured cells swell, damaged blood vessels leak, and absorption pathways stop thus forcing the fluid to shift into the brain tissues [13]. The hydrostatic force produced by the mass effect of ion transport and the osmotic force produced by the derangements in ion transport drives the bulk flow of edema [12].

Cellular and blood vessel damage leads to an activation of an injury cascade. The cascade begins with releasing glutamate into the extracellular compartment. Calcium (Ca) and sodium (Na) entry channels on cell membranes are opened by glutamate stimulation. Membrane ATPase pumps extrude one calcium ion in exchange for three sodium ions. Sodium builds up within the cell making an osmotic gradient and rising

cell volume by water influx. An increase in fluid causes cell swelling and dysfunction but not necessarily permanent or irregular damage. Finally, hypoxia consumes the cells' energy stores weakening the sodium–potassium ATPase and decreasing calcium exchange [13].

Pathogenesis

Brain edema is created by an increasing buildup of intracerebral water and represents a brain reaction against most injuries. The volume of the brain parenchyma enlarges to the detriment of the other two intracranial components: Blood and the cerebrospinal fluid (CSF) which causes changes in the ratios between intracranial volume and intracranial pressure [14].

Several mediators have been identified to play a role in edema formation after traumatic brain injury (TBI). The most exciting recent developments include the identification of aquaporin water channels as critical participants in the formation of brain edema, and the focus on agents that affect the blood-brain barrier (BBB); and therefore, the vascular contribution to brain swelling. These mediators are Aquaporins, vasoactive agents, and matrix metalloproteinases [15].

The development of cerebral edema occurs in two stages. It begins with the disturbance of the glioneuronal metabolic circuits by changing the transport mechanisms. Then, extension and expansion – when the specified features of cellular/extracellular injury are defined and developed by covering wide areas of the brain tissue [14].

Edema is hazardous because it causes cell swelling. This swelling alters cellular metabolite concentration and thus cellular physiology, and biochemistry which results in abnormal function. When the swelling involves not only the cells themselves but also the brain parenchyma, there is a fast increase in intracranial pressure (ICP), which causes a compression of blood vessels, minimized tissue blood flow, decreased oxygenation and later tissue shift down pressure gradients (herniation) that may suppress vital brain centers such as centers responsible for respiration and cardiac function [15].

Epidemiology

Since cerebral edema is not an easily determined simple disease but a different continuum created by several causes and presents in combination with some other common cerebral pathologies, the epidemiology of this disorder is not easily defined [3,6]. The incidence of brain edema should be considered in terms of its potential etiology. Cerebral edema presents in most cases of traumatic brain injury (TBI), central nervous system tumors, brain ischemia, and intracerebral hemorrhage/bleeding [6].

References

1- Kumar, V. (n.d.). *Robbins basic pathology*.
https://l.facebook.com/l.php?u=https%3A%2F%2Fdrive.google.com%2Ffile%2Fd%2F1766V9MOsir-f_OSDpfYKdKHWVHVby2Fv%2Fview%3Fusp%3Ddrivesdk%26fbclid%3DIwAR1wzJ_NdrU94tRxXgnmW9h-br8GcR2vpce_KR0vFHxdEQ15-heBgcaVlcM&h=AT0AHn9NNdDu913mmpGLHGF2NtUnV1xbZUEdPx0EaT6J6g4
2- Medicalnewstoday. (n.d.). *cerebral edema*. https://www.medicalnewstoday.com/articles/322475
3- Sciencedirect. (n.d.). *Raised intracranial pressure and brain edema*.
https://www.sciencedirect.com/science/article/pii/B9780128023952000043?via%3Dihub
4- Radiopaedia. (n.d.-a). *cerebral-oedema-2*.
5- AJR. (n.d.). *Cerebral Edema*. https://www.ajronline.org/doi/full/10.2214/AJR.11.8081
6- Winkler, E. A., Minter, D., Yue, J. K., & Manley, G. T. (2016). Cerebral Edema in Traumatic Brain Injury: Pathophysiology and Prospective Therapeutic Targets. *Neurosurgery Clinics of North America*, *27*(4), 473–488.
https://doi.org/10.1016/j.nec.2016.05.008
7- Radiopaedia. (n.d.-c). *Vasogenic cerebral edema*. https://radiopaedia.org/articles/vasogenic-cerebral-oedema?lang=us
8- ResearchGate. (n.d.). *vasogenic edema*. https://www.researchgate.net/figure/Intraparanchymal-hematoma-and-vasogenic-edema-in-the-left-parieto-occipital-lobe_fig2_321734115
9- Radiopaedia. (n.d.-b). *Cytotoxic cerebral edema*. https://radiopaedia.org/articles/cytotoxic-cerebral-oedema
10- Pubmed. (n.d.). *summary-17329953*. https://pubmed.ncbi.nlm.nih.gov/17329953/
11- Healthgrades. (n.d.). *cerebral edema*. https://www.healthgrades.com/right-care/brain-and-nerves/brain-swelling
12- NCBI. (n.d.-b). *Molecular pathophysiology of cerebral edema*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4776312/
13- NCBI. (n.d.-a). *Cerebral Edema and its Management*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4923559/#bib2
14- Iencean, S. M. (2003). Brain edema -- a new classification. *Medical Hypotheses*, *61*(1), 106–109. https://doi.org/10.1016/s0306-9877(03)00127-0
15- Donkin, J. J., & Vink, R. (2010). Mechanisms of cerebral edema in traumatic brain injury: therapeutic developments. *Current Opinion in Neurology*, *23*(3), 293–299. https://doi.org/10.1097/WCO.0b013e328337f451

Article Topic: Amyotrophic Lateral Sclerosis (ALS).

Author: Boshra Alajarma.

Editor: Marah Bassam Akhdar, Noor AlOsta.

Reviewer: Ethar Hazaimeh.

Keywords: Neurons, Frontotemporal Dementia, Free Radicals, Motor Muscle

Introduction

This disease has many names, such as Lou Gehrig's disease, Motor Neuron Disease (MND) and Charcot disease. Amyotrophic Lateral Sclerosis (ALS) is a set of rare neurological diseases that affects the neurons responsible for controlling voluntary muscle movement such as the muscles responsible for chewing food, speaking, and walking.

This disease is progressive. Motor neuron loss continues until the ability to eat, speak, move, and breathe is lost. Most people with ALS die within 3 to 5 years from when the first symptom appears, because of respiratory failure. However, only about 10 percent of people with ALS survive for 10 or more years [1]. ALS results from the death of lower motor neurons in the spinal cord and brain stem as well as upper motor neurons (Betz cells) in the motor cortex [7].

Although the primary symptoms of ALS are associated with motor dysfunction as muscle weakness, spasticity and dysphagia, up to 50% of patients develop cognitive and/or behavioral impairment, and 13% of patients present with concomitant behavioral variant frontotemporal dementia (FTD) during the course of the disease [2].

Epidemiology

ALS is the most common motor neuron disease in adults and the third most common neurodegenerative disease [3]. The number of new cases a year in Europe is 2.6 people per 100,000 with the number of affected people being 7-9 per 100,000. In the United States in 2015, there were 5.2 people per 100,000 diagnosed with ALS. In Addition, it was higher in white people, males, and those over 60 years of age [5]. Also, there are differences in the genetics of ALS between different ethnic groups. The most common ALS gene in Europe is C9orf72, then SOD1, TARDBP, and FUS. However, the most common ALS gene in Asia is SOD1, followed by FUS, C9orf72, and TARDBP [6].

Pathogenesis

Most cases of ALS are sporadic and about 10% of the cases are familial, mostly with autosomal dominant inheritance. Familial diseases begin earlier in life than sporadic diseases. However, once the symptoms appear, the clinical course is similar in both forms [7]. The basic feature of ALS is the death of both upper motor neurons located in the motor cortex of the brain and lower motor neurons located in the brainstem and spinal cord. In people who suffer from ALS with frontotemporal dementia, neurons throughout the frontal and temporal lobes of the brain die. The pathological hallmark of ALS is the presence of inclusion bodies, which are abnormal aggregations of bunina bodies (proteins in the cytoplasm of motor neurons) [14].

Scientists have identified 25 genes to be associated with Amyotrophic Lateral Sclerosis (ALS). The pathogenic mutation in the C9orf72 gene is a hexanucleotide repeat expansion [GGGGCC]. The C9orf72 gene is the most commonly associated gene with ALS, accounting for 40% of familial ALS and 7% of sporadic ALS cases [8].

Superoxide Dismutase Gene (SOD1) on chromosome 21 was the first identified genetic cause of ALS and accounts for about 20% of the familial forms. These mutations are thought to generate abnormal misfolded forms of the SOD1 protein which may trigger the unfolded protein response and cause apoptotic death of neurons [7]. Superoxide Dismutase (SOD1) enzyme is a powerful antioxidant that protects the body from damage caused by superoxide, which is a toxic free radical generated in the mitochondria. During normal metabolism, cells generate free radicals which are highly reactive molecules, those free radicals can cause damage to the DNA and proteins within cells. To date, over 110 different mutations in SOD1 have been linked with the disorder, some of which as H46R have a very long clinical course, while others such as A4V are exceptionally aggressive. When the defenses against oxidative stress fail, apoptosis is upregulated. Moreover, up to 180 different mutations in SOD1 gene are known to cause familial ALS [9].

TARDBP, which codes for TAR DNA-binding protein (TDP-43), was found to be associated with 1–5% of familial ALS and less than 1% of sporadic ALS [10].

Gene	Location	FALS locus	Inheritance	Strategy	Associated phenotype	Protein function
SOD1	21q22.11	ALS 1	AD, AR	LA	ALS, PMA, juvenile ALS	Superoxide metabolism
ALS2	2q33.2	ALS 2	AR	LA	Juvenile ALS, infantile HSP	Vesicle trafficking
SETX	9q34.13	ALS 4	AR	LA	Juvenile ALS, dHMN, AOA2	RNA metabolism
SPG11	15q21.1	ALS 5	AR	LA, CGA	Juvenile ALS, HSP	DNA damage repair
FUS	16p11.2	ALS 6	AD, AR	LA, CGA	ALS, ALS-FTD, FTD	RNA metabolism
VAPB	20q13.33	ALS 8	AD	LA	ALS, PMA	Vesicle trafficking
ANG	14q11.1	ALS 9	AD	CGA	ALS, ALS-FTD	Angiogenesis
TARDBP	1p36.22	ALS 10	AD	LA, CGA	ALS, ALS-FTD, FTD	RNA metabolism
FIG4	6q21	ALS 11	AD, AR	CGA	ALS, PLS, CMT	Vesicle trafficking
OPTN	10p13	ALS 12	AD, AR	HM	ALS, FTD	Vesicle trafficking; autophagy
ATXN2	12q24.12	ALS 13	–	CGA	ALS, SCA2	Endocytosis; RNA translation
VCP	9p13.3	ALS 14	AD	WES	ALS, FTD, IBM, PDB	Proteasome; vesicle trafficking
UBQLN2	Xp11.21	ALS 15	XL	LA	ALS, ALS-FTD, juvenile ALS	Proteasome
SIGMAR1	9p13.3	ALS 16	AR	HM	juvenile ALS, dHMN	Proteasome
CHMP2B	3p11.2	ALS 17	AD	LA, CGA	ALS, FTD	Vesicle trafficking
PFN1	17p13.3	ALS 18	AD	WES	ALS	Cytoskeletal dynamics
C9orf72	9p21.2	ALF-FTD	AD	GWAS, LA	ALS, FTD, ALS-FTD	RNA metabolism
MATR3	5q31.2	–	AD	WES	ALS, distal myopathy	RNA metabolism
CHCHD10	22q11.23	–	AD	WES	ALS, FTD, cerebellar ataxia, myopathy	Mitochondrial dysfunction
SQSTM1	5q35.3	–	AD	CGA	ALS, FTD, IBM, PDB	Ubiquitination; autophagy
HNRNPA1	12q13.13	–	AD	WES	ALS, FTD, IBM, PDB	RNA metabolism
HNRNPA2B1	7p15.2	–	AD	WES	ALS, FTD, IBM, PDB	RNA metabolism
TBK1		–	AD	WES	ALS, FTD	Autophagy

Table1: Summary of genes linked to Amyotrophic Lateral Sclerosis (ALS)[15].

Environmental Factors

Environmental factors play a role in the development of ALS where no family history of the disease is present, those represent around 90% of cases. The main causative factor may be head injury. A review conducted in 2015 found that moderate to severe traumatic brain injury is a risk factor for ALS, but whether mild traumatic brain injury increases rates is still unclear [11].

Several studies identified sports as soccer and american football to be risk factors of ALS. However, this study was based on small sample size of ALS cases [12]. Moreover, a 2011 meta-analysis concluded that smoking increases the risk of ALS. Among smokers, the younger they started smoking, the higher the risk of ALS was found to be. However, neither the duration of years of smoking nor the number of cigarettes smoked per day affected their risk of developing ALS [13].

References

[1]. **[**Amyotrophic Lateral Sclerosis (ALS) Fact Sheet | National Institute of Neurological Disorders and Stroke (nih.gov)]
[2]. [Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, Shaw PJ, Simmons Z, van den Berg LH (October 2017). "Amyotrophic lateral sclerosis" (PDF). *Nature Reviews. Disease Primers*. 3 (17071): 17071. doi:10.1038/nrdp.2017.71. PMID 28980624. S2CID 1002680.**]**
[3].[Renton AE, Chiò A, Traynor BJ (January 2014). "State of play in amyotrophic lateral sclerosis genetics". Nature Neuroscience. 17 (1): 17–23. doi:10.1038/nn.3584. hdl:2318/156177. PMC 4544832. PMID 24369373]
[4]. [Hardiman O, Al-Chalabi A, Brayne C, Beghi E, van den Berg LH, Chio A, Martin S, Logroscino G, Rooney J (July 2017). "The changing picture of amyotrophic lateral sclerosis: lessons from European registers". *Journal of Neurology, Neurosurgery, and Psychiatry*. **88** (7): 557–63. doi:10.1136/jnnp-2016-314495. PMID 28285264. S2CID 52871105]
[5].Mehta P, Kaye W, Raymond J, Punjabi R, Larson T, Cohen J, Muravov O, Horton K (November 2018). "Prevalence of Amyotrophic Lateral Sclerosis – United States, 2015". *Morbidity and Mortality Weekly Report*. **67** (46): 1285–1289. doi:10.15585/mmwr.mm6746a1. PMC 5858037. PMID 30462626.]
[6].[Zou ZY, Zhou ZR, Che CH, Liu CY, He RL, Huang HP (July 2017). "Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis". *Journal of Neurology, Neurosurgery, and Psychiatry*. **88** (77): 540–49. doi:10.1136/jnnp-2016-315018. PMID 28057713. S2CID 41974606.]
[7]. [Robbins basic pathology 10th p.880]
[8]. [Nguyen, Hung Phuoc; Van Broeckhoven, Christine; van der Zee, Julie (June 2018). "ALS Genes in the Genomic Era and their Implications for FTD". *Trends in Genetics*. **34** (6): 404–423. doi:10.1016/j.tig.2018.03.001. PMID 29605155.]
[9]. [Tokuda E, Furukawa Y (2016). "Copper Homeostasis as a Therapeutic Target in Amyotrophic Lateral Sclerosis with SOD1 Mutations". *International Journal of Molecular Sciences*. **17** (5): 636. doi:10.3390/ijms17050636. PMC 4881462. PMID 27136532]
[10]. [Renton, Alan E.; Chiò, Adriano; Traynor, Bryan J. (January 2014). "State of play in amyotrophic lateral sclerosis genetics". *Nature Neuroscience*. **17** (1): 17–23. doi:10.1038/nn.3584. hdl:2318/156177. PMC 4544832. PMID 24369373]
[11]. [Gardner RC, Yaffe K (May 2015). "Epidemiology of mild traumatic brain injury and neurodegenerative disease". *Molecular and Cellular Neurosciences*. **66** (Pt B): 75–80. doi:10.1016/j.mcn.2015.03.001. PMC 4461453. PMID 25748121]
[12]. [Couratier P, Corcia P, Lautrette G, Nicol M, Preux P, Marin B (January 2016). "Epidemiology of amyotrophic lateral sclerosis: A review of literature". *Neuroepidemiology*. **172** (1): 37–45. doi:10.1016/j.neurol.2015.11.002. PMID 26727307]
[13]. [Wang H, O'Reilly ÉJ, Weisskopf MG, Logroscino G, McCullough ML, Thun MJ, Schatzkin A, Kolonel LN, Ascherio A (February 2011). "Smoking and risk of amyotrophic lateral sclerosis: a pooled analysis of 5 prospective cohorts". *Archives of Neurology*. **68** (2): 207–13. doi:10.1001/archneurol.2010.367. PMC 3319086. PMID 21320987]
[14]. [https://en.wikipedia.org/wiki/Amyotrophic_lateral_sclerosis]
[15]. PubMed Central, Table 1: Ann Transl Med. 2016 Jan; 4(2): 27. doi: 10.3978/j.issn.2305-5839.2016.01.16 (nih.)

Article Topic: Cholinergic Agonists.

Author: Mohammad Khader Altal.

Editor: Marah Bassam Akhdar.

Reviwer: Ethar Hazaimeh.

Keyword: Cholinergic, Nicotinic, Muscarinic, Agonist.

Overview

Cholinergic receptors are the receptors that bind the neurotransmitter, Ach. They are the main receptors on the preganglionic fiber of both SNS & PSNS and on the postganglionic fiber of the PSNS. Also, they are found at the neuromuscular junction of skeletal muscles and the postganglionic neuron of sweat glands which are part of the SNS.

Cholinergic receptors are divided into two types: Nicotinic & Muscarinic. They differ in their location, formation, and function but they both bind Ach.

In brief:

- Muscarinic R: They are mainly GPCRs that bind Ach & Muscarine and then activate signal transduction pathway to give their effect.
- Nicotinic R: They are ligand-gated ion channels that are composed of five subunits that bind Ach & Nicotine which causes a conformational change to happen to open the channel.

The cholinergic agonist is a substance (drugs) that stimulates (activates) these receptors mainly by two mechanisms: Direct & Indirect:

Direct Cholinergic Agonists

These drugs act by binding directly to the receptor and exerting their effect they are classified into two groups:

The first group includes:

-Endogenous Choline Esters (Ach): These ones have no therapeutic importance because they have a very wide action (non-specific) and are inactivated very rapidly by AchE. The action includes:

Increased	Decreased
GIT secretion	Heart rate
Intestinal motility (Peristalsis)	Arterioles tone
Salivation	Blood pressure
Lacrimation	Pupil size (Miosis)
Bronchial tone & secretion	-
Urinary bladder body tone	Urinary bladder sphincter

-**Synthetic Choline Esters:** Include mainly:

- Bethanechol: It has a similar structure to Ach but this drug acts only on muscarinic receptors (doesn't affect nicotinic receptors) and has a long duration of about 1 hour. AchE do not hydrolyze it, but it gets hydrolyzed by other esters. Its major action is on the smooth muscle of the urinary bladder and causes an increased bladder wall muscular contraction and sphincter relaxation. Its side effect:

Increased	Decreased
GIT secretion	Arterioles tone
Intestinal motility(peristalsis)=diarrhea	Blood pressure
Sweating	-
Salivation	-
Flushing	-

- Carbachol: A non-specific drug (affecting both Nicotinic & Muscarinic R) thus it has many S/E. It is a poor substrate for AchE that is why it is degraded slowly by it. This drug has the same action and effect as Ach.

The second group includes: Naturally Occurring Alkaloids, such as: Pilocarpine: It is a muscarine-specific drug that has a tertiary amine structure which means that it can penetrate the BBB and exert a CNS effect. It is a potent secretion stimulant and used especially on the eye (given topically) because it induces miosis and accommodation. That is why it is useful in glaucoma and xerostomia. Its S/E include Blurred vision, brow ache, and could cause night blindness. (1)

Indirect Cholinergic Agonists

Indirect cholinergic agonists are also called anticholinesterases. They inhibit the enzyme AchE which is responsible for the degradation of Ach NT. They are classified into two groups based on their binding to AchE:

1. **Reversible Anticholinesterase**
2. **Irreversible Anticholinesterase**

In brief, AchE as we said degrades Ach to Choline and Acetate. Therefore, by inhibiting this enzyme, Ach will accumulate in the synaptic cleft and give its effect, thus it indirectly activates the cholinergic receptors (for both muscarinic & nicotinic R).

Reversible Anticholinesterase: These drugs bind reversibly (non-covalently) to the receptors. This group includes:

- Edrophonium: The prototype, this drug is quaternary amine so it cannot penetrate the BBB and has a short duration of action (10-20). Thus, it is useful in diagnosis, not treatment. It is used for the diagnosis of Myasthenia Gravis disease (an autoimmune disease where there is a destruction of the nicotinic receptors on the NMJ).
- Physostigmine: This drug is a tertiary amine drug that can penetrate BBB and give a CNS effect. It has an intermediate duration of action. Usually, it's used with constipation or urine retention to induce muscle contraction and with the treatment of anticholinergic drug toxicity such as: Atropine. Usually its S/E rise with high doses. It can cause convulsions as it can penetrate BBB, bradycardia & hypotension, and skeletal muscle paralysis especially in high doses.
- Neostigmine: It is like physostigmine, but it is a quaternary amine thus it does not have a CNS effect, and its effect is concentrated on the NMJ. That is why it is used for the management of Myasthenia Gravis symptoms. Its S/E are the same as systemic cholinergic stimulation which include Diarrhea, salivation flushing, etc.

Irreversible Anticholinesterase: These are synthetic organophosphate compounds that are usually used as either antiacid (such as malathion & parathion) or in the biological warfare (Sarin gas/nerve gas) because they are very toxic. They bind irreversibly (covalently) by a phosphate group, so their effect is very long-lasting. Note that covalent bonds need time to stabilize (increase bond strength) and this is called aging. A drug with therapeutic use is called Echothiophate.

Echothiophate: It binds covalently to AchE by phosphate group and inactivates it permanently. Its therapeutic use is in glaucoma, but it is rarely used now because it has

a very wide/generalized effect on the body. Its S/E are the same as systemic cholinergic activation and paralysis and may cause convulsions. (2)

Reactivation of AchE

As aforementioned, covalent bonds need time so if the bond stabilizes the only way to restore AchE function is to synthesize a new AchE enzyme. However, if the bond has not aged yet, an enzyme/drug called Pralidoxime can be used.

Pralidoxime (2-PAM): It can restore AchE before aging by displacing the phosphate group. Thus, it can reverse the peripheral effect of organophosphate toxins but not the CNS effect because it cannot penetrate the BBB. Note that at high-doses Pralidoxime can cause similar side effects to other AchE inhibitors.

References

1. Rosenfeld GC, David S. Loose. Pharmacology (Board Review). 6th ed.
2. Whalen K. Lippincott Illustrated Reviews: Pharmacology. 6th ed.

Article Topic: The Autonomic Nervous System.

Author: Mohammad Khader Altal.

Scientific Editor: Marah Bassam Akhdar.

Reviewer: Ethar Hazaimeh.

Keywords: Autonomic, Sympathetic, Parasympathetic, Enteric Nervous System.

Overview and History

The autonomic nervous system is part of both the central and peripheral nervous systems. It has (afferent, connector, efferent) neurons. The afferent neurons transmit the sensation from the visceral receptor to the CNS where it is transmitted by connector neurons and then the efferent neurons carry the signals to the visceral effector. It is divided into three parts: The sympathetic, parasympathetic, and enteric nervous system (gut brain). Both sympathetic and parasympathetic opposite each other in the effect in most organs and thus they are considered physiological antagonists. However, both systems function in conjunction with one another. It is the balance in the activities that maintain a stable internal environment and homeostasis.

Sympathetic Nervous System

The sympathetic nervous system is responsible for the “fight or flight” response where the heart rate is increased, arterioles of the skin and intestine are constricted, arterioles of skeletal muscle are dilated, and the blood pressure is elevated. Preganglionic SNS neurons originate from the spinal cord's thoracic and lumbar regions (T1 to L2) with cell bodies spread around four areas of gray matter, bilaterally and symmetrically, in the spinal cord [1]. The preganglionic fiber is short and myelinated while the postganglionic is long unmyelinated. They innervate the eyes and cause mydriasis, as well as the heart, and cause increased heart rate, conductivity, and contractility. They also innervate the GIT smooth muscle and relax them to prevent peristalsis. Additionally, they innervate every other organ [2], Figure 1.

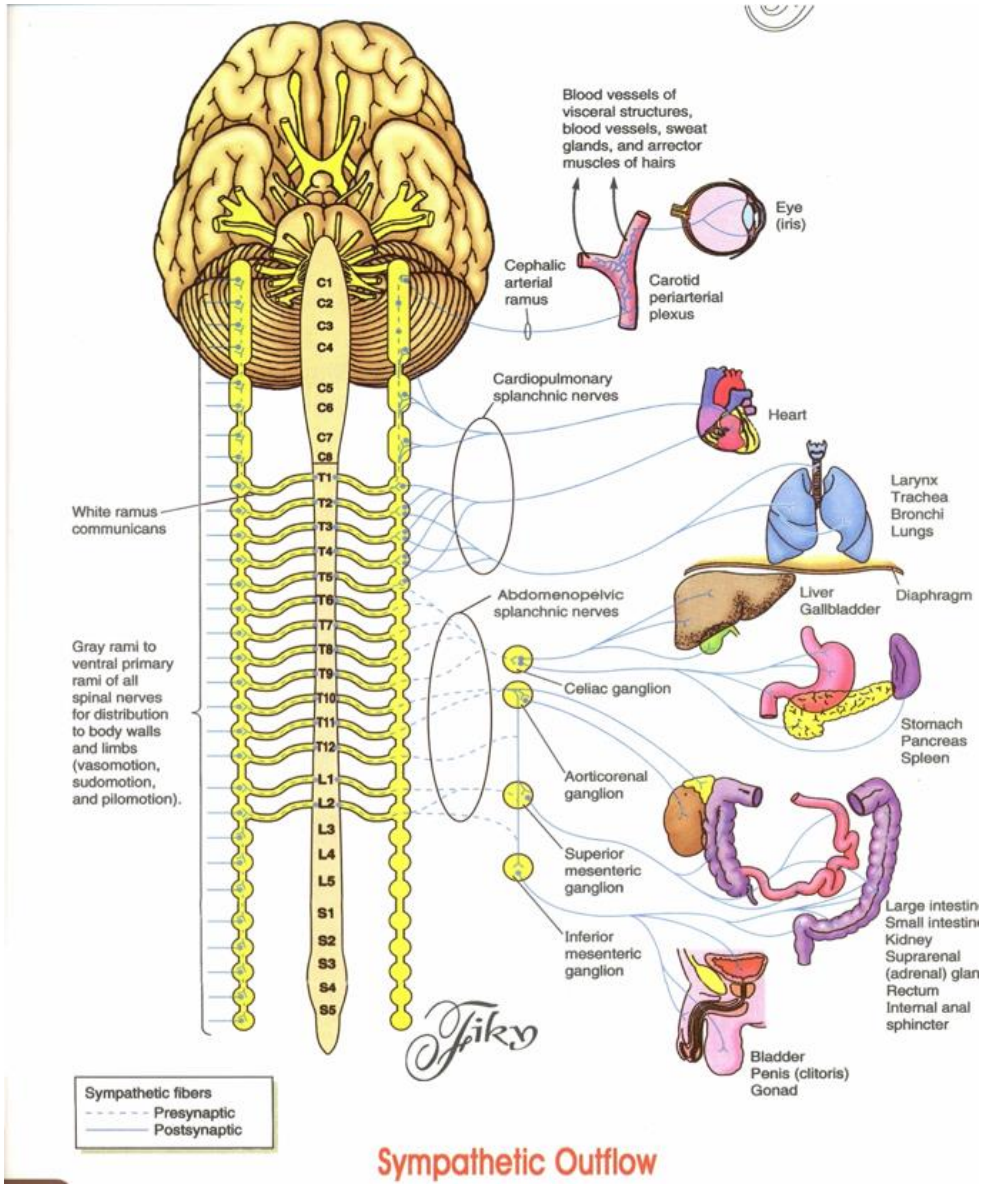


Figure 1: Sympathetic Outflow, [3]

Parasympathetic Nervous System

The PSNS in contrast to SNS is responsible for the “rest and digest “state. Also, its preganglionic neurons are long and myelinated while the postganglionic neurons are unmyelinated and short because in the PSNS the autonomic ganglia are very close to the effector organ. The nuclei of the preganglionic neurons are located in the brainstem and the sacral segment of the spinal cord(S2-S4). Moreover, the brainstem nuclei are located in the following cranial nerves: III Oculomotor nerve, VII Facial nerve, IX Glossopharyngeal nerve, X vagus nerve [4], Figure 2. In the “rest and digest” state the PSNS innervates the heart and decreases the heart rate, innervates the GIT and

increases peristalsis, innervates the eyes and constricts the pupils, affects the urinary bladder by relaxing the sphincter and constricting its wall, and many other changes [2].

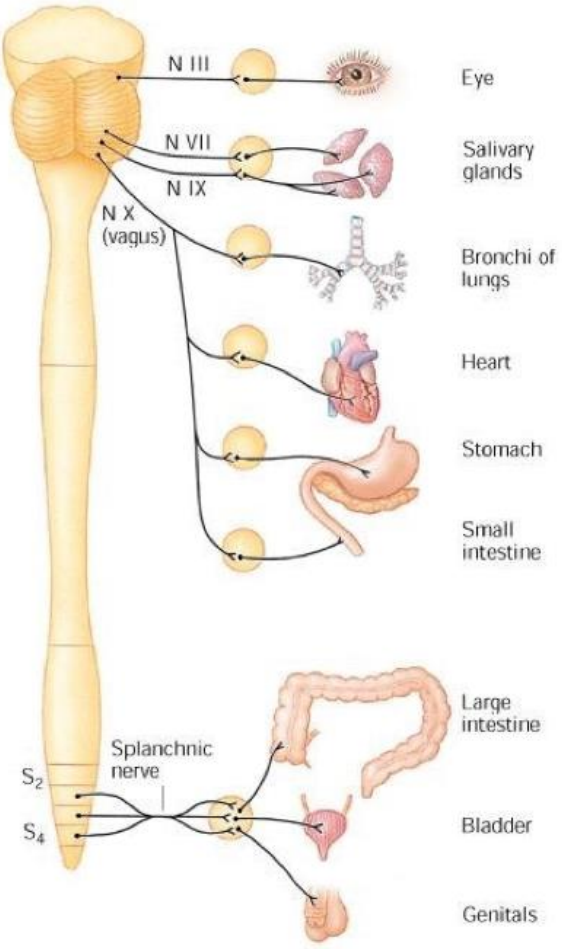


Figure 2: Parasympathetic Nervous System. [5]

Enteric Nervous System

The enteric nervous system (gut-brain) can function on its own and independently of the SNS and PSNS; however, they do regulate its function. The enteric nervous system is found in the GIT and plays a key role in it. This division is extended along and around the GIT from the esophagus to the anal canal. It is collected in two types of ganglia: The submucosal (Meissner plexus) that lies between the circular muscular layer and the mucosal membrane. This plexus controls glands of the mucous membrane. The second one is the Myenteric (Auerbach) plexus which is found between the circular and the longitudinal muscular layer and controls the muscle movement (Peristalsis) of the gut wall.

Cranial Nerves

An important part of the peripheral nervous system is the cranial nerves. They emerge from the brain and exit the skull through foramina and fissures to innervate the head and neck. Some of them have either a sensory function or a motor function only while others have both functions. They consist of 12 pairs named as follows:

1. Olfactory: It exits through the cribriform plate of the ethmoid bone and has a sensory function(smelling).
2. Optic: It exits through the optic canal and has a sensory function(vision).
3. Oculomotor: It passes through the superior orbital fissure and has a motor function in the eye muscle such as accommodation, pupil constriction, raising the upper eyelid, and turning the eyeball upward and downward.
4. Trochlear: It passes through the superior orbital fissure and has a motor function in the eye by assisting in turning the eyeball downward and laterally.
5. Trigeminal: It consists of three branches:**V1(Ophthalmic nerve)* passes through the superior orbital fissure and has a sensory function in the scalp, forehead, cornea, etc. **V2(Maxillary nerve)* passes through the Foramen rotundum and has a sensory effect in teeth of the upper jaw, etc.**V3(Mandibular nerve)* passes through foramen ovale and has both sensory and motor function in muscles of mastication.
6. Abducent: It passes through the superior orbital fissure and has a sensory function on the lateral rectus muscle to turn the eyeball laterally.
7. Facial: It passes through the internal acoustic meatus, facial canal, stylomastoid foramen and has a sensory function (taste from anterior two-thirds of the tongue), a motor function as well as a parasympathetic function.
8. Vestibulocochlear: It passes through internal acoustic meatus and has a sensory function.
9. Glossopharyngeal: It passes through the jugular foramen and has a sensory (taste from the posterior third of the tongue and pharynx), motor, and parasympathetic function.
10. Vagus: This cranial nerve is special because it innervates the heart, lung, and digestive tract and passes through the jugular foramen. It also possesses significant motor and sensory functions.
11. Accessory: It passes through the jugular foramen and has two roots: The spinal roots that innervate the Sternocleidomastoid and trapezius muscles as well as the cranial root the innervates the muscles of soft palate.
12. Hypoglossal: It passes through the hypoglossal canal and has a motor function that innervates the tongue and controls its movement and shape [4], Figure 3.

The cranial nerves can be remembered by the following mnemonic:

OOO To Take A Family Vacation Go Vegas After Hour

Cranial Nerves with PSNS Function

As aforementioned, there are four cranial nerves with PSNS function, and they are:

- Oculomotor: It controls the ciliary muscle (responsible for accommodation) and iris sphincter muscle (for Miosis).
- Facial: It controls the secretion of the salivary glands (sublingual and submandibular) and the glands of the nose and palate as well as the lacrimal glands.
- Glossopharyngeal: It innervates and controls the secretion of the Parotid salivary gland
- Vagus: It innervates most of the thoracic and abdominal organs. It decreases the heart rate and increases the peristalsis (smooth muscle contraction) and glandular secretion in GIT.

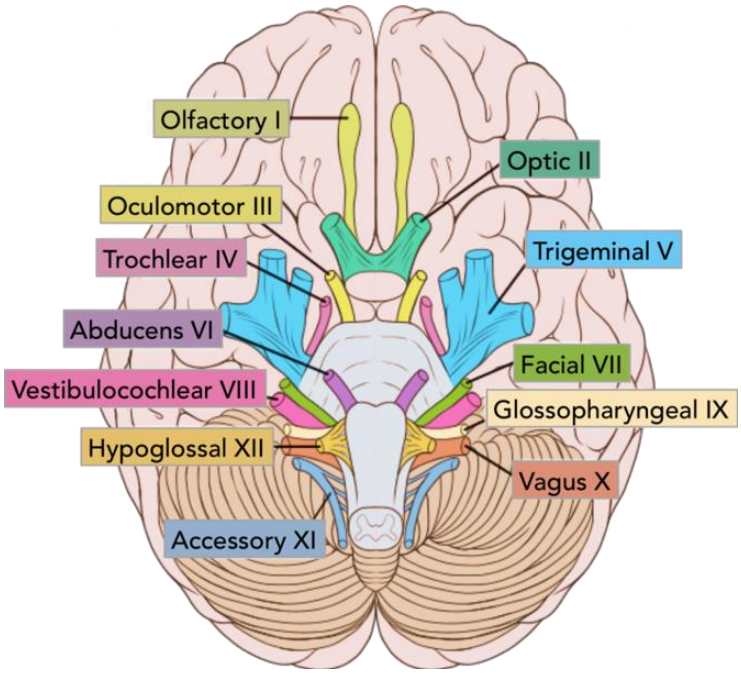


Figure 3: The location of the cranial nerves on the cerebrum and brainstem. [6]

Communicating Rami

The communicating rami or white communicating branch contains the preganglionic sympathetic nerve and connects it to the spinal nerve. It contains both myelinated and unmyelinated fibers but the myelinated are in higher concentration thus its name (white). They are present on both sides of the spinal column and function ipsilaterally. They originate from the thoracolumbar region (T1-L2) only. In the thoracic region(T1-T12) segment, the thoracic nerve is divided into anterior and ventral rami, and the white rami originate from the anterior rami while in the lumbar region (L1&L2) segment, white rami originate directly from the lumbar nerves. above T1 and Below L2 white rami are absent [7].

Neurotransmitters

Neurotransmitters are chemical substances that transmit messages from nerve cells across the synaptic cleft to a target cell.

In the autonomic nervous system, the neurotransmitter that is released from the preganglionic fiber in both SNS and PSNS and postganglionic PSNS is Acetylcholine which is quickly terminated (within 2-3 msec) by the hydrolysis action of acetylcholine-esterase.

Ach receptors are found on protein molecules that penetrate the plasma membrane. Once Ach binds to it the structure of the protein will change, and an inhibitory or excitatory effect will take place. There are two Ach receptors (cholinergic receptors):

1. Nicotinic receptors: They are named so because they respond specifically to nicotine (found in tobacco). These receptors are found predominantly on the preganglionic receptor on both SNS and PSNS and in some postganglionic SNS, such as Sweat glands.
2. Muscarinic receptors: They are named so because they respond specifically to muscarine (poison from toadstool fungus). It is found predominantly in the postganglionic receptors of PSNS.

The neurotransmitters that are released from the postganglionic SNS are EN and NE while the neurotransmitter released for the sweat glands is Ach. These receptors are called adrenergic receptors (Alpha1 and 2) and (Beta1-3) [4],[8].

References

1. Alshak MN, M Das J. Neuroanatomy, Sympathetic Nervous System [Internet]. StatPearls. StatPearls Publishing; 2019 [cited 2021 Jan 4]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31194352
2. Douglas J. Gould. Neuroanatomy (Board Review Series) 5th Edition.
3. Mohammed El-Fiky. Fiky's Atlas of Anatomy.
4. Snell RS. Clinical Neuroanatomy.
5. Rohit R. Arora. Parasympathetic Nervous System [Internet]. Available from: https://autonomicdysfunction.com/parasympathetic-nervous-system/
6. Patrick J. Lynch. The location of the cranial nerves on the cerebrum and brainstem [Internet]. Available from: https://teachmeanatomy.info/head/cranial-nerves/summary/
7. Cheng A V., Tadi P. Neuroanatomy, White Rami Communicans. 2020 Jul 31 [cited 2021 Jan 11]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK549910/
8. Wehrwein EA, Orer HS, Barman SM. Overview of the Anatomy, Physiology, and Pharmacology of the Autonomic Nervous System [Internet]. Vol. 6, Comprehensive Physiology. Compr Physiol; 2016 [cited 2021 Jan 11]. p. 1239–78. Available from: https://pubmed.ncbi.nlm.nih.gov/27347892/

Article Topic: Adrenergic Agonists.

Author: Ayah Bani Mustafa.

Editors: Marah Bassam Akhdar, Noor AlOsta.

Reviewer: Ethar Hazaimeh.

Keywords: Adrenergic, Adrenergic Agonists, Adrenergic Receptors, Alpha Receptors, Beta Receptors, Adrenergic Drugs, Adrenaline, Noradrenaline, SABA, LABA.

Overview

The word adrenergic is defined as the mimicking of adrenaline/noradrenaline effects upon binding with an adrenergic receptor. Adrenergic receptors are the receptors that the adrenergic drugs get attached to. These receptors are classified into alpha-1, alpha-2, beta-1, beta-2, and beta-3. They are all G-coupled receptors. Moreover, adrenergic drugs are often referred to as sympathomimetics which means mediating a sympathetic nervous system effect-like. There are many types of sympathomimetics. On one hand, adrenergic agonists can be classified according to the type of receptor they bind to and the effect they mediate because of this binding as [1]:

1. **Alpha-1 receptor binding agonist:** Causes smooth muscle contraction (Action potential generation), mydriasis of the eye, vasoconstriction thus increasing blood pressure, and urinary retention.
2. **Alpha-2 receptor binding agonist:** Causes mixed smooth muscle effects (according to the type and action of the muscle) and decreases insulin secretion.
3. **Beta-1 receptor binding agonist:** Causes an increase in cardiac chronotropic (heart rate) and inotropic (contractility) effects, increases renin release, and increases blood pressure.
4. **Beta-2 receptor binding agonist**: Causes bronchodilation, increased glycogenolysis, and vasodilation in skeletal muscle.
5. **Beta-3 receptor binding agonist:** Causes increased lipolysis in adipose tissue and relaxation of the smooth muscle of the bladder.

Note: An adrenergic drug can bind to one or more of these receptor sub-types with different selectivity and they bind to more receptors as their concentration increases [1].

On the other hand, adrenergic agonists can be classified according to their mechanism of action as:

Direct acting adrenergic agonists: These are agents that bind directly to the receptor producing the effect of sympathetic nerve end depolarization/ releasing of epinephrine from the medulla of the kidney. These agonists include:

-*Epinephrine:* It is a synthetic catecholamine as the product of methylation of norepinephrine. It is released from the medulla of the kidney and binds to all sub-types of the adrenergic receptors with different selectivity according to different concentrations. Its effects are:

1. Cardiovascular system: Positive inotropic and chronotropic (Beta-1 action) effects, which leads to increased cardiac output, increased renin release from the kidneys (Beta-1 action) which leads to vasoconstriction in skin, mucous membranes, and viscera. It also leads to vasodilation in skeletal muscles and liver (Beta-2 effect).
2. Respiratory system: Bronchodilation as an effect of the relaxation of the smooth muscle of bronchiole (Beta-2 effect). It also decreases allergic mediators release, such as histamine.
3. Hyperglycemia as a result of increased glycogenolysis in the liver and increased glucagon release (Beta-2 effects), decreased insulin release (Alfa-2 effect).
4. Lipolysis because of beta receptors in adipose tissue.

Side effects of epinephrine include:

1. CNS effects, such as: Anxiety, fear, headache and tremor.
2. Cardiac arrhythmias (especially with digoxin).
3. Pulmonary edema.

- *Norepinephrine:* It is the neurotransmitter of nerve ends. With that being said, it affects all types of adrenergic receptors by binding directly to them. On high doses, it activates alpha-1 receptors, while on low doses, it predominantly activates beta-1 receptors [2]. Its structure is the same as epinephrine except that it lacks one methyl group compared to epinephrine. Its effects are:

1. Vasoconstriction: Intense vasoconstriction (Alpha-1 effect) which leads to increased peripheral resistance and increased blood pressure.
2. Baroreceptors may be activated which leads to increased activation of the vagus nerve and thus causing bradycardia.

Side effects of norepinephrine include:

1. Decreased end-organ perfusion.
2. Pulmonary vascular resistance which could be an effect of interest in patients with pulmonary hypertension.
3. Decreased hepatic blood flow, which may affect drugs metabolism [3].

-*Isoproterenol:* It is a synthetic catecholamine that binds directly to beta receptors, non-selectively. Its effects are:

1. Elevated heart rate (positive chronotropy), contractility (positive inotropy) and cardiac output (Beta-1 effect).
2. Arterioles dilation in skeletal muscle (Beta-2 effect) which results in decreased peripheral resistance.
3. Bronchodilation (Bronchial relaxation), relaxation of gastrointestinal and uterine smooth muscles (Beta-2 effect).
4. Hepatic glycogenolysis and glucagon release from the pancreas (Beta-2 effect)[4].

Side effects of isoproterenol include headache, dizziness, stomach upset, fatigue, angina, flushing, dyspnea, nausea, vomiting, tremor and shaking.

-*Dopamine:* It is a physiological neurotransmitter in the CNS and medulla. It affects all adrenergic receptors by binding directly to them. It is a precursor in norepinephrine synthesis. Its effects are [5]:

1. Positive inotropic by beta 1 receptor stimulation
2. Positive chronotropic by beta 1 receptor stimulation

Side effects of Dopamine include Increased urinary flow, adversely affects functions of the kidney, addiction, impulse control disorders, and irregular heartbeats.

-*Dobutamine:* It is a synthetic catecholamine that works as a beta-1 selective agonist. It increases heart rate and contractility leading to increased cardiac output and increased atrioventricular conduction.

Side effects of dobutamine include increasing systolic blood pressure, premature ventricular beats, hypokalemia, nausea, headache, shortness of breath (rarely) [6].

-*Phenylephrine:* It is a synthetic adrenergic agonist that binds directly to alpha-1 receptors leading to:

1. Vasoconstriction which increases systolic and diastolic pressure, and reflex bradycardia.
2. Nasal decongestion.
3. Mydriasis of the eye.

Side effects of phenylephrine include nausea, vomiting, headache, and nervousness [7].

-*Clonidine:* It is an alpha-2 agonist which affects presynaptic alpha-2 receptors centrally, resulting in the inhibition of sympathetic outflow to peripheral nerves. It also causes a decrease in circulating epinephrine. Its effects are:

1. Decrease cardiovascular nerve activation.
2. Decrease arterial blood pressure.

Side effects of clonidine: abdominal pain, headache, hypotension,sedation,and xerostomia[8].

-*SABA (Albuterol, terbutaline), LABA (Salmeterol, formoterol):* These two groups are beta-2 agonists which differ in their onset of action. SABA is short acting beta-2 agonist, while LABA is a long-acting beta-2 agonist. Their effects are:

1. Bronchodilation.
2. Uterine relaxation (especially terbutaline).

Side effects of SABA and LABA include: tremor, restlessness,anxiety, tachycardia, arrhythmias and other cardiovascular events.

-*Mirabegron:* It is a beta-3 agonist that relaxes detrusor muscle to increase bladder capacity. It also increases blood pressure.

Side effects of mirabegron include hypertension, nasopharyngitis, urinary tract infection, headache, abdominal pain, and fatigue [9].

Indirect-acting adrenergic agonist: These increase the concentration of norepinephrine and epinephrine through various mechanisms including Inhibiting their reuptake, inhibiting the degradation, or increasing the release of epinephrine and norepinephrine. These agonists include:

-*Amphetamine:* It is structurally similar to catecholamine neurotransmitter. This drug is a central nervous system (CNS) stimulant that results in an increase in the amounts of dopamine, norepinephrine and serotonin (to a lesser extent) in the synaptic cleft through a variety of mechanisms. These mechanisms are entering the presynaptic axon terminal through diffusion/uptake by the monoamine transporters DAT, NET and SERT. When it is inside the presynaptic terminal, amphetamine increases concentrations of monoamine neurotransmitters in the cytosol by the inhibition of vesicular monoamine transporter 2 (VMAT2) and through the disruption of the electrochemical gradients required for vesicular transporter function. Amphetamine also decreases the metabolism of monoamine neurotransmitters by inhibiting monoamine oxidase (MAO) enzyme. Its effects are [10]:

1. Increased blood pressure.
2. Heart stimulation.

Side effects of amphetamine include stunted growth in children, risk of cardiovascular events, insomnia, headache, and dry mouth [10,11,12].

-*Cocaine:* Cocaine enhances the sympathetic nerve by accumulating epinephrine in synaptic spaces. Its mechanism of action is to block the sodium-chloride (Na+/Cl-)-dependent norepinephrine transporter needed for the cellular uptake of norepinephrine into the adrenergic neuron. The latter leads to the amplification of catecholamine concentration and increases their duration of action. It has an anesthetics effect, and it can increase blood pressure.

Side effects of cocaine include acute myocardial infarction, cerebrovascular accident, euphoria, rupture of the aorta, cardiac arrhythmia, and sudden death [13].

Mixed-action adrenergic agonist (*Ephedrine, Pseudoephedrine*): they belong to the amphetamine family. They don't only increase the release of norepinephrine stored in nerve endings (indirect action), but also directly stimulate both α and β receptors (direct action). Their effects are similar to epinephrine but are less potent, with longer duration of action. Their effects are:

1. Raise systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation.
2. Increase alertness, decrease fatigue, and prevent sleep.
3. Improve athletic performance.

Side effects include episodic hypertension, myocardial infarction, stroke, neurological symptoms, hypolipidemia, and appetite suppression [14].

References

1)(Khashayar Farzam; Ariel Kidron; Anand D. Lakhkar n.d.)
2)(Maani n.d.)
3)(Maani n.d.)
4)(Szymanski MW n.d.)
5) (sonne J , Goyal A , Bansal P, n.d.)
6)(ashkar H n.d.)
7)(richards E, Lopez MJ n.d.)
8)(Saadabadi. n.d.)
9)(Bragg, Rebecca; Hebel, Danielle; Vouri, Scott Martin; Pitlick n.d.)
10)(Le n.d.)
11)(Erin Richardson, Tasa Seibert n.d.)
12)(ADHD Medications and Serious Cardiovascular Events in Children and Youth n.d.)
13)(Cregler n.d.)
14)(O. Laccourreyea, . Werner, J.-P. Giroudc, V. Couloigner and Bondon-Guitton. n.d.)
15) Lippincott illustrated reviews ,pharma 6th edition , unit 2 , chapter 6

Article Topic: Multiple Sclerosis.

Author: Kafa Al-Zoubi.

Editor: Marah Bassam Akhdar, Noor AlOsta.

Reviwer: Ethar Hazaimeh.

***Keywords*: *Multiple Sclerosis (MS), B cells, Pathogenesis, Classification*.**

Definition

Multiple sclerosis is a chronic inflammatory demyelinating disease affecting the central nervous system in which oligodendrocytes are damaged and neuronal function is progressively lost (1). It is characterized by transient and frequent episodes of inflammation that result in demyelination and subsequent damage of the underlying axons in the brain, optic nerve, and spinal cord (2). The word sclerosis is derived from the Greek word “skleros”, meaning hard, and “Multiple” refers to the many different parts of the nervous system that may have damaged myelin. Multiple sclerosis is the most common autoimmune disease of the CNS (3).
The onset of multiple sclerosis typically develops in early adulthood between 20 and 40 years. Moreover, it affects women two to three times more than men (4). This has led to extensive studies of variation between women and men in the immune system or nervous system, which may be caused by the influence of gonadal hormones, genetic differences, as well as numerous environmental and current lifestyle exposures in men and women (5). Although MS appears in all regions of the world, its prevalence varies significantly, being highest in North America and Europe (140 and 108 per 100,000, respectively) and lowest in Sub-Saharan Africa and East Asia (2.1 and 2.2 per 100,000, respectively) (6).

Etiology

The cause of MS is not clear but there are genetic and environmental factors that affect the disease:

Genetic factors

In first degree relatives of MS patients, the risk of MS is higher than the risk of the general population (absolute risk, 2-5%) (7). In the general population, the probability of developing MS is nearly 0.1 %. The chance for a child to develop the disease if one of his parents have MS is about 2%, and the risk for relatives with second and third degree is about 1% (2). The human leukocyte antigen (HLA) complex contains the strongest

genetic associations with MS. The main risk allele is the class II allele HLA-DRB1*1501 which increases the risk of MS three times in most populations (8). More recently, alleles of interleukin-2 receptor alpha gene (IL2RA) and interleukin-7 receptor alpha gene (IL7RA) have also been identified as inheritable risk factors (7).

Environmental factors

There are some environmental factors strongly associated with MS risk such as:

1-EPSTEIN BARR VIRUS (EBV)

The risk of developing MS is about 15-fold higher among people with a history of early childhood EBV infection and about 30-fold higher among those infected later in life with EBV (6). Primary EBV infection occurs mostly in young children and is asymptomatic in general. When it occurs in early adulthood it is more often associated with symptoms manifesting as infectious mononucleosis (IM), and there is an association between infectious mononucleosis occurrence and the development of MS (9).

2-VITAMIN D DEFICIENCY

Many studies have demonstrated that in some vulnerable patients, higher vitamin D levels have a potential protective effect (10). So, the low level of vitamin D increases the risk of MS. Vitamin D is not only an environmental risk factor that contributes to the risk of developing MS but may also modulate the activity and progression of the disease. In many studies, low serum levels of vitamin D have been associated with an increased relapse rate, increased impairment, and increased lesion load seen in magnetic resonance imaging (11).

3-SMOKING

There is a correlation between smoking and MS. Smoking also raises the risk of producing antibodies that neutralizes biologics, such as natalizumab and interferon β, used in the treatment of MS (10). Also, the intensity of smoking effect on MS susceptibility is low (relative risk 1.5) but still significant (12).

Pathogenesis

There are two major interconnected mechanisms describing the pathophysiology of MS, which are neuroinflammation and neurodegeneration (13). The inflammatory portion of the pathophysiology of MS includes abnormally excessive activation of the immune system against CNS antigen(s), resulting in interactions between autoreactive leukocytes and the inflamed cerebral endothelium, disintegration of the blood-brain barrier (BBB), and penetration of these activated leukocytes into the CNS parenchyma (14). Infections with a variety of viruses, such as EBV, has been proposed to be the activating factor for the T lymphocytes that are sensitized against viral proteins that share identical structures with CNS proteins, such as, Myelin basic protein (MBP), the so-called “molecular mimicry hypothesis (13).

Various scientific studies, as experimental autoimmune encephalomyelitis (EAE) the closest animal model of MS, have demonstrated that autoreactive CNS-antigen(s)-directed T lymphocytes ($CD4^+$, $CD8^+$) play major roles in the development of CNS demyelinating lesions. IL-17, a potent inflammatory cytokine, stimulates CNS inflammation by disrupting the BBB, allowing greater permeation of autoreactive peripheral $CD4^+$ T cells into the CNS (15).

Inflammation of white and gray matter tissue in the central nervous system is the main cause of damage in MS (16). Several studies suggested that the involvement of T helper (Th) cells (also known as $CD4^+$ T cells) and adaptive immune responses initiated by interaction between antigen-presenting cells (APCs) with T lymphocytes play a key role in the initiation and progression of MS (17). Simultaneously, pathogen-associated molecules bind to toll-like APCs receptors, stimulating the production of specific cytokines including interleukin (IL)-12, IL-23, and IL-4 . These cytokines induce $CD4^+$ T cell differentiation into Th1, Th2, or Th17 phenotypes that can release specific cytokines (18).

Th1 cells produce Interferon-gamma (IFNγ) and tumor necrosis factor-alpha (TNF-α). These cytokines can stimulate inflammation by suppressing Th2 differentiation, which releases the anti-inflammatory cytokines IL-4, and IL-13. IL-4 reduces pathological inflammation through the increase in M2 macrophage (repair macrophages), and alternative activation of M1 macrophages that promote inflammation (18). Th17 is another $CD4^+$ T cell that releases a large number of cytokines (IL-17, IL-21, IL-22, and IL-26) which are capable of inducing inflammation (19).

Another $CD4^+$ T cell type involved in the pathogenesis of MS is regulatory T cells (T reg). The function of T reg cells is to regulate effector Th1, Th2, and Th17 cells. Studies have demonstrated that for both MS and control patients, the number of T reg cells is the same, but MS patients have decreased T reg function (20). IFN-β improves $CD4^+$ regulatory T-cell function, however, the specific mechanism of action of IFNβ-1a on the T reg function is still unclear and requires more investigation.

In MS lesions, $CD8^+$ T cells are present and may have a regulatory role in the progression of the disease. $CD8^+$ cells mediate the inhibition of the proliferation of $CD4^+$ T cells by secreting perforin, which is cytotoxic to $CD4^+$ T cells, resulting in their inactivation (17). $CD8^+$ cells also destroy glial cells, leaving exposed axons. In addition, $CD8^+$ T cells transect axons, facilitate vascular permeability, and activate the death of oligodendrocytes (21).

Under normal conditions, B lymphocytes do not cross the BBB. During MS along the massive immune cascade, B lymphocytes become initiated, produce antibodies, and cross the BBB (13). There are multiple roles of B cells in MS. While antigen-activated B cells differentiate into plasma cells that secrete antibodies, they act as strong APCs. Also,

it can exert anti inflammatory properties that modulate the effector role of other immune cells (22).

The precursors of antibody-secreting plasma cells, B cells

The development of these polyclonal antibodies is known as oligoclonal bands (OCB)in the cerebrospinal fluid of patients with MS (16). About 90% of MS patients have IgG OCBs, but just 30 %-40 % have IgM OCBs and the hallmark diagnostic finding in the cerebrospinal fluid (CSF) are elevated numbers of clonally expanded B cells and oligoclonal immunoglobulin bands (23).
Plasma cells and antibodies produced from B cells are present in the majority of inflammatory CNS plaques. The involvement of antibodies in MS pathogenesis is provided by the identification of antibodies that bind to myelin fragments within phagocytes and complement depositions in perivascular MS lesions (24). In addition, studies have demonstrated that antibodies produced by plasma cells clonally expanded in the CSF of Patients with MS can bind to CNS tissue, causing demyelination mediated by complement (25).
Some CNS autoantigens, including myelin oligodendrocyte glycoprotein (MOG), myelin basic protein myelin-derived lipids, neurofascin, contactin-2, KIR4-1, as well as some intracellular autoantigens such as DNA and RNA have been identified as targets for serum or CSF antibodies (26).

B cells as antigen-presenting cells (APCs) for activation of T cells

B cells can contribute as APCs for T cell activation to the development and progression of CNS autoimmune diseases. Recognition of T-cell antigen must occur twice, once in the periphery that helps activated-T cells to enter the CNS, and another time inside the CNS that activates and directs encephalitogenic T-cell effector function. In CNS autoimmune diseases, many forms of APCs may lead to T-cell activation. They can be classified into APCs that are resident (CNS) and nonresident (bone-marrow-derived). In comparison, non-resident, peripheral APCs play a more significant role in inducing CNS demyelinating disease (28).
Activation of myelin-specific T cells requires recognition of myelin antigen in association with MHC class II molecules expressed on antigen-presenting cells. In MS pathogenesis, many forms of APC can participate in T cell activation (29). B cells are more successful in presenting protein antigens and tend to be the strongest APCs at low concentrations of antigen since their unique receptor can detect neoantigens (30). Besides, CNS resident microglia and astrocytes have the ability under inflammatory conditions to express the molecules necessary for antigen presentation (29).
B-cell activation by a combination of the T-cell products CD40L and interleukin (IL)-4, but not by unspecific factors such as toll-like receptor ligand and IL-2-rendered B-cells capable of stimulating T-cells in a myelin-antigen-specific way. These data demonstrate that T-cell-mediated activation of B cells is extremely important for their capability to

process and present antigen to T cells and that both populations thereby reciprocally stimulate each other (31).

The role of cytokines secreted by B cells in MS

B cells may regulate inflammatory processes through the release of pro and anti-inflammatory cytokines. B cells of MS patients produce abnormally high levels of IL-6, tumor necrosis factor α (TNFα), lymphotoxin α (LT-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF) (32). Enhanced production of these pro-inflammatory cytokines by B cells can stimulate other immune cells leading to disease progression IL-6 secreted by B cells can promote Th17 cell differentiation and conversely can inhibit differentiation of regulatory T cells (33).
Also, B cells can regulate immune responses by producing anti-inflammatory cytokines such as IL-10, IL-35 and transforming growth factor-b (34). Studies have demonstrated that B-cell-produced IL-10 plays a key role in recovery from an acute attack of CNS autoimmunity (35). These IL-35-producing B cells can regulate immune responses through induction of IL-10-producing B cells, indicating that IL-35 can be used to stimulate regulatory B cells to treat
autoimmune diseases (36). B-cell-derived transforming growth factor-b1 limits the early induction phase of EAE by inhibition of Th1/Th17 responses and activity of dendritic cell APC (37).

Types of MS

There are four types of MS (38):
1- Relapsing-remitting MS: The most common type, affecting around 85% of MS patients. It is characterized by flare-ups (relapses or exacerbations) of symptoms followed by periods of remission when symptoms improve or vanish.

2- Secondary progressive MS: It may evolve in some patients with the relapsing-remitting disease. Disease-modifying agents help delay the progression of this type of MS in many patients. The disease course continues to worsen with or without intervals of remission or leveling off of symptom severity (plateaus).

3- Primary progressive MS: It affects about 10% of patients with MS. Symptoms continue to steadily escalate from the onset. There are no relapses or remissions, but periodic plateaus can be present. This form of MS is more resistant to drugs that are usually used to treat the disease.

4- Progressive-relapsing MS: This is an unusual form, affecting less than 5% of patients. It is gradual from the onset, with occasional flare-ups of deteriorating symptoms along the way. There are no remission intervals.

References

1. Katz Sand I. Classification, diagnosis, and differential diagnosis of multiple sclerosis. Curr Opin Neurol. 2015 Jun;28(3):193–205.
2. Bishop M, Rumrill PD. Multiple sclerosis: Etiology, symptoms, incidence and prevalence, and implications for community living and employment. Work. 2015;52(4):725–34.
3. Berer K, Krishnamoorthy G. Microbial view of central nervous system autoimmunity. FEBS Lett. 2014 Nov;588(22):4207–13.
4. Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: clinical aspects. Curr Opin Neurol. 2018 Dec;31(6):752–9.
5. Harbo HF, Gold R, Tintoré M. Sex and gender issues in multiple sclerosis. Ther Adv Neurol Disord [Internet]. 2013 Jul;6(4):237–48. Available from: https://pubmed.ncbi.nlm.nih.gov/23858327
6. Yamout BI, Alroughani R. Multiple Sclerosis. Semin Neurol. 2018 Apr;38(2):212–25.
7. Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain Behav. 2015 Sep;5(9):e00362.
8. Hedström AK. Smoking and its interaction with genetics in MS etiology. Mult Scler. 2019 Feb;25(2):180–6.
9. Guan Y, Jakimovski D, Ramanathan M, Weinstock-Guttman B, Zivadinov R. The role of Epstein-Barr virus in multiple sclerosis: from molecular pathophysiology to in vivo imaging. Neural Regen Res. 2019 Mar;14(3):373–86.
10. Alfredsson L, Olsson T. Lifestyle and Environmental Factors in Multiple Sclerosis. Cold Spring Harb Perspect Med. 2019 Apr;9(4).
11. Feige J, Moser T, Bieler L, Schwenker K, Hauer L, Sellner J. Vitamin D Supplementation in Multiple Sclerosis: A Critical Analysis of Potentials and Threats. Nutrients. 2020 Mar;12(3).
12. Wingerchuk DM. Smoking: effects on multiple sclerosis susceptibility and disease progression. Ther Adv Neurol Disord [Internet]. 2012 Jan;5(1):13–22. Available from: https://pubmed.ncbi.nlm.nih.gov/22276073
13. Maghzi AH, Borazanci A, McGee J, Steven Alexander J, Gonzalez-Toledo E, Minagar A. Multiple Sclerosis: Pathophysiology, Clinical Features, Diagnosis, and Management. In: Neuroinflammation. 2011.
14. Bar-Or A. The immunology of multiple sclerosis. Semin Neurol. 2008 Feb;28(1):29–45.
15. Kebir H, Kreymborg K, Ifergan I, Dodelet-Devillers A, Cayrol R, Bernard M, et al. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. Nat Med. 2007 Oct;13(10):1173–5.
16. Loma I, Heyman R. Multiple sclerosis: pathogenesis and tr1. Loma I, Heyman R. Multiple sclerosis: pathogenesis and treatment. Curr Neuropharmacol. 2011 Sep;9(3):409–16. eatment. Curr Neuropharmacol. 2011 Sep;9(3):409–16.
17. Kasper LH, Shoemaker J. Multiple sclerosis immunology: The healthy immune system vs the MS immune system. Vol. 74 Suppl 1, Neurology. United States; 2010. p. S2-8.
18. Ghasemi N, Razavi S, Nikzad E. Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy. Cell J. 2017;19(1):1–10.

19. Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity. 2008 Apr;28(4):454–67.
20. Haas J, Hug A, Viehöver A, Fritzsching B, Falk CS, Filser A, et al. Reduced suppressive effect of CD4+CD25high regulatory T cells on the T cell immune response against myelin oligodendrocyte glycoprotein in patients with multiple sclerosis. Eur J Immunol. 2005 Nov;35(11):3343–52.
21. Salou M, Nicol B, Garcia A, Laplaud D-A. Involvement of CD8(+) T Cells in Multiple Sclerosis. Front Immunol. 2015;6:604.
22. Lehmann-Horn K, Kronsbein HC, Weber MS. Targeting B cells in the treatment of multiple sclerosis: recent advances and remaining challenges. Ther Adv Neurol Disord [Internet]. 2013 May;6(3):161–73. Available from: https://pubmed.ncbi.nlm.nih.gov/23634189
23. Gharibi T, Babaloo Z, Hosseini A, Marofi F, Ebrahimi-Kalan A, Jahandideh S, et al. The role of B cells in the immunopathogenesis of multiple sclerosis. Immunology. 2020 Aug;160(4):325–35.
24. Genain CP, Cannella B, Hauser SL, Raine CS. Identification of autoantibodies associated with myelin damage in multiple sclerosis. Nat Med. 1999 Feb;5(2):170–5.
25. Blauth K, Soltys J, Matschulat A, Reiter CR, Ritchie A, Baird NL, et al. Antibodies produced by clonally expanded plasma cells in multiple sclerosis cerebrospinal fluid cause demyelination of spinal cord explants. Acta Neuropathol [Internet]. 2015/10/28. 2015 Dec;130(6):765–81. Available from: https://pubmed.ncbi.nlm.nih.gov/26511623
26. Brennan KM, Galban-Horcajo F, Rinaldi S, O'Leary CP, Goodyear CS, Kalna G, et al. Lipid arrays identify myelin-derived lipids and lipid complexes as prominent targets for oligoclonal band antibodies in multiple sclerosis. J Neuroimmunol. 2011 Sep;238(1–2):87–95.
27. de Bock L, Somers K, Fraussen J, Hendriks JJA, van Horssen J, Rouwette M, et al. Sperm-associated antigen 16 is a novel target of the humoral autoimmune response in multiple sclerosis. J Immunol. 2014 Sep;193(5):2147–56.
28. Weber MS, Hemmer B. Cooperation of B cells and T cells in the pathogenesis of multiple sclerosis. Results Probl Cell Differ. 2010;51:115–26.
29. Waisman A, Johann L. Antigen-presenting cell diversity for T cell reactivation in central nervous system autoimmunity. J Mol Med (Berl). 2018 Dec;96(12):1279–92.
30. Pierce SK, Morris JF, Grusby MJ, Kaumaya P, van Buskirk A, Srinivasan M, et al. Antigen-presenting function of B lymphocytes. Immunol Rev. 1988 Dec;106:149–80.
31. Harp CT, Lovett-Racke AE, Racke MK, Frohman EM, Monson NL. Impact of myelin-specific antigen-presenting B cells on T cell activation in multiple sclerosis. Clin Immunol. 2008 Sep;128(3):382–91.
32. Duddy ME, Alter A, Bar-Or A. Distinct profiles of human B cell effector cytokines: a role in immune regulation? J Immunol. 2004 Mar;172(6):3422–7.
33. Korn T, Mitsdoerffer M, Croxford AL, Awasthi A, Dardalhon VA, Galileos G, et al. IL-6 controls Th17 immunity in vivo by inhibiting the conversion of conventional T cells into Foxp3+ regulatory T cells. Proc Natl Acad Sci U S A. 2008 Nov;105(47):18460–5.

34. Shen P, Fillatreau S. Antibody-independent functions of B cells: a focus on cytokines. Nat Rev Immunol. 2015 Jul;15(7):441–51.
35. Fillatreau S, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. Nat Immunol. 2002 Oct;3(10):944–50.
36. Wang R-X, Yu C-R, Dambuza IM, Mahdi RM, Dolinska MB, Sergeev Y V, et al. Interleukin-35 induces regulatory B cells that suppress autoimmune disease. Nat Med. 2014 Jun;20(6):633–41.
37. Bjarnadóttir K, Benkhoucha M, Merkler D, Weber MS, Payne NL, Bernard CCA, et al. B cell-derived transforming growth factor-β1 expression limits the induction phase of autoimmune neuroinflammation. Sci Rep. 2016 Oct;6:34594.
38. Goldenberg MM. Multiple sclerosis review. P T [Internet]. 2012 Mar;37(3):175–84. Available from: https://pubmed.ncbi.nlm.nih.gov/22605909

Article topic: **Antipsychotic Drugs.**

Author: Ahmad Aljbali.

Editor: Yazan S. Al-Zamer.

Reviewer: Omar Jbarah, Hassan Abushukair.

***keywords**: psychosis, schizophrenia, depression.*

Overview

History

The history of the concept of psychosis is stemmed from the time it was referred to in 1845 to the present day. within a time, it had become synonymous (scientifically not true) with the two terms "psychopathy" and "psychoneurosis". Soon, all psychiatric disorders became subsumed under its umbrella heading amidst a confusing set of terminology. Psychosis is examined as it then became distinct from psychopathy and neurosis.[1]

Pathophysiology

Based on the dopamine hypothesis that the dopamine pathway changes may result in signs and symptoms of psychosis. As we know the dopamine may be found as a chemical substance or act as neurotransmitters in CNS (the important one). So the dopamine is the messenger between the sender and receiver structures inside the CNS that have receptors for that neurotransmitter. Dopamine receptors may be inhibitory or excitatory. And this theory has its pros and cons and even that the pathophysiology is not well understood generally.

Psychosis (disease)

Psychosis is an abnormal condition of the mind (mental) that results in difficulties determining what is real and what is not real. Symptoms may include delusions and hallucinations. Other symptoms may be incoherent speech and behavior that is inappropriate for the situation. There may also be sleep problems, social withdrawal, lack of motivation, and difficulties carrying out daily activities. Then Psychosis can have serious outcomes.[2]

Causes

Psychosis has different causes. These include mental illness, such as schizophrenia or bipolar disorder, sleep deprivation, some medical conditions, certain medications, and drugs such as alcohol or cannabis. One type, known as postpartum psychosis, can occur after giving birth (concomitant with conditions). The neurotransmitter dopamine is believed to play a role (dopamine hypothesis). [2] Psychosis may be considered primary if it results from a psychiatric condition and secondary if it is caused by a medical condition.[2]

Diagnosis

The diagnosis of a mental illness requires excluding other potential causes. Testing may be done to check for central nervous system diseases, toxins, or other health problems as a cause.[2]

Treatment

Here the topic which we will focus on may include antipsychotic medication, counseling, and social support (essential role). Early treatment appears better to improve outcomes. Medications appear to have a moderate effect, so they are not only the choice. Outcomes depend on the causes.[2]

Pharmacology of psychotic drug

The antipsychotic drugs (also called neuroleptics or major tranquilizers) are used basically to treat schizophrenia, but they are also effective in other psychotic and manic (agitated) states. So, these drugs are able to reduce psychotic symptoms in a wide variety of conditions, including schizophrenia, bipolar disorder, psychotic depression, senile psychosis, various organic psychosis, and drug-induced psychosis.[3]

They are not curative and do not eliminate chronic thought disorders, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment. [3]

The antipsychotic drugs are divided into first- (Typical, Classic, conventional, or traditional antipsychotics) and second-generation (atypical, or newer antipsychotics) agents. The first-generation drugs are further classified as “low potency” or “high potency”. This classification does not indicate the clinical effectiveness of the drugs but rather specifies affinity for the dopamine D2 receptor, which, in turn, may influence the adverse effect profile of the drug.[4]

In more details about the generations of the antipsychotic drugs:[4]

The first generation

They are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopaminergic D2 receptors. These antipsychotics are classified as high-potency, mid-potency, or low-potency based on their potency for the D2 receptor.

First-generation antipsychotics are more likely to be associated with movement disorders (like side effects) known as extrapyramidal symptoms (EPS, or extrapyramidal side effects), particularly drugs that bind tightly to dopaminergic neuroreceptors, such as haloperidol and other examples.

Examples of first-generation are Chlorpromazine, Haloperidol, and Fluphenazine. We know that each drug has its own mechanism of action, therapeutic uses, and adverse effects. So that we will discuss briefly them.

The second generation

They have a lower incidence of EPS than the first-generation agents but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain. The second-generation drugs owe their unique activity to blockade of both serotonin and dopamine and other receptors. The Second-generation agents are used as first-line therapy for schizophrenia to minimize the risk of debilitating EPS associated with the first-generation drugs that act primarily at the dopamine D2 receptor.

The second-generation antipsychotics exhibit an efficacy that is equivalent to and may exceed, that of the first-generation antipsychotic agents. Examples of some drugs are in figure (1).

Figure (1) Examples of some antipsychotic drugs.

Mechanism of action

Mechanism of action of antipsychotics is exerted at a variety of receptors such as dopamine, serotonin, and others.

Dopamine antagonism

Dopamine hypothesis- The dopamine hypothesis proposes that the disorder is caused by a relative excess of activity of the neurotransmitter dopamine in specific neuronal tracts in the brain. So, all of the first-generation and most of the second-generation antipsychotic drug's block D2 dopamine receptors in the brain and the periphery.[4]

Remember that the dopamine pathways in the brain are fives pathways: [5]

1. The first pathway—the one most closely related to behavior and psychosis—is the **mesolimbic-mesocortical pathway** which projects from cell bodies in the ventral tegmentum in separate bundles of axons to the limbic system and neocortex.

Note that each pathway has its own beginning and ending inside the brain.

2. The second pathway—**the nigrostriatal pathway**— blocking of the D2 receptors in the nigrostriatal pathway is responsible for EPS.

3. The third pathway is **the tuberoinfundibular pathway** that the Dopamine released by these neurons physiologically inhibits prolactin secretion from the anterior pituitary.

4. The fourth pathway is **the medullary-periventricular pathway** that may be involved in eating behavior.

5. The fifth pathway is the **incertohypothalamic** pathway.

Serotonin receptor–blocking activity: [6]

Most of the second-generation agents appear to exert part of their unique action through inhibition of **serotonin receptors** (**5-HT**), particularly **5-HT2A receptors**.

Therapeutic uses [4]

1. Treatment of schizophrenia: The antipsychotics are considered the only efficacious pharmacological treatment for schizophrenia specifically.

2. Prevention of nausea and vomiting: Older antipsychotics are useful in the treatment of drug-induced nausea.

3. Other uses: Antipsychotic drugs can be used as tranquilizers (major tranquilizers) to manage agitated and disruptive behavior secondary to other disorders.

Absorption and metabolism [3]

After oral administration, the antipsychotics show variable absorption that is unaffected by food and these agents readily pass into the brain and have a large volume of distribution. They are metabolized to many different metabolites, usually by the cytochrome P450 system in the liver.

Adverse effects [3][4][7]

Adverse effects of antipsychotic drugs can occur in all patients and are significant in about 80%.

- Extrapyramidal effects

The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects.

- Neuroleptic malignant syndrome

This potentially fatal reaction to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia.

- Tardive dyskinesia (TD)

Long-term treatment with antipsychotics can cause this motor disorder. Patients display involuntary movements, including bilateral and facial jaw movements and “fly-catching” motions of the tongue. A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear within a few months.

- Other effects

Drowsiness occurs due to CNS depression and antihistaminic effects, usually during the first few weeks of treatment. Confusion sometimes results and so on.

References

[1] Beer MD. Psychosis: A history of the concept. Compr Psychiatry 1996;37:273–91. https://doi.org/10.1016/S0010-440X(96)90007-3.
[2] wikipedia. Psychosis n.d. https://en.wikipedia.org/wiki/Psychosis.
[3] Katzung BG. Basic & Clinical Pharmacology, Fourteenth Edition. 2018.
[4] Nurul mas’ud waqiah. Lippincott Illustrated Reviews Pharmacology, 6th edition. vol. 53. 2013.
[5] All G, Stuff T, You T, Online CG. katzung-pharmacology-12thedition. n.d.
[6] All G, Stuff T, You T, Online CG. Katzung_&_Trevor’s_Pharmacology_Examination_and_Board_Review,_11th. n.d.
[7] All G, Stuff T, You T, Online CG. USMLE Step 1 Lecture Notes - Pharmacology n.d.

Article topic: Autonomic Nervous System.

Author: Ayah Bani Mustafa.

Editor: Yazan S. Al-Zamer.

Reviewer: Ethar Hazaimeh.

Keywords: Autonomic, Sympathetic, Parasympathetic, Enteric Nervous System.

Overview

The nervous system is divided into the central nervous system (CNS) and peripheral nervous system; the latter is also divided into the afferent and efferent nervous system; the autonomic nervous system (ANS) is a part of the efferent system. The autonomic nervous system transmits electrical impulses through nerve fibers that terminate at effector cells (most body organs), exerting a variety of effects specific to different organs. The autonomic outputs may be divided into the sympathetic, parasympathetic, or enteric systems.

ANS regulates many everyday requirements of vital body functions (including heart rate, blood pressure, respiration, digestion, gland secretions, urination, and sexual arousal) without consciousness, Because of the involuntary nature of the ANS and its functions, it is also known as the visceral, vegetative, or involuntary nervous system.

Anatomy and position of ganglia and fibers:

The sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) contain both are composed of:

- Afferent neurons: which transmit sensory input by cranial nerves toward the CNS (hypothalamus/brainstem and spinal cord mainly). this input is analyzed, and a response is made out by the transmission of nerve signals that influence the activity of efferent neurons (specifically preganglionic nerve) of the system. (1) It is an important part of the reflex regulation of the ANS.
- Efferent neurons: which is the motor output of the system, the autonomic nervous system transmits its nerve impulses from the central nervous system to the effector organs by two means: the preganglionic neuron's fibers and the postganglionic neuron's fibers. The cell body of the preganglionic neuron is in the CNS, emerging out from either the brainstem/spinal cord (specifically from the lateral horn of the gray matter) and it makes a synapse in ganglia (which is an aggregation of a large number of nerve cells found outside the central nervous system), its functions include the transmission of signals from the preganglionic neurons to the postganglionic neurons. The postganglionic neuron, leaving out

from the ganglia, innervates the effector tissue, it is a nonmyelinated neuron and terminates in effector tissue making a neuro-effector junction, where the axons of these nerve fibers enter a specific tissue, they end up in a number of swellings known as varicosities. When neurons are stimulated by any means, these varicosities release specific neurotransmitters along the whole length of the axon and over a large area in the target organ. The neurotransmitter diffuses and binds to its specific receptors that are located in the target tissues. This diffused type of release of neurotransmitters affects many tissue cells at the same time. (1)(2) preganglionic neurons of both divisions of the ANS (the SNS and PNS) release acetylcholine (ACh) as their neurotransmitter. Postganglionic sympathetic neurons release norepinephrine (NE) as their effector neurotransmitter to affect target organs or they could release epinephrine, while postganglionic parasympathetic neurons release Acetylcholine as their only neurotransmitter. (2)

The efferent ANS is also divided:

1. Sympathetic neurons: The sympathetic and parasympathetic neurons both emerge from the CNS and start from two different spinal cord origins. The preganglionic neurons of the sympathetic system origins extend all the way from the thoracic and lumbar regions (T1 to L2) of the spinal cord, and they make a junction in two chains of ganglia, preganglionic neurons of the sympathetic system are highly branched allowing each preganglionic neuron to interact and connect with multiple postganglionic neurons, which usually functions as one unit. The preganglionic neurons are short in comparison to the postganglionic ones. neurons of the postganglionic neuron extend from these ganglia to the target tissues that they innervate. The adrenal medulla (considered ganglia–like) receives preganglionic neuron fibers and responds to stimulation by releasing epinephrine (mostly) or norepinephrine directly into the blood. The sympathetic nervous system mediates a ‘fight or flight reaction. Postganglionic sympathetic neurons release Norepinephrine that acts on adrenergic receptors in the target tissue. The subtype of the receptor, alpha-1, alpha-2, beta-1, beta-2, or beta-3. The effect is to increase heart rate and blood pressure, to mobilize energy stores of the body to produce free energy, and to increase blood flow to skeletal muscles and the heart while reducing blood flow to the skin and internal organs. Sympathetic stimulation mediates the dilation of the pupils and the bronchioles. It also reduces GI motility and the function of the bladder and sexual organs (2). It also increases renin secretion from the kidney leading to increased intravascular volume (3)

2. Parasympathetic neurons: The parasympathetic preganglionic fibers originate from cranial nerves III, VII, IX, and X and from the sacral region (S2 to S4) of the spinal cord and junction in ganglia near/on the effector organs. Thus, in contrast to the sympathetic neurons, the preganglionic neurons are longer in comparison to the postganglionic ones. Since the preganglionic nerve is not branched, it can make a one-to-one connection

between preganglionic and postganglionic neurons, allowing a more discrete response for every neuron. The parasympathetic nervous system mediates a ‘rest or digest ‘reaction. This is required for maintaining life, since it maintains essential bodily functions, such as digestion and elimination of wastes, promotes cardiac relaxation, promote salivation, contraction of eye muscles, constriction, and increased secretion of trachea and bronchioles, and increased motility of the gastrointestinal tract. Postganglionic parasympathetic neurons release Acetylcholine that acts on muscarinic and nicotinic receptors, each with various subunits: M1, M2, M3, and N1, N2(for sweat glands innervations). (2)

3. Enteric neurons: It is an intrinsic collection of nerve fibers that entirely innervate the gastrointestinal (GI) tract, plus the pancreas, and gallbladder, also known as the “brain of the gut.” It is made of two plexuses 1) the myenteric (Auerbach) plexuse and 2) the submucosal (Meissner) plexuse. (2) The enteric nervous system all originate from neural crest cells (4). This system works independently of the CNS and regulates the functions of motility, exocrine and endocrine secretions, and microcirculation of the GI tract. It is regulated by both the sympathetic and parasympathetic nervous systems.

Most body organs are innervated by both the sympathetic and parasympathetic systems. Usually, one system effect is dominating over the other. This organization is finely tuned to regulate the homeostatic function of the body. The exceptions are the adrenal medulla, kidney, sweat gland, poliomotor muscle, which are innervated only by the sympathetic nervous system.

References

1)(*Physiology of the Autonomic Nervous System*, n.d.)
2)(Anatomy, n.d.)
3)(*Neuroanatomy, Sympathetic Nervous System*, n.d.)
4)(*The Enteric Nervous System*, n.d.)
5) *Lippincott illustrated reviews ,pharma 6th edition , unit 2 , chapter 6*

Article Topic: Synthesis of Adrenergic Neurotransmitters

Author: Osama Khaldoun Batiha

Editors: Yazan S. Al-Zamer.

Reviewer: Ethar Hazaimeh.

Keywords: Catecholamines, Neurotransmitter, synapse.

Overview

Adrenergic neurotransmitters are catecholamines compounds (They are called catecholamines because of the catechol group in their structures) and it divides into epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine. Catecholamines act both as neurotransmitters and hormones vital to the maintenance of homeostasis through the autonomic nervous system [1].

These Neurotransmitters are secreted from postganglionic nerve fiber in a junction called a synapse (the site of transmission of the electrical impulses between two nerve cells (neurons) or between a neuron and a gland or muscle cell (effector)) [2]. The adrenergic receptors are targets of catecholamines, many cells in the body have these receptors and the binding to them will stimulate the sympathetic nervous system (SNS).

Adrenergic neurotransmitter life cycle (pathway)

Norepinephrine (NE) is the primary neurotransmitter for postganglionic sympathetic adrenergic nerves. It is synthesized inside the nerve axon, stored within vesicles, and then released by the nerve, once the action potential arrives, calcium influx happens, and NE is released. Below are the details for the release and synthesis of NE:

The amino acid tyrosine is transported into the sympathetic nerve axon and then Tyrosine (Tyr) is converted to DOPA by tyrosine hydroxylase (rate-limiting step for NE synthesis). DOPA is converted to dopamine in the cytoplasm by dopa-decarboxylase. Now depending on the type of the nerve the dopamine can be converted either to NE or Epi by beta-hydroxylase,

if the neuron is norepinergic, dopamine will be converted to norepinephrine but if the neuron is dopaminergic the dopamine will not be converted, and it will stay in the vesicle. An action potential traveling down, the axon depolarizes the membrane and causes calcium to enter the axon, increased intracellular calcium causes the vesicles to

migrate to the axonal membrane (The vesicular monoamine transporter (VMAT) is a transport protein and its function in loading the neurotransmitters into transport vesicles) and fuse with the membrane, which permits the NE to diffuse out of the vesicle into the extracellular (junctional) space and then The NE binds to the postjunctional receptor and stimulates the effector organ response[3]. It can also bind to the receptor in the presynaptic neuron (alpha 2 receptor) which is responsible for the negative feedback inhibition of a further release of NE, and it can also be engulfed back to the presynaptic neuron by sodium chloride dependent norepinephrine transporter (NET) for future use.

Epinephrine Synthesis and Release

Epinephrine (Epi) is produced in the adrenal medulla, where the amino acid tyrosine is transformed through a series of reactions to norepinephrine. An enzyme known as phenylethanolamine N-methyltransferase, which is found in the chromaffin cells of the adrenal medulla, catalyzes the methylation of norepinephrine to epinephrine. In addition to the release of epinephrine from the adrenal glands, small amounts of the Epi are also released from the ends of sympathetic nerves[4]. Adrenal medulla secretions are 80% Epi and 20% NE.

Deactivation

They may diffuse to the liver and get deactivated by MAO (monoamine oxidase) or reuptaken by COMT (catechol methyltransferase) in the postsynaptic membrane and return to packaging in vesicles.

References

[1] (Paravati, Rosani, & Warrington., Physiology, Catecholamines, n.d.)
[2] The Editors of Encyclopaedia Britannica, Synapse Anatomy, Britannica.
[3] Richard E. Klabunde, Norepinephrine, Epinephrine, and Acetylcholine - Synthesis, Release, and Metabolism, Cardiovascular Pharmacology Concepts
[4] Kara Rogers, Epinephrine hormone, Britannica.

Article topic: Parkinson's Disease.

Author: Kafa Al-Zoubi.

Editors: Yazan S. Al-Zamer.

Reviewer: Ethar Hazaimeh.

***Keywords**: Parkinson's disease (PD), PARK7 (Parkinsonism Associated Deglycase), LRRK2 (leucine-rich repeat kinase 2), PINK1 (PTENinduced putative kinase 1), SNA (alpha-synuclein).*

Overview

Parkinson’s disease (PD) is a chronic progressive neurodegenerative movement disease with early prominent death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) (1), The second most common disease of neurodegeneration after Alzheimer’s disease is Parkinson's disease (2). The disease was first identified in 1817 by a British physician named James Parkinson who described it in "An Essay on the Shaking Palsy"(3).

Because of the dopamine deficit in the basal ganglia lead to movement disorder (4). PD is characterized by four cardinal signs, resting tremor, rigidity, bradykinesia, and postural instability, and they are all motor symptoms (5). PD also involves nonmotor symptoms such as depression, sleep disturbances, and orthostatic hypotension (6). It is associated with severe disability and a negative impact on quality of life.

The prevalence of PD is 0.3% in the general population, 1.0% in people older than 60 years, and 3.0% in people older than 80 years, and incidence rates of PD are estimated to range between 8 and 18 per 100,000 person-years (7). Most Parkinson's disease cases are sporadic, with just 10% of patients having a disease-causing genetic mutation. There are significant sex-related differences in epidemiological and clinical characteristics of the disease (8). Men are twice as likely as women to develop Parkinson's disease(9), but women have a higher mortality rate and a rapid disease progression(10).In addition, as compared to men, women show different symptoms as well as differences in response to pharmacological treatments and deep brain stimulation procedures, as well as in personal assessments of the quality of life(11).

Etiology

PD is a multifactorial disorder that involves both genetic and environmental factors. Around 80% of people with Parkinson's disease are considered idiopathic, while the remaining 20% are genetic (12). The most important risk factor for Parkinson's disease is age, with the median age of onset being 60 years old (13).

Environmental factors

- **Cigarette smoking**

Several studies demonstrate that there is an inverse association between smoking and PD (14). They also observed an inverse relationship between the number of pack-years, years of smoking, and the risk of PD. Compared to nonsmokers, heavy or long-term smokers have a significantly lower chance of developing Parkinson's disease (15). The reasons underlying this association are not well understood. But activation of nicotinic acetylcholine receptors on dopaminergic neurons by nicotine or selective agonists is neuroprotective in experimental models of PD (16).

- **Caffeine**

It has been reported that coffee drinkers have a 25% lower chance of developing PD (17). Caffeine is an adenosine receptor antagonist, which is believed to be protective in PD (18). This association is weak in females because estrogen competitively inhibits caffeine metabolism and in post-menopausal women that depend on hormone replacement therapy (19).

- **Pesticides, herbicides, and heavy metals**

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is metabolized into the neurotoxin, MPP+ (1-methyl-4-phenylpyridinium) which is a mitochondrial complex-I inhibitor that selectively destroys dopaminergic cells in the substantia nigra (20). The discovery of MPTP as a cause of nigral degeneration led to the hypothesis that PD could be caused by an environmental toxin such as Paraquat (an herbicide) and rotenone (a pesticide) are also selective complex-I inhibitors and induce dopaminergic depletion in animal models of PD (21).

Genetics factor

- **Autosomal recessive**

Parkin (PARK2) was the first gene detected that causes an early-onset autosomal recessive type of PD before 40 years old (22). It is located on chromosome 6q25.2–q27

and encodes an E3 ubiquitin ligase involved in the cellular ubiquitination-protein degradation pathway (23). Because of this gene mutation leading to loss of function of the protein, impacting many different pathways, including the ubiquitin-proteasome system degradation pathway, oxidative/dopaminergic stress, and mitochondrial function. In addition, it does not associate with the Lewy body (24).

PINK1 (PARK6) encodes 581-amino acid protein which includes a mitochondrial-targeting motif and a highly conserved protein kinase domain with homology to the serine/threonine kinases of the calcium/calmodulin family (25). PINK1 is steady on mitochondria with lower membrane potential, and it recruits Parkin from the cytosol Parkin becomes enzymatically active and initiates the autophagic clearance of mitochondria through lysosomes (26).

- **Autosomal dominant**

SNCA (PARK1–4), the gene encoding for a-synuclein, was the first gene related to autosomal-dominant Parkinson's disease and A53T was the first pathogenic SNCA mutation detected (27) that result in a higher inclination to a-synuclein to misfolded and aggregate. Other pathogenic mutations affect the quantity of a-synuclein (either through duplications or triplications) and alter its post-transcriptional modifications or its interaction with other cellular organelles and transport systems (7).

LRRK2 (PARK8) mutations are the most known cause of late-onset autosomal-dominant and encode the 2527-amino acid (28). It contains The LRRK2 protein contains putative GTPase, protein kinase, WD40 repeat, and leucine-rich repeat (LRR) domains of unidentified functions (29). LRRK2 mutations are associated with dopaminergic neuronal loss and gliosis in the substantia nigra (30).

Pathogenesis

The main pathological features of PD are the absence of dopaminergic neurons followed by depigmentation of the SNpc and the presence of LB. LBs are intraneuronal, round, eosinophilic inclusions with a hyaline core and a pale peripheral halo that contains more than 90 proteins a-synuclein and ubiquitin (31)(32).

Oxidative stress

Oxidative stress has obtained the most attention in PD due to the capacity of the oxidative metabolism of dopamine to yield hydrogen peroxide (H_2O_2) and other reactive oxygen species (33). Oxidant stress and consequent cell death could develop in the SNc underneath circumstances in which there are elevated dopamine turnover, leading to excess peroxide formation, a deficiency in glutathione (GSH), thereby

diminishing the brain's capability to clean H2O, or an increase in reactive iron, that may promote OH formation (34).

Studies have confirmed that iron levels are elevated inside the substantia nigra of PD patients, and it accumulates mostly within neuromelanin granules of dopaminergic neurons (33). How iron accumulates inside the SNc in PD is not recognized. Elevated lactoferrin receptors were detected on nigral neurons in PD patients and can account for preferential accumulation of iron inside those cells (35). It is not clear if iron accumulation in PD is primary or secondary. In addition, elevated SNc iron has been observed following MPTP treatment or 6-hydroxydopamine (6-OHDA) lesions. These results indicate that iron may accumulate secondary to cell degeneration caused by many factors and still cause cell death (36).

In Parkinson's disease, a deficiency in one or more of the antioxidant defenses could lead to neurodegeneration (37). Reduction in GSH can inhibit H2O2 clearance and promote OH formation in the presence of elevated iron. The cause of GSH deficiency in PD is unclear (33).

There is an elevated in the level of γ -glutamyltranspeptidase (γ -GTT), the enzyme responsible for the translocation of glutathione precursors and metabolism of the oxidized form of glutathione and this is elevation may reflect an attempt by surviving cells to recruit glutathione precursors into the cell to replenish reduced levels of GSH or a compensatory mechanism to remove potentially toxic GSSG produced as a consequence of oxidant stress(38).

There is evidence of oxidative damage in the brains of PD patients. The lipid peroxidation products malondialdehyde (MDA) and lipid hydroperoxide have been found higher in the SNc of PD patients, but not in the cerebellum (39). In surviving dopaminergic neurons, increased staining for 4-hydroxynonenal, a product of lipid peroxidation that can modify proteins and induce cell toxicity (40). Increased amounts of protein carbonyls and 8-hydroxy-2-deoxyguanosine, which indicate oxidative damage to proteins and DNA, have also been discovered in the SNc and other brain regions of PD patients (41).

Mitochondrial Dysfunction

Studies demonstrated that in the SNc of PD patients there is a reduction in complex I function of the mitochondrial respiratory chain for unclear reasons (42). A mitochondrial complex I defect could lead to cell degeneration in PD through reduced ATP synthesis and a bioenergetic defect. A mitochondrial complex I defect could also lead to cell damage through free radicals generated directly on-site or as a result of a compensatory increase in respiration at complex II. A complex I defect can also play a role in the onset of apoptosis. Since complex I is the primary site of proton pumping, a

complex I defect in PD could cause neuronal weakness and apoptosis. A reduction in the mitochondrial membrane potential caused by defective proton pumping can lead to the opening of a mitochondrial permeability transition pore and the release of small mitochondrial proteins that signal for the decrease in mitochondrial membrane potential caused by defective proton pumping may result in the opening of a mitochondrial permeability transfer pore and the release of small mitochondrial proteins that signal the beginning of apoptosis(33).

Neuroinflammatory markers

Neuroinflammation is the CNS's inflammatory reaction to toxic stimuli, which disrupts neuronal homeostasis and leads to a variety of neurological disorders (43)**.** Neuroinflammation in PD arises alongside the loss of dopaminergic neurons and is related to altered microglia activity in of CNS and other parts. Recent studies have found the presence of activated microglia either inside substantia nigra (SN) and putamen of patients with a PD prognosis (44). After activating microglia, tumor necrosis factor (TNF-) releases a variety of free radicals and activates many genes and proteins, including iNOS and proinflammatory cytokines (IL-1β, IL-6, and α) (45).

Overexpression of the central immune system may compromise the production of neurotrophic factors and cytotoxic factors from the microglia cell. IL-1β family of cytokines that is a pro-inflammatory molecule also activates toll-like receptors (TLRs), which may disrupt the clearance of microglia. studies show that disrupting IRAK-4 (interleukin-1 receptor-associated kinase 4), an essential downstream kinase of TLRs and receptors for IL-1β, moves microglia cells from a pro-inflammatory phenotype toward an anti-inflammatory phenotype (46).

References

1. Beitz JM. Parkinson's disease: a review. Front Biosci (Schol Ed). 2014 Jan;6:65–74.
2. Sherer TB, Chowdhury S, Peabody K, Brooks DW. Overcoming obstacles in Parkinson's disease. Mov Disord. 2012 Nov;27(13):1606–11.
3. Hayes MT. Parkinson's Disease and Parkinsonism. Am J Med. 2019 Jul;132(7):802–7.
4. Kalia LV, Lang AE. Parkinson's disease. Lancet (London, England). 2015 Aug;386(9996):896–912.
5. Earhart GM, Falvo MJ. Parkinson's disease and exercise. Compr Physiol. 2013 Apr;3(2):833–48.
6. Lew M. Overview of Parkinson's disease. Pharmacotherapy. 2007 Dec;27(12 Pt 2):155S-160S.
7. Balestrino R, Schapira AH V. Parkinson disease. Eur J Neurol. 2020 Jan;27(1):27–42.
8. Cerri S, Mus L, Blandini F. Parkinson's Disease in Women and Men: What's the Difference? J Parkinsons Dis. 2019;9(3):501–15.
9. Baldereschi M, Di Carlo A, Rocca WA, Vanni P, Maggi S, Perissinotto E, et al. Parkinson's disease and parkinsonism in a longitudinal study: two-fold higher incidence in men. ILSA Working Group. Italian Longitudinal Study on Aging. Neurology. 2000 Nov;55(9):1358–63.
10. Dahodwala N, Shah K, He Y, Wu SS, Schmidt P, Cubillos F, et al. Sex disparities in access to caregiving in Parkinson disease. Neurology. 2018 Jan;90(1):e48–54.
11. Georgiev D, Hamberg K, Hariz M, Forsgren L, Hariz G-M. Gender differences in Parkinson's disease: A clinical perspective. Acta Neurol Scand. 2017 Dec;136(6):570–84.
12. Bhat S, Acharya UR, Hagiwara Y, Dadmehr N, Adeli H. Parkinson's disease: Cause factors, measurable indicators, and early diagnosis. Comput Biol Med. 2018 Nov;102:234–41.
13. Lees AJ, Hardy J, Revesz T. Parkinson's disease. Lancet (London, England). 2009 Jun;373(9680):2055–66.

14. Grandinetti A, Morens DM, Reed D, MacEachern D. Prospective study of cigarette smoking and the risk of developing idiopathic Parkinson's disease. Am J Epidemiol. 1994 Jun;139(12):1129–38.
15. Breckenridge CB, Berry C, Chang ET, Sielken RLJ, Mandel JS. Association between Parkinson's Disease and Cigarette Smoking, Rural Living, Well-Water Consumption, Farming and Pesticide Use: Systematic Review and Meta-Analysis. PLoS One. 2016;11(4):e0151841.
16. Bordia T, McGregor M, Papke RL, Decker MW, McIntosh JM, Quik M. The α7 nicotinic receptor agonist ABT-107 protects against nigrostriatal damage in rats with unilateral 6-hydroxydopamine lesions. Exp Neurol. 2015 Jan;263:277–84.
17. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson's disease. Ann Neurol. 2012 Dec;72(6):893–901.
18. Ross GW, Abbott RD, Petrovitch H, Morens DM, Grandinetti A, Tung KH, et al. Association of coffee and caffeine intake with the risk of Parkinson's disease. JAMA. 2000 May;283(20):2674–9.
19. Xu K, Xu Y, Brown-Jermyn D, Chen J-F, Ascherio A, Dluzen DE, et al. Estrogen prevents neuroprotection by caffeine in the mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. J Neurosci. 2006 Jan;26(2):535–41.
20. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science. 1983 Feb;219(4587):979–80.
21. Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov A V, Greenamyre JT. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nat Neurosci. 2000 Dec;3(12):1301–6.
22. Takahashi H, Ohama E, Suzuki S, Horikawa Y, Ishikawa A, Morita T, et al. Familial juvenile parkinsonism: clinical and pathologic study in a family. Neurology. 1994 Mar;44(3 Pt 1):437–41.
23. Lopez G, Sidransky E. Autosomal recessive mutations in the development of Parkinson's disease. Biomark Med. 2010 Oct;4(5):713–21.
24. Xiong H, Wang D, Chen L, Choo YS, Ma H, Tang C, et al. Parkin, PINK1, and DJ-1 form a ubiquitin E3 ligase complex promoting unfolded protein degradation. J Clin Invest. 2009 Mar;119(3):650–60.
25. Valente EM, Salvi S, Ialongo T, Marongiu R, Elia AE, Caputo V, et al. PINK1 mutations are associated with sporadic early-onset parkinsonism. Ann Neurol. 2004 Sep;56(3):336–41.
26. Youle RJ, Narendra DP. Mechanisms of mitophagy. Nat Rev Mol Cell Biol. 2011 Jan;12(1):9–14.
27. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997 Jun;276(5321):2045–7.
28. Klein C, Westenberger A. Genetics of Parkinson's disease. Cold Spring Harb Perspect Med. 2012 Jan;2(1):a008888.
29. MacLeod D, Dowman J, Hammond R, Leete T, Inoue K, Abeliovich A. The familial Parkinsonism gene LRRK2 regulates neurite process morphology. Neuron. 2006 Nov;52(4):587–93.
30. Singleton AB, Farrer MJ, Bonifati V. The genetics of Parkinson's disease: progress and therapeutic implications. Mov Disord. 2013 Jan;28(1):14–23.
31. Wakabayashi K, Tanji K, Odagiri S, Miki Y, Mori F, Takahashi H. The Lewy body in Parkinson's disease and related neurodegenerative disorders. Mol Neurobiol. 2013 Apr;47(2):495–508.
32. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. Vol. 388, Nature. England; 1997. p. 839–40.
33. Olanow CW, Tatton WG. Etiology and pathogenesis of Parkinson's disease. Annu Rev Neurosci. 1999;22:123–44.
34. Halliwell B. Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. Plant Physiol [Internet]. 2006 Jun;141(2):312–22. Available from: https://pubmed.ncbi.nlm.nih.gov/16760481
35. Faucheux BA, Nillesse N, Damier P, Spik G, Mouatt-Prigent A, Pierce A, et al. Expression of lactoferrin receptors is increased in the mesencephalon of patients with Parkinson disease. Proc Natl Acad Sci U S A. 1995 Oct;92(21):9603–7.
36. Kienzl E, Puchinger L, Jellinger K, Linert W, Stachelberger H, Jameson RF. The role of transition metals in the pathogenesis of Parkinson's disease. J Neurol Sci [Internet]. 1995;134:69–78. Available from: https://www.sciencedirect.com/science/article/pii/0022510X9500210S
37. Jenner P, Olanow CW. Oxidative stress and the pathogenesis of Parkinson's disease. Neurology. 1996 Dec;47(6 Suppl 3):S161-70.
38. Zeevalk GD, Manzino L, Sonsalla PK, Bernard LP. Characterization of intracellular elevation of glutathione (GSH) with glutathione monoethyl ester and GSH in brain and neuronal cultures: relevance to Parkinson's disease. Exp Neurol [Internet]. 2006/10/17. 2007 Feb;203(2):512–20. Available from: https://pubmed.ncbi.nlm.nih.gov/17049515
39. Dexter DT, Wells FR, Lees AJ, Agid F, Agid Y, Jenner P, et al. Increased nigral iron content and alterations in other metal ions occurring in brain in Parkinson's disease. J Neurochem. 1989 Jun;52(6):1830–6.
40. Yoritaka A, Hattori N, Uchida K, Tanaka M, Stadtman ER, Mizuno Y. Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson disease. Proc Natl Acad Sci U S A [Internet]. 1996 Apr 2;93(7):2696–701. Available from: https://pubmed.ncbi.nlm.nih.gov/8610103
41. Alam ZI, Jenner A, Daniel SE, Lees AJ, Cairns N, Marsden CD, et al. Oxidative DNA damage in the parkinsonian brain: an apparent selective increase in 8-hydroxyguanine levels in substantia nigra. J Neurochem. 1997 Sep;69(3):1196–203.
42. Schapira AH, Cooper JM, Dexter D, Clark JB, Jenner P, Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. J Neurochem. 1990 Mar;54(3):823–7.
43. Vivekanantham S, Shah S, Dewji R, Dewji A, Khatri C, Ologunde R. Neuroinflammation in Parkinson's disease: role in neurodegeneration and tissue repair. Int J Neurosci. 2015;125(10):717–25.
44. Kaur R, Mehan S, Singh S. Understanding multifactorial architecture of Parkinson's disease: pathophysiology to management. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2019 Jan;40(1):13–23.

45. Shabab T, Khanabdali R, Moghadamtousi SZ, Kadir HA, Mohan G. Neuroinflammation pathways: a general review. Int J Neurosci. 2017 Jul;127(7):624–33.
46. Arcuri C, Mecca C, Bianchi R, Giambanco I, Donato R. The Pathophysiological Role of Microglia in Dynamic Surveillance, Phagocytosis and Structural Remodeling of the Developing CNS. Front Mol Neurosci. 2017;10:191.

Article Topic: Acquired Metabolic and Toxic Disturbances.

Author: Taqwa Haweeleh.

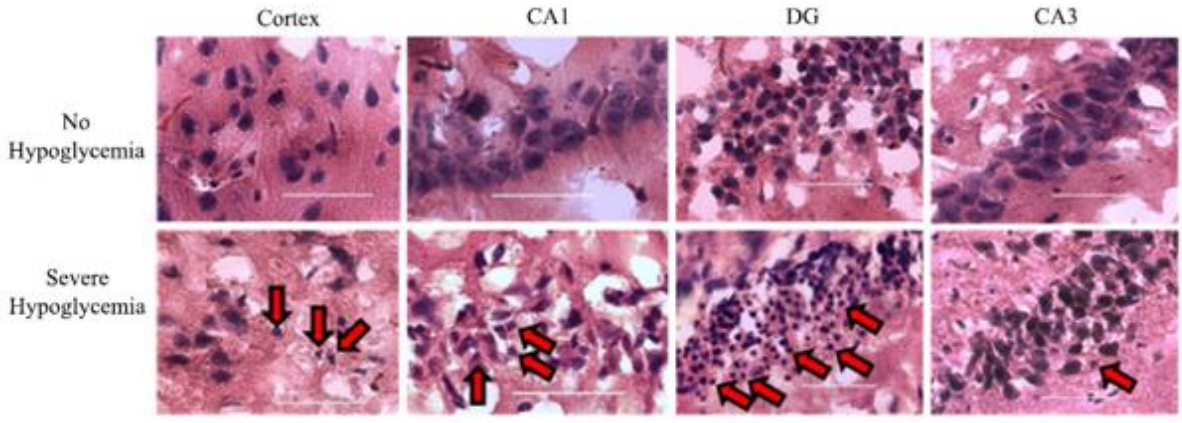
Editor: Yazan S. Al-Zamer.

Reviewer: Ethar Hazaimeh.

Keywords: hypoglycemia, brain damage, hyperglycemia, diabetes mellitus, diabetes, hyperglycemic hyperosmolar syndrome, HHS, ketoacidosis, diabetic ketoacidosis, hepatic encephalopathy.

Hypoglycemia

Insulin secretion from pancreatic β cells is regulated depending on the body's glucose levels, insulin acts as a glucose sensor, the corollary being that insulin secretion is regulated to prevent hyperglycemia or hypoglycemia. Diabetic patients treated with insulin therapy are the most susceptible group of patients to hypoglycemia, whether it is type 1 or type 2, where type 1 occurs due to loss of the insulin-secreting β cells of the pancreas and type 2 occurs because of reduced response to insulin. Hypoglycemia is a medical condition in which the body's glucose falls below normal levels, and hyperglycemia is the opposite. Hypoglycemia can arise due to multiple causes other than diabetes such as starvation, kidney failure, liver disease, some tumors, severe infections, inborn errors of metabolism, and certain drugs including alcohol. Prolonged hypoglycemia is suspected to cause brain damage in the cortex and regions within the hippocampus depending on its severity. Rarely, extreme hypoglycemia causes brain death; animal studies revealed that neuronal death happens when blood glucose levels fall below 1 mM for an extended period, correlated with an isoelectric "flat line" EEG. 2. [2]



This figure shows the results of a study done on rats, the rats that did not undergo hypoglycemia in comparison to rats who underwent severe hypoglycemia. The rats that underwent severe

hypoglycemia developed brain damage in the cortex and certain regions in the hippocampus [CA1 and dentate gyrus (DG)], the cells' morphology revealed brain cells characterized by condensed shrunken morphology and pyknotic nuclei (red arrows) with eosinophilic staining.[3]

This figure shows the results of a study done on rats, the rats that did not undergo hypoglycemia in comparison to rats who underwent severe hypoglycemia. The rats that underwent severe hypoglycemia developed brain damage in the cortex and certain regions in the hippocampus [CA1 and dentate gyrus (DG)], the cells' morphology revealed brain cells characterized by condensed shrunken morphology and pyknotic nuclei (red arrows) with eosinophilic staining. [3]

Glucose is considered the most vital energy substrate in brain metabolism; the brain functions are consequently at risk when it is deprived of adequate glucose supplies. The brain is unable to synthesize glucose or store considerable amounts of glycogen in astrocytes, thus requiring a continuous supply of glucose from the circulation. In a healthy individual, counter-regulatory mechanisms protect the brain from the effects of hypoglycemia if a sudden fall in plasma glucose occurs, these autonomic counter-regulatory responses include the inhibition of insulin secretion and the sequential release of glucagon, epinephrine, norepinephrine, cortisol (ACTH), and growth hormone. However, patients who experience recurrent bouts of hypoglycemia may subsequently exhaust their counter-regulatory mechanisms giving them impaired, which makes detecting hypoglycemia by the body's autonomic system harder and causes states of hypoglycemia unawareness thereby endangering the brain. Brain glycogen stores can be used as a source of glucose under extreme hypoglycemia. However, one study concluded that glycogenolysis can account for most of the glucose deficit through the slow rates of glycogen depletion and its inability to provide adequate energy supplies in cases of prolonged hypoglycemia. [4] [5]

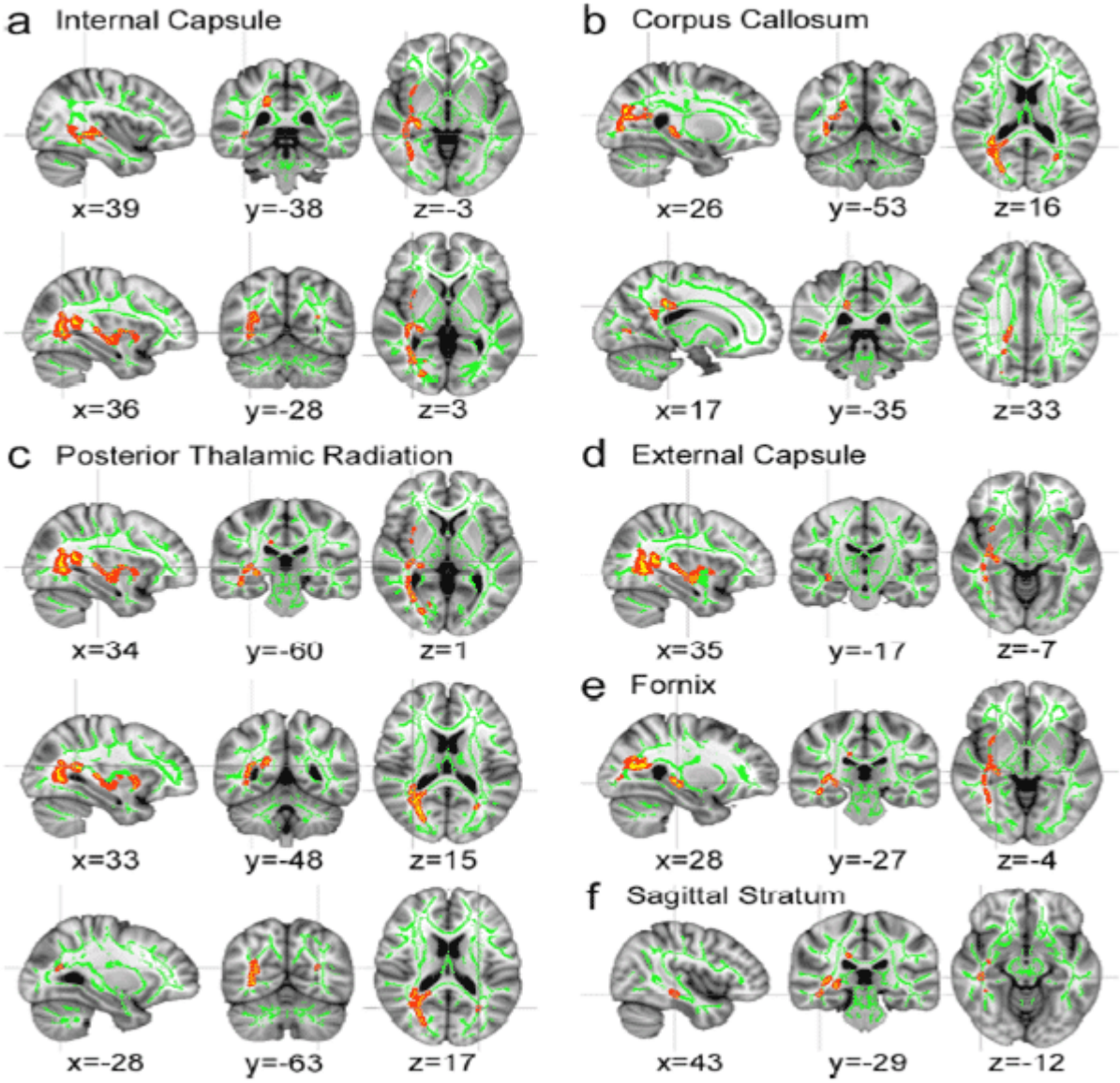
Mild hypoglycemia occurring in both healthy and diabetic patients can affect cognitive functions, cognitive impairment is associated with vascular changes in the brain causing symptoms such as reduced concentration, blunted short-term memory, and weakened verbal skills. Studies conducted on patients treated with insulin or other hypoglycemic medications revealed that neurons within the hippocampus are the most affected by hypoglycemia, followed by neurons within the basal ganglia and thalamus. However, neurons within the brain stem, cerebellum, and spinal cord appeared to be more resistant to hypoglycemia. cerebral autopsy preparations from hypoglycemic cases also exhibited traces of myelin damage and glial changes; glial changes due to hypoglycemia include swelling and proliferation of astrocytes and oligodendrocytes in regions of neuronal damage. [6, 7]

Hypoglycemia is the most prevalent metabolic problem in newborns, and it occurs in about 19% of infants overall and reaches up to 51% in neonates at high risk for hypoglycemia. Neonatal hypoglycemia can be either asymptomatic or mildly symptomatic, yet its symptoms are nonspecific and subtle and vary wildly between

patients. Infants with hypoglycemia are at increased risk for brain injury and so it is crucial to ensure they reach a euglycemic state. There are many risk factors for neonatal hypoglycemia and can be related to the mother or the baby itself, one of which is hyperinsulinemia caused by maternal gestational diabetes or type 2 diabetes mellitus (DM), IUGR, post maturity, placental insufficiency, birth asphyxia. Another risk factor is increased glucose utilization in sick or stressed infants due to perinatal hypoxia or ischemia. The exact blood glucose number for determining neonatal hypoglycemia is still unclear, furthermore, an ideal treatment strategy is yet to be established. [8]

Hyperglycemia

The brain was signified to be an important target of diabetic complications by previous research. Diabetes, whether it be type 1 or type 2, is a chronic, metabolic disease characterized by hyperglycemia which over time will cause serious damage to the blood vessels in the eyes, kidneys, nerves, and heart. Furthermore, chronic hyperglycemia in diabetic patients may lead to the disruption of the brain's topological integration, thereby causing mental slowing and cognitive impairment. To ascertain the correlation between white matter microstructural alteration and glycemic control, voxel-wise TBSS on DTI images was performed to determine if the altered brain networks in diabetic participants are due to microstructural changes in the local regions of white matter, the FA values are believed to reflect white matter's overall health, maturation and organization Moreover, severe hyperglycemia affects newborns and is associated with worsened outcomes in the developing brain in preterm infants. [9] [10]



Regional fractional anisotropy (FA) values in participants with type 2 diabetes mellitus were decreased in the distributed white matter regions including commissural, projection, and association fibers (TFCE corrected P<0.05). Significant TBSS results (red-yellow, P<0.05, family-wise error corrected) in sagittal, coronal, and axial views overlap the group averaged FA skeleton (green) and the MNI152 T1 template. 9

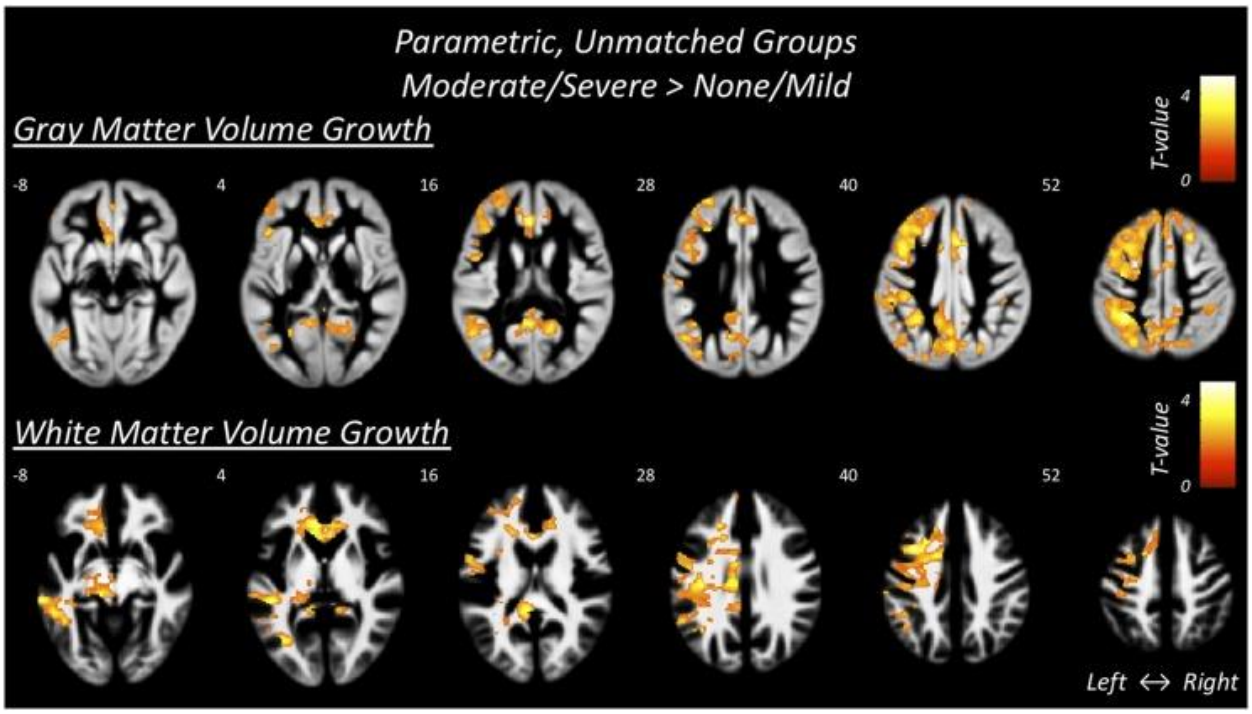
Regional fractional anisotropy (FA) values in participants with type 2 diabetes mellitus were decreased in the distributed white matter regions including commissural, projection, and association fibers (TFCE corrected P<0.05). Significant TBSS results (red-yellow, P<0.05, family-wise error corrected) in sagittal, coronal, and axial views overlap the group averaged FA skeleton (green) and the MNI152 T1 template. 9

The injurious effects of hyperglycemia include an increase in oxidative stress, activation of inflammatory cascades, tissue acidosis, endothelial dysfunction, and an increase in blood-brain barrier permeability. Abnormalities of blood vessels occurring in diabetes

include white matter lesions, microbleeds, silent brain infarcts, and lacunar abnormalities, indicative of cognitive decline. Stimulation of N-Methyl-D-aspartate receptors further incapacitates microcirculatory perfusion and leads to the activation of apoptotic pathways. At a systemic level, hyperglycemia causes an increase in blood osmolarity, it also stimulates diuresis which can result in hypovolemia, hyperglycemia may also cause inflammation and a depressed immune function, which leaves the individual prone to sepsis and organ dysfunction.[11][12]

Diabetes is considered one of the major risk factors for stroke, it does not only affect stroke's probability as it also affects stroke's outcome. 20–50% of patients are hyperglycemic on presentation of an acute ischemic stroke and that is typically followed with significantly poor outcomes. Hyperglycemia also causes vasogenic edema, which causes collateral flow impairment and thus increasing the hyperthrombotic state, and thereby decreasing cerebral blood flow and impairing cerebral autoregulation.[13]

Diabetic ketoacidosis (DKA) is one of the most common complications of diabetes, manifestations of DKA include cerebral edema and cerebral infarction and their etiology in the present time is still undetermined. Urea is increased in DKA causing an increase in the duration of osmotic diuresis and thus causing progressive dehydration. Children with a history of moderate to severe DKA were evidenced to have lower than average IQ scores when compared to those who never experienced DKA or were only exposed to mild levels, the comparison took place 18 months after baseline. This discrepancy signifies that moderate to severe DKA results in altered brain growth in young children, nevertheless, this topic needs to be studied further.[14][15]



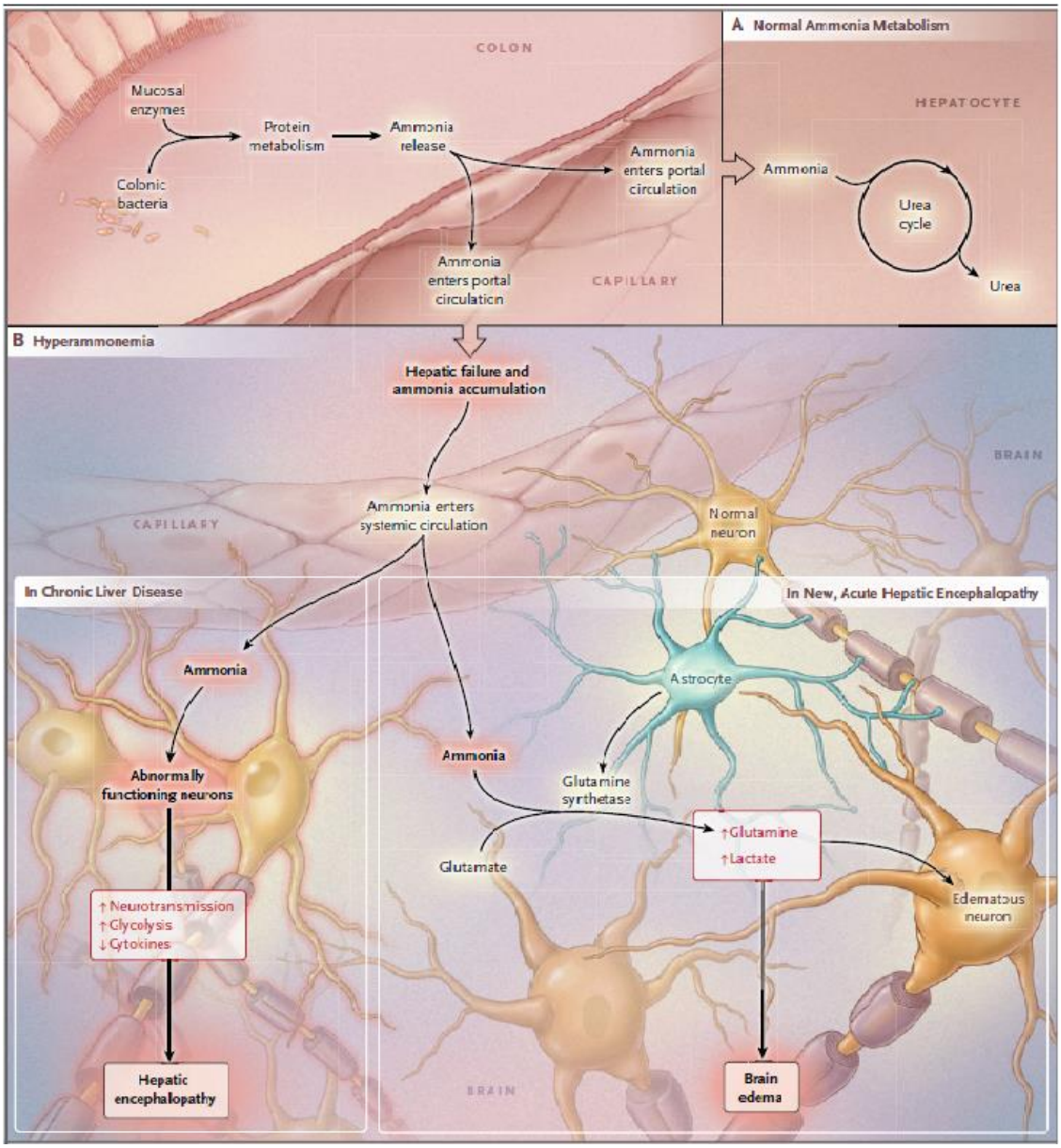
Gray and white matter regions where participants with a history of moderate/severe DKA compared with those who experienced none/mild DKA had more growth.

This image shows the gray and white matter in participants with a history of moderate to severe DKA in comparison with those who experienced none/mild DKA. The color map demonstrates the statistical significance of growth differences between groups.[15]

Hepatic encephalopathy

Hepatic encephalopathy is a serious and progressive but potentially reversible syndrome of neuropsychiatric dysfunction caused by liver failure that affects the brain. Acute-on-chronic liver failure is clear initially as abnormal behavior and impaired cognition. The clinical manifestation of hepatic encephalopathy ranges from mild alteration of cognitive and motor function to coma and death.[16]

It is known that 30–45% of patients with cirrhosis progress into hepatic encephalopathy. The pathogenesis is multifactorial and is not completely understood, Ammonia has been implicated as a key molecule due to its frequent elevation in patients with hepatic cirrhosis and its cellular toxicity. Nevertheless, the exact mechanisms of ammonia-induced neurologic dysfunction are still unclear. Other factors in addition to the neurotoxicity of ammonia include oxidative stress, astrocyte swelling leading to cerebral edema and inducing mitochondrial oxidative dysfunction. and multiple other factors. The following figure includes a potential pathway for this pathology.[17]



Putative Mechanisms Underlying Hepatic Encephalopathy and Brain Edema.

Three different types of HE has been recognized according to their underlying cause: Type A, which is associated with acute liver failure, type B which is associated with portosystemic shunts in the absence of liver dysfunction, and type C in patients suffering from liver cirrhosis and portosystemic shunts. [18] HE can also be classified into covert/overt and low-grade/high-grade according to West Haven's semi-quantitative criteria. Covert HE encompasses HE grade 1 and MHE whilst Overt HE is classified into 3 stages conforming to the severity of consciousness, intellectual function, and behavior disability. [19]

Minimal hepatic encephalopathy (MHE) is considered the earliest form of hepatic encephalopathy and can affect almost 80% of liver cirrhosis patients. MHE, previously known as subclinical or latent hepatic encephalopathy, refers to subtle changes in cognitive functions that can be observed in patients with liver disease, it is the principal cause of cognitive dysfunction in cirrhotic patients. Although MHE is not a lethal condition and hospitalization is often unnecessary, it imposes a significant economic and social burden for both the patient and the health institutions. It has been observed that MHE patients' social connections are mostly impaired, communication and emotional stability change, and mobility, sleep/rest, home management, and recreational activities are all disrupted. Overall, half of MHE patients have no permanent job compared to 15% of cirrhotic patients without impaired cognitive functions. [20]

References

1. Shah P, Rahman SA, Demirbilek H, Güemes M, Hussain K. Hyperinsulinaemic hypoglycaemia in children and adults. 2016;8587(16). doi:10.1016/S2213-8587(16)30323-0
2. Suh SWON, Hamby AM, Swanson RA. Hypoglycemia , Brain Energetics , and Hypoglycemic Neuronal Death. 2007;1286(August 2006):1280-1286. doi:10.1002/glia
3. Bree AJ, Puente EC, Daphna-iken D, Fisher SJ. Diabetes increases brain damage caused by severe hypoglycemia. Published online 2009:194-201. doi:10.1152/ajpendo.91041.2008.
4. Choi I, Seaquist ER, Gruetter R. Effect of Hypoglycemia on Brain Glycogen Metabolism In Vivo. 2003;32:25-32.
5. Cryer PE, Cryer PE. Hypoglycemia , functional brain failure , and brain death. 2007;117(4):868-870. doi:10.1172/JCI31669.868
6. Mohseni S. Hypoglycemic neuropathy. Published online 2001:413-421. doi:10.1007/s004010100459
7. Rehni AK, Dave KR. Impact of Hypoglycemia on Brain Metabolism During Diabetes. 2018;(January).
8. Puchalski ML. Neonatal Hypoglycemia Is There a Sweet Spot ? Hypoglycemia Neonatal hypoglycemia Glucose Hyperinsulinemia Neonate. *Crit Care Nurs Clin NA*. 2018;30(4):467-480. doi:10.1016/j.cnc.2018.07.004
9. Kim DJ, Yu JH, Shin MS, Shin YW, Kim MS. Hyperglycemia reduces efficiency of brain networks in subjects with type 2 diabetes. *PLoS One*. 2016;11(6):1-14. doi:10.1371/journal.pone.0157268
10. Tayman C, Yis U, Hirfanoglu I, Oztekin O, Göktaş G, Bilgin BC. Effects of hyperglycemia on the developing brain in newborns. *Pediatr Neurol*. 2014;51(2):239-245. doi:10.1016/j.pediatrneurol.2014.04.015
11. Godoy DA, Behrouz R, Di Napoli M. Glucose control in acute brain injury: Does it matter? *Curr Opin Crit Care*. 2016;22(2):120-127. doi:10.1097/MCC.0000000000000292
12. Rom S, Zuluaga-ramirez V, Gajghate S, et al. Hyperglycemia-Driven Neuroinflammation Compromises BBB Leading to Memory Loss in Both Diabetes Mellitus (DM) Type 1 and Type 2 Mouse Models. 2018;(DM).
13. Haratz S, Tanne D. Diabetes, hyperglycemia and the management of cerebrovascular disease. *Curr Opin Neurol*. 2011;24(1):81-88. doi:10.1097/WCO.0b013e3283418fed
14. Eisenhut M. In diabetic ketoacidosis brain injury including cerebral oedema and infarction is caused by interleukin-1. *Med Hypotheses*. 2018;121(September):44-46. doi:10.1016/j.mehy.2018.09.005
15. Aye T, Mazaika PK, Mauras N, et al. Impact of early diabetic ketoacidosis on the developing brain. *Diabetes Care*. 2019;42(3):443-449. doi:10.2337/dc18-1405
16. Eroglu Y, Byrne WJ. Hepatic Encephalopathy. *Emerg Med Clin North Am*. 2009;27(3):401-414. doi:10.1016/j.emc.2009.04.005
17. Eelco F.M. Wijdicks, M.D. PD. Hepatic Encephalopathy. Published online 2016. doi:10.1056/NEJMra1600561
18. Weissenborn K. Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles. *Drugs*. 2019;79(0123456789):5-9. doi:10.1007/s40265-018-1018-z
19. Bajaj JS. Hepatic encephalopathy: classification and treatment. *J Hepatol*. 2018;68(4):838-839. doi:10.1016/j.jhep.2017.11.005
20. Nardone R, Taylor AC, Höller Y, Brigo F, Lochner P, Trinka E. Minimal hepatic encephalopathy: A review. *Neurosci Res*. 2016;111:1-12. doi:10.1016/j.neures.2016.04.009

Article Topic: Adrenergic Antagonist

Author: Mohammad Khader Altal.

Editor: Yazan S. Al-Zamer.

Reviewer: Ethar Hazaimeh.

Keywords: Postganglionic, sympathetic, neurotransmitter, dopamine, receptors.

Overview

Adrenergic receptors are found mainly on most of the postganglionic fibers of the sympathetic nervous system (SNS) except sweat glands. They bind several neurotransmitters which include Epinephrine (EN), NorEpinephrine (NE), and Dopamine, and all these neurotransmitters activate it. These receptors are divided into:

- Alpha-Adrenergic receptors: which are subdivided into Alpha-1 and Alpha-2.
- Beta-Adrenergic receptors: which are subdivided into Beta-1, Beta-2, and Beta-3.

Each one of these receptors has a specific location and function summarized in this table below:

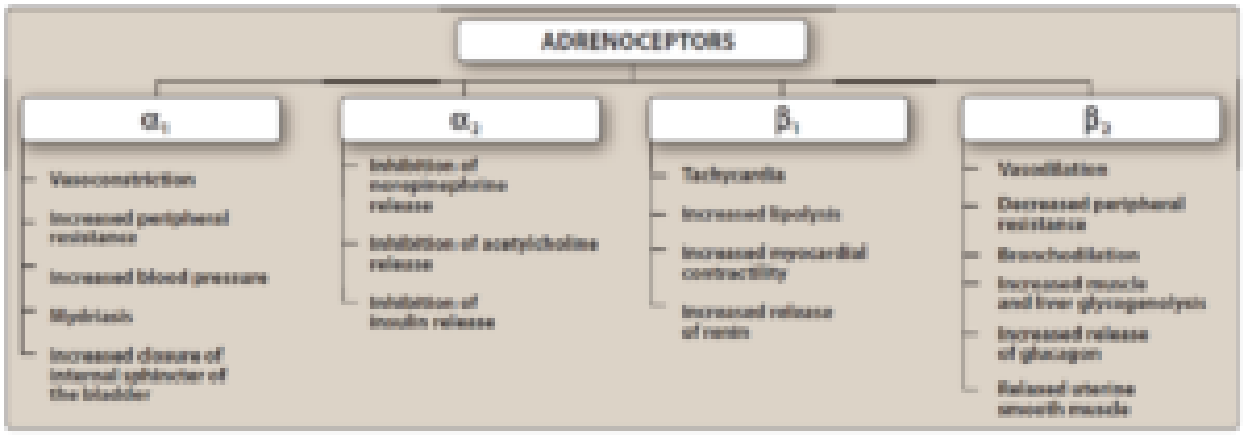


Figure-1 Major effects mediated by α- and β-adrenoceptors (1).

Adrenergic antagonist (sympatholytic)

They are drugs that bind adrenoreceptors and inhibit their activity and are classified by their affinity to alpha and beta-adrenoreceptors:

Alpha-Adrenergic antagonist

Target alpha receptors, these drugs affect blood pressure by reducing it and result in a reflex tachycardia.

1. **Selective alpha-1 blockers**

A group of drugs includes Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin. All of them are useful in hypertension treatment but have minor differences: doxazosin has the longest duration, Tamsolosine and Alfozosine can be used for benign prostatic hyperplasia (BPH).

1. Mechanism of action (MOA): they decrease blood pressure by reducing peripheral vascular resistance.
2. Therapeutic use: for hypertension & as an alternative to surgery with BPH patients.
3. Adverse effect: can cause:
4. The first dose phenomenon: can cause Orthostatic hypotension which might lead to syncope/fainting, this effect can be minimized by lowering the 1st dose to the third or fourth, taking it at bedtime, and then increasing the dose gradually.
5. dizziness, a lack of energy, nasal congestion, and male sexual dysfunction.

2. Selective alpha-2 blockers: Yohimbine.

Found naturally in the bark of the Yohimbine tree, this drug works at the CNS level to increase the sympathetic outflow to the periphery and can be used to treat erectile dysfunction. This drug is contraindicated in psychiatric conditions, renal dysfunction, and cardiovascular diseases (2).

Beta-Adrenergic antagonist

They are competitive antagonists that target beta receptors, including:

1. **Non-selective beta-blockers:** which include:

- Propranolol: the prototype, has an equal affinity for β1&β2 receptors.
- MOA: nodal activity thus decreases cardiac output, causes bradycardia by decreasing atrioventricular and atrial the also block β2 which prevent vasodilation in smooth muscles and increase the peripheral vascular resistance.

Its Contraindicated(C/I) to non-selective β-blockers to (COPD) or Asthma patient because they block β-receptor in the lungs thus worsening their condition. By blocking β2 they decrease glycoglyesis& glucagon secretion.

- **Therapeutic use**

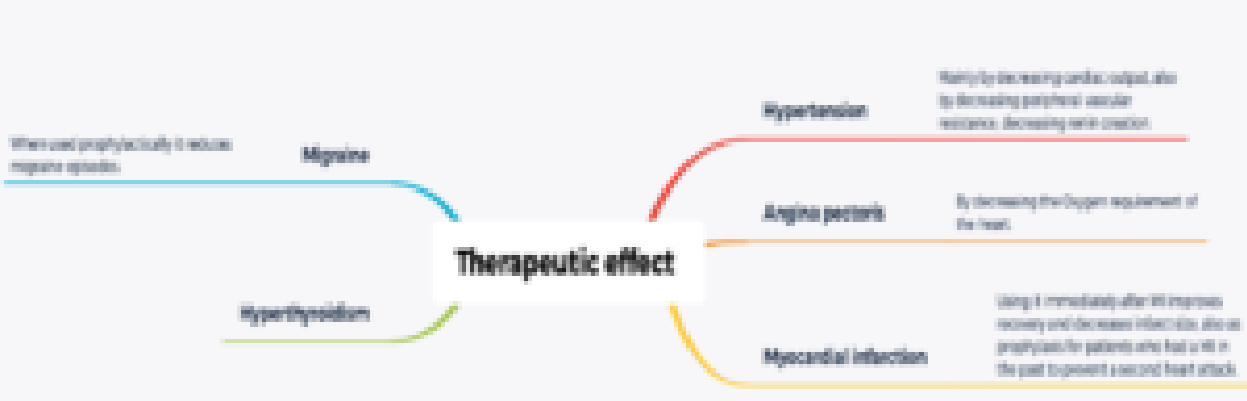


Figure.2 therapeutic effect of Propranolol.

Adverse effect

- Bronchoconstriction.
- Arrhythmia: especially in abrupt stopping the drug, must gradually be tapered off.
- Metabolic disturbance.
- CNS effect: depression, dizziness, fatigue.
- Sexual dysfunction.
- Drug-drug interaction:

Drugs increase the metabolism	**Drugs decrease the metabolism**
barbiturates, phenytoin, and rifampin.	cimetidine, fluoxetine, paroxetine, and ritonavir.

- Timolol & Nadolol: more potent than propranolol and have a longer duration of action. Can be used in the treatment of Glaucoma: by decreasing the secretion of aqueous humor.

2. selective beta-1-blockers

- Acebutolol, atenolol, betaxolol, bisoprolol, nebivolol, esmolol, and metoprolol:
- MOA: selectively blocks β-1 receptors thus decreasing blood pressure, they have a lower effect on pulmonary state and can be used in an asthmatic patient, and they must be monitored.
- Therapeutic use: first-line drug for chronic stable angina, can be used for hypertension, angina.
- Note that bisoprolol& metoprolol can be used for chronic heart failure.

Drugs with intrinsic sympathomimetic activity (Acebutol & Pindolol):

Have the ability to weakly stimulate β receptors they bind and inhibit the binding of a potent agonist, thus called partial agonists. They can be used for hypertension.

Drugs that block α& β adrenoreceptors (Labetalol&Carvedalol)

They non-selectively block β and α-1 receptors thus reducing blood pressure.

- Labetalol: used in pregnancy-induced hypertension.
- Carvedilol: can be used on chronic heart failure.
- S/E: Orthostatic hypotension and dizziness.

All the drugs we mentioned are summarized in this schedule:

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
[illegible]	[illegible]	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
[illegible]	[illegible]	Hypertension
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	Hypertension Angina Myocardial infarction
[illegible]	[illegible]	Hypertension
[illegible]	[illegible]	Hypertension
[illegible]	[illegible]	Hypertension

Figure-3, Summary of β-adrenergic antagonist. NO = nitric oxide. 1Acebutolol and pindolol are partial agonists, as well. 2Bisoprolol, metoprolol, and carvedilol are also used for the treatment of heart failure (3).

Drugs affecting neurotransmitter release or uptake (Reserpine)

They work by preventing the transport of biogenic amines (dopamine, serotine, norepinephrine) from the cytoplasm to storage vesicles thus decreasing sympathetic function in general. Reserpine has a slow onset and long duration of action.

References

1. Karen Whalen. Lippincott Illustrated Reviews Pharmacology. 6th editio. 81 p.
2. Taylor BN, Cassagnol M. Alpha Adrenergic Receptors [Internet]. StatPearls. StatPearls Publishing; 2021 [cited 2021 Mar 13]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30969652
3. Karen Whalen. Lippincott Illustrated Reviews Pharmacology. 6th, editor. 104 p.

Article topic: Neuronal Storage Diseases.

Author: Nour Nedal Al-Bzour.

Editors: Bashar Abualsiba, Sadeen Eid.

Reviewer: Ethar Hazaimeh.

Keywords: Neuronal storage diseases, lysosomal storage diseases, Tay-Sachs, rare diseases, CNS, NSD, LSD, Gaucher, Fabry

Introduction

Neuronal Storage Diseases (aka Lysosomal Storage Diseases (LSDs)) are chronic rare inherited metabolic diseases. LSDs are caused by a deficiency of the lysosomal enzymes that are needed to catabolize substances in the cells of the central nervous system (CNS)[1]. This enzymatic deficiency causes accumulation of the substrates in the lysosome and thus initiates a cascade of cellular events including inflammatory and apoptotic responses. The accumulation and storage of these substrates may begin in early embryonic development and causes inborn metabolic errors. [2] Although LSDs are considered rare diseases, the prevalence of LSDs is 1 in 2000.[3]

History

LSDs are a set of diseases in which there is a storage of substrates in the lysosomes. Some of them develop prenatally, directly after birth, or in childhood or adulthood. The first disease discovered in this set was Gaucher in 1882, followed by Fabry in 1898. The diseases are classified according to the type of substrate being accumulated. For example, Fabry's disorder results from the accumulation of glycosphingolipid globotriaosylceramide in the lysosome and can progressively develops and lead to organ failure and resulting in premature death.[4]

Epidemiology

LSDs are considered rare when studying them solely, yet when they are combined with each other, they are much more common. Many factors increase the incidence rate of developing LSDs, these include ethnicity and geography. For example, there is a higher incidence rate of Gaucher's disease in Jews (Eastern European Jews), it can be as high as 1 in 800, likewise, in Tay-Sachs disease, the chance of developing the disease is 1 in 3900.[5]

Types and Symptoms

LSDs contain more than 70 inherited disorders. Although the signs and symptoms vary from group to group, they share the main cause behind the disease which is an enzymatic deficiency.

Table 1 summarizes some of these disorders and their characteristics

Disease	Clinical features
Galactosialidosis	Cerebellar ataxia, myoclonus, visual failure; onset in late childhood or adolescence
GM1-gangliosidosis	Coarse facial features, corneal clouding, hepatomegaly, skeletal dysplasia, learning disability, myoclonus
Infantile-free sialic acid storage disease (ISSD)	Coarse facies, fair complexion, hepatosplenomegaly, severe psychomotor retardation, nephrotic syndrome
Tay-Sachs disease	Exaggerated acoustic motor reflex, Megalocephaly
Sandhoff disease	Exaggerated acoustic motor reflex, splenomegaly
Niemann-Pick disease type A	Hepatosplenomegaly, spasticity
Neuronal ceroid lipofuscinosis (NCL)	Cerebellar ataxia, myoclonus, visual failure, onset by late childhood or adolescence

Table 1: Lysosomal Storage Disease types and characteristics

Diagnosis

For a definitive diagnosis of LSDs, advanced laboratory biochemical and genetics are required. The diagnosis of LSDs has been confirmed by assaying specific deficient enzymes or accumulated substrates using serum, white blood cells, urine, amniotic

fluid, and cultured skin fibroblasts.[6] Some secondary changes may occur in cells with a lysosomal deficiency which may lead to modifications of proteins and other cellular components that can be a useful biomarker for the detection and diagnosis of LSDs.[7]

The tests used to diagnose LSDs can be classified into six categories, the most common of which are.

1. ***Urinary oligosaccharides***
   This test is performed by high-performance thin-layer chromatography. However, this technique has some limitations. Metabolite quantification is not possible, and the identification of metabolites is assumed based on migration rates. Because of these limitations, this technique can be used as an initial diagnosis for LSDs, but further investigations will be needed to confirm the diagnosis.
2. ***Urinary glycosaminoglycans (GAGs) Mucopolysaccharidoses*** which is a type of LSDs can be suspected by the measurements of urinary GAGs. First, the GAGs are centrifuged and isolated, then quantified by colorimetric assay. The pitfall of this technique is the progressive decrease of urinary GAGs that occurs with age. Thus, the normal-age decline in urinary GAGs should be taken into consideration when diagnosing LSDs.[9]
3. ***Global Tests***
   It has been found that LAMP-1, LAMP-2, saposins, and GM2-ganglioside are elevated in all LSDs. [10]

Treatments

Back in history, there was no treatment used for LSDs. The aim back then was to alleviate the pain and reduce the symptoms without working on the underlying pathogenesis. Other treatments used before had bad outcomes, such as Gaucher disease, bone marrow transplantation proved to be successful treatment although with a mortality rate of 10%. Same as in Fabry's disease, renal translation turned out to be successful but cannot correct the multi-organ manifestations of the disease. Enzymatic therapy was then introduced, first used for the treatment of Gaucher disease, then Fabry, mucopolysaccharidosis type I (MPS I), MPS VI, and Pompe disease, and is under development for MPS II (Hunter syndrome).[11]

The currently available treatments for LSDs have some limitations. Neurodegenerative disease in LSDs is challenging to treat, and the efficient treatments available do not meet the patients' needs. Thus, a combination of early diagnosis and therapeutic approaches may be required. A prudent approach is to prevent lysosomal storage, increase lysosomal degradation (autophagy), increase lysosomal exocytosis, and enhance lysosomal function.

LSDs treatment, as well as targeted therapy methods, are mentioned in table 2 below:

Treatment Target	Potential Therapy	Lysosomal Storage Diseases in which the Therapy was Trailed
Aberrant activation inflammation	Pentosan polysulfate	MPS I, II In vitro in MPS I, IIIA, VI
	Intraperitoneal high-dose aspirin	MPS IIIB
	Miglustat	Niemann–Pick disease, type C1
Increase cellular energy	Resveratrol	Neuronal ceroid lipofuscinosis
Autophagic pathway	-	In vitro in Pompe disease
	Arimocromol	Niemann–Pick disease, type C1
	-	Krabbe disease
Reduction in mitochondrial ROS generation	Coenzyme Q10	Gaucher disease + Fabry disease
	GSH ethyl-ester	Niemann–Pick disease, type C1
	N-acetylcysteine	Krabbe disease Niemann–Pick disease, type C1
Lysosomal calcium signaling	Curcumin	Niemann–Pick disease, type C1
	Diltiazem	Gaucher disease
mTOR signaling/transcription factor TFEB	Rapamycin	Multiple Sulfatase Deficiency
Apoptotic pathway	Z-DEVD-FMK	Niemann–Pick disease, type C1
	Z-VAD-FMK	GM1 gangliosides
Modulation of sitrulins	Resveratrol	Infantile NCL
Inhibition of GSK-3-signalling	L803-mts	Krabbe disease

Table 2: LSDs treatment and targeted therapy[12]

Future Directions

Therapeutic treatments under investigation include hematopoietic stem cell transplantation (HSCT) with autologous cells that have been modified genetically to

express supra-physiological enzyme levels. Moreover, recombinant enzyme trials administered intravenously and intrathecally have been undertaken or are ongoing.[13] In addition, gene therapy with oligodendroglia, neural progenitor, and embryonic and microencapsulated recombinant cells is being investigated as well.[14]

Conclusions

LSDs are chronic and can affect the quality of life and lead to shortened lifespans, especially with neuropathic involvement. Pathophysiological factors such as neurodegeneration, neuroinflammation, impaired autophagy, and microgliosis are major causes of progressive neurogenerative decline in patients with neurological LSD. Our knowledge and understanding of the structure and function of the lysosomes are still developing, and there is still needed for more information and studies to find more efficient therapeutic strategies for treating LSDs.

References

1. Yamano, Tsunekazu; Shimada, Morimi; Okada, Shintaro; Yutaka, Toru; Yabuuchi, Hyakuji; Nakao, Yuzo (1979). Electron microscopic examination of skin and conjunctival biopsy specimens in neuronal storage diseases. , 1(1), 16–25. doi:10.1016/S0387-7604(79)80030-3
2. Stepien KM, Cufflin N, Donald A, Jones S, Church H, Hargreaves IP. Secondary Mitochondrial Dysfunction as a Cause of Neurodegenerative Dysfunction in Lysosomal Storage Diseases and an Overview of Potential Therapies. Int J Mol Sci. 2022 Sep 12;23(18):10573. doi: 10.3390/ijms231810573. PMID: 36142486; PMCID: PMC9503973.
3. Pastores GM, Maegawa GH. Clinical neurogenetics: neuropathic lysosomal storage disorders. Neurol Clin. 2013 Nov;31(4):1051-71. doi: 10.1016/j.ncl.2013.04.007. PMID: 24176423; PMCID: PMC3988112.
4. Mehta A, Beck M, Linhart A, et al. History of lysosomal storage diseases: an overview. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11615/
5. Rajkumar V, Dumpa V. Lysosomal Storage Disease. [Updated 2022 Jan 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563270/
6. Yamano, Tsunekazu; Shimada, Morimi; Okada, Shintaro; Yutaka, Toru; Yabuuchi, Hyakuji; Nakao, Yuzo (1979). Electron microscopic examination of skin and conjunctival biopsy specimens in neuronal storage diseases. , 1(1), 16–25. doi:10.1016/S0387-7604(79)80030-3
7. Bekri S. Laboratory diagnosis of lysosomal storage diseases. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 8. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11594/
8. Bekri S. Laboratory diagnosis of lysosomal storage diseases. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 8. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11594/
9. Bekri S. Laboratory diagnosis of lysosomal storage diseases. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 8. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11594/
10. Bekri S. Laboratory diagnosis of lysosomal storage diseases. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 8. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11594/
11. Mehta A, Beck M, Linhart A, et al. History of lysosomal storage diseases: an overview. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11615/
12. Stepien KM, Cufflin N, Donald A, Jones S, Church H, Hargreaves IP. Secondary Mitochondrial Dysfunction as a Cause of Neurodegenerative Dysfunction in Lysosomal Storage Diseases and an Overview of Potential Therapies. Int J Mol Sci. 2022 Sep 12;23(18):10573. doi: 10.3390/ijms231810573. PMID: 36142486; PMCID: PMC9503973.
13. Auclair D, Finnie J, Walkley SU, White J, Nielsen T, Fuller M, Cheng A, O'Neill CA, Hopwood JJ. Intrathecal recombinant human 4-sulfatase reduces accumulation of glycosaminoglycans in dura of mucopolysaccharidosis VI cats. Pediatr Res. 2012 Jan;71(1):39-45. doi: 10.1038/pr.2011.13. PMID: 22289849.

14. Pastores GM, Maegawa GH. Clinical neurogenetics: neuropathic lysosomal storage disorders. Neurol Clin. 2013 Nov;31(4):1051-71. doi: 10.1016/j.ncl.2013.04.007. PMID: 24176423; PMCID: PMC3988112.

Article topic: ICP Monitoring: Types and Indications.

Authors: Diana Bashashi, Wassim Hamadeh.

Editors: Rahmeh Adel.

Reviewer: Ethar Hazaimeh.

Keywords*: *Intracranial pressure, cerebrospinal fluid, invasive monitoring, non-invasive, infection, hemorrhage, micro-transducer, optic nerve sheath diameter.

Abstract

Intracranial pressure (ICP) is the pressure within the craniospinal compartment, which comprises a fixed volume of neural tissue, blood, and cerebrospinal fluid (CSF). The importance of keeping this parameter constant and the signs and symptoms that should raise suspicion for an elevated ICP are described in this article.

This article aims to demonstrate the importance of using ICP monitoring systems, their types, and their indications in the management of patients with abnormal intracranial pressure due to intracranial pathologies or other medical conditions.

ICP monitoring is a powerful tool because an elevated ICP could lead to devastating neurological problems and ultimately to coma and death. Additionally, it has the potential to help physicians in their judgment of the correct timing of intervention to evaluate the therapy efficacy and consequently, to influence the clinical outcome in the short and long term.

Introduction

Intracranial pressure (ICP) is defined as the pressure exerted by the intracranial contents (blood, CSF, and brain parenchyma) on the dural envelope. The pressure inside the cranial vault is usually measured in millimeters of mercury (mmHg) and is under normal conditions lower than 20 mm Hg.

An abnormally high ICP may occur in a myriad of medical conditions, for instance, by any intracranial masses, either intrinsic to the brain parenchyma (e.g., a tumor like a glioma or a brain abscess) or extrinsic to it (e.g., an extradural hematoma). A diffuse brain swelling following severe hypoxia, ischemia, or Reye syndrome, in liver failure (uremic encephalopathy and hyperammonemia), hypertensive encephalopathy. It may occur following an impaired circulation, absorption, or production of CSF, such as in obstructive hydrocephalus, meningitis, and choroid plexus tumor, which might lead to

CSF build-up around the brain. ICP might also get abnormally high in the context of skull deformities (e.g., craniosynostosis), trauma, and hyponatremia.

The skull and vertebral canal, together with the dura, form a semi-rigid box, such that any increase in the volume of any of its contents (neuronal tissue, blood, or CSF) will raise the ICP. These components exist in a state volume equilibrium so an increase in any one of these elements must be at the expense of the other two, otherwise, an increase of ICP will ensue (this is known as the *Monroe-Kellie model* and was stated centuries ago). In other terms, the combined volume of the intracranial content is constant under normal conditions and to maintain a homeostatic intracranial pressure, any increase or decrease in one of these elements, blood, CSF, or brain will lead to a reciprocal and opposite change in the others. However, because of the buffering effect of CSF being displaced from the cranial cavity into the spinal canal, minor increases in brain volume do not instantly induce an increase in ICP.

Once these compensating measures have been exhausted, any further augmentation in brain volume necessarily reduces the intracranial blood volume contained in the veins and dural sinuses which might jeopardize the blood drainage and flow to the brain. A high ICP may also result in the "herniation" of brain tissue from one compartment into another, which is a potentially fatal consequence that further inhibits CSF flow and feeds the cycle of increasing intracranial pressure. Ultimately the content of the cranium is displaced downwards due to the high ICP. It is noteworthy that the CSF develops more slowly when the ICP is elevated.

All these accommodative volume-pressure relationships occur concurrently and are subsumed under the term intracranial elastance (**Figure 1**)[1].

Figure 1: Pressure-volume curve for ICP. The pressure-volume curve has four 'zones': (1) baseline intracranial volume with good compensatory reserve and high compliance (blue); (2) gradual depletion of compensatory reserve as intracranial volume increases (yellow); (3) poor compensatory reserve and increased risk of cerebral ischemia and herniation (red); and (4) critically high ICP causing the collapse of cerebral microvasculature and disturbed cerebrovascular reactivity (grey).

As the volume of brain, blood, or CSF continues to increase, the accommodative mechanisms fail and ICP rises exponentially, in an idealized elastance (compliance) curve. At an ICP of about 25 mm Hg, the normal curve's form starts to ascend steeply. After this point, small increases in intracranial volume result in marked elevations in ICP. This is particularly important because in clinical practice an ICP below 15- or 20-mm Hg is often given as a therapeutic target because the elastance curve becomes steep beyond this level and small increments in cerebral volume may cause large elevations in ICP.

Accordingly, a raised intracranial pressure is a medical emergency because it might jeopardize cerebral perfusion and damage the neuronal tissue by leading to ischemia and infarction. The typical clinical manifestations of an increased ICP are drowsiness, nausea, headache, ataxia, vomiting, confusion, ocular palsies, and papilledema which is the optic disk swelling. It is usually present if the raised pressure has been longstanding, but because it takes time to develop it may be absent on physical examination. It is a medical emergency; as permanent vision loss can ensue. Visual changes can range from blurred vision, double vision from cranial nerve defects and palsies, photophobia, and ultimately optic atrophy. Hypertension, bradycardia, and irregular respiration are

clinical signs that are known as the Cushing triad and reflect an impending brain herniation.

In infants and small children, whose skull sutures have not yet closed, the clinical signs of an increased ICP take on special features: the clinical presentation may be a rapidly enlarging head size, bulging eyes, and a minimal neurological compromise. Nowadays, monitoring ICP has permitted approximate correlations to be made between the clinical signs and the levels of ICP. However, there are conditions in which the dissociation between ICP and clinical signs is striking, g and some of these signs might not bear a strict relation with the level of ICP. For instance, a mass that is contiguous to the third cranial nerve might compress this nerve at a time when ICP is little raised, and a slowly growing mass lesion might raise ICP gradually and allow for compensation to occur and cause few clinical signs.[2]

ICP is an essential parameter that must be within a narrow range and be able to measure it. Nils Lundberg reported on the earliest clinical studies conducted in this field. He is considered a pioneer in the direct cannulation of the ventricular system and has been credited with recording and analyzing intraventricular pressures over extended periods in volunteers with a multiplicity of intracranial pathologies. He discovered that ICP is subject to periodic spontaneous fluctuations and that the cardiac and respiratory activities create a pulsatile component via cyclical changes in cerebral blood volume. He discussed three different pressure wave types, denoted by the letters A, B, and C.

Lundberg A waves (Plateau waves) are ICP increases that have amplitudes of 50– 100 mmHg and last on average for 5 to 15 minutes. They always reflect underlying pathological conditions in which intracranial compliance is markedly reduced and should alert for an impending herniation if the ICP is left untreated. B waves are ballistic waveforms that follow the blood pressure wave and are the result of blood entering the basal cerebral vessels but still have an unclear value in clinical practice. They might reflect vasomotor changes that are associated with an unstable ICP. C waves follow the respiratory cycle and are a complex result of several transmitted pressures from the thorax to the spinal fluid compartment, so they reflect normal interactions between the cardiac and pulmonary cycles. They have been documented in healthy adults and have no clinical significance. (**figure 2**)[3]

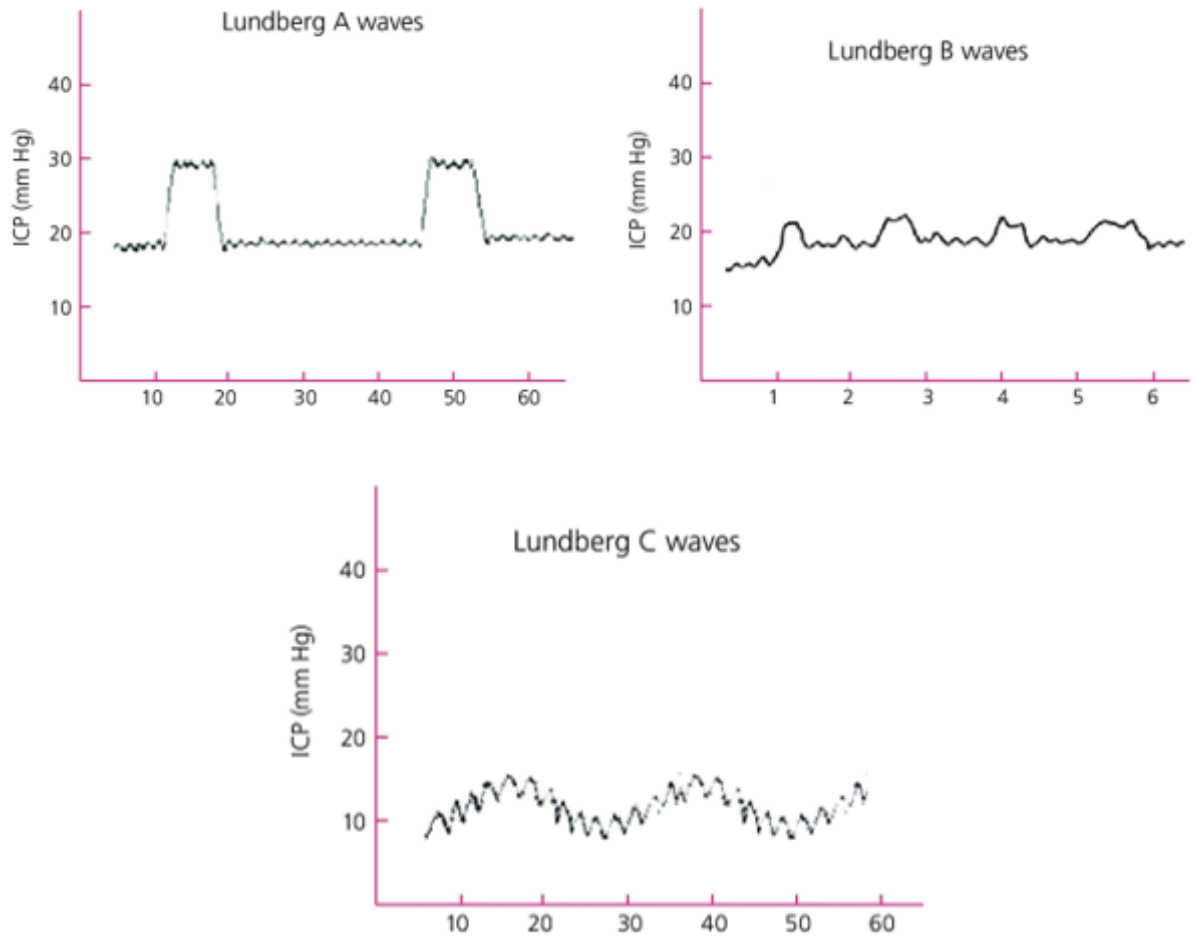


Figure 2: Lundberg waves. Lundberg A waves are ICP rises for 5 to 10 minutes, indicating upcoming herniation. Lundberg B waves have clouded value clinically. Lundberg C waves are related to the normal interactions between the cardiac and pulmonary cycles. 62[/caption]

Indications of intracranial pressure monitoring

ICP monitoring has been investigated in many ways as a diagnostic and treatment approach for a variety of clinical disorders that culminate in neurological damage. ICP monitoring is helpful—if not necessary—in cases of head injury, poor-gradee subarachnoid hemorrhage, stroke, intracerebral hemorrhage, meningitis, acute liver failure, hydrocephalus, benign intracranial hypertension, craniosynostosis, etc. CSF dynamic testing in hydrocephalus helps with diagnosis and subsequent shunt function monitoring.[4]

Traumatic brain injury (TBI) is the most common cause of ICP monitoring (TBI).[5] Clear recommendations for ICP monitoring in TBI are provided by the American Brain Trauma Foundation (BTF) standards. ICP monitoring is suggested in patients with

severe TBI and a normal CT scan if two or more of the following characteristics are present at admission: Older than 40 years; Systolic blood pressure less than 90 mmHg.[6] The foundation recommends (Level II B) the use of ICP monitoring in patients with TBI to decrease in-hospital and two-week post-injury mortality [58] based on the quality of the existing data. It's important to note that the lower limit for intracranial hypertension in the current BTF guidelines is 22 mm Hg, whereas it was 20 mm Hg in the previous one.[58] Additionally, it's essential to consider the most practical site to place the ICP monitor and the effects of regional intracranial pressure gradients when ICP monitoring is being done. However, a recent multi-centric controlled trial (BEST TRIP trial) found that for patients with severe TBI, Imaging- and clinical-based care were not superior to treatment aiming at maintaining ICP at 20 mm Hg or less.[7]

Invasive Methods in ICP Monitoring

The preferred and suggested procedures include an intraparenchymal strain gauge or fiber optic monitor and an intraventricular monitor utilizing a ventriculostomy (EVD).[8]

Several different invasive methods of measuring ICP exist. Depending on the technique, ICP measuring can be undertaken in different intracranial anatomical locations: intraventricular, intraparenchymal, epidural, subdural, and subarachnoid. (**figure 3**)[9]

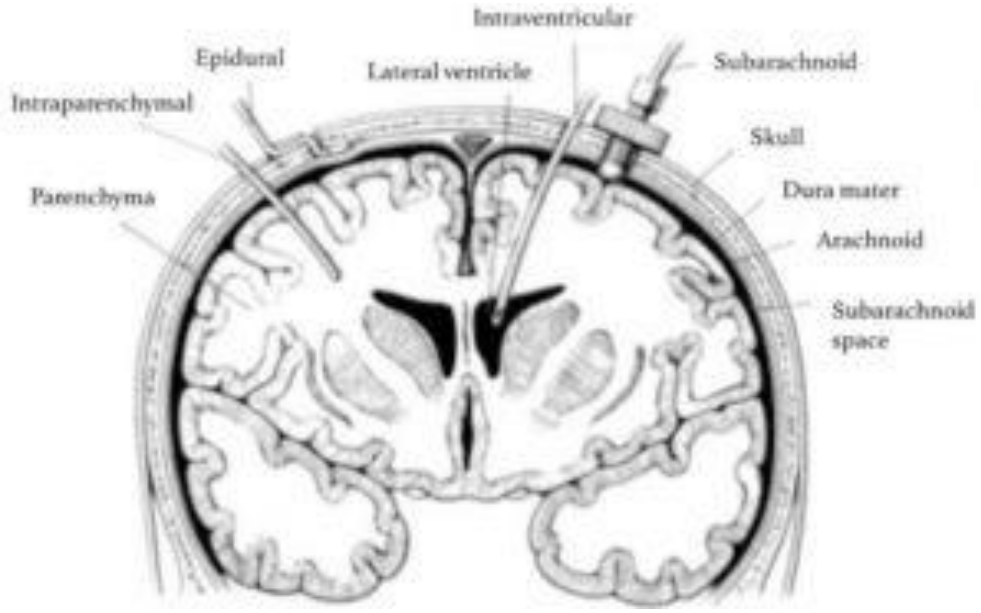


Figure 3: Sites for invasive ICP monitoring. These sites represent actual and potential spaces in the intracranial cavity in which ICP can be measured. Intraventricular monitoring with EVDs is the most commonly accessed site in clinical practice, followed by intraparenchymal probes.

External Ventricular Drainage (EVD)

The gold standard of ICP monitoring is invasive monitoring using the EVD technique, in which a catheter is inserted into one of the lateral ventricles through a burr hole. This approach is the standard against which more recent monitors are calibrated. [10, 11, 12, 13] It entails attaching a fluid-coupled external strain gauge to the catheter in one of the ventricles. An advantage of such an assembly is recalibration. Although the Foramen of Monroe is the ideal reference point for this calibration, it is typically more convenient to use the external auditory meatus. With each change in head position, the EVD requires adjusting the transducer level. (**figure 4**)[14]

The most accurate method in the current use is direct intraventricular ICP monitoring, which also has the benefit of being inexpensive.

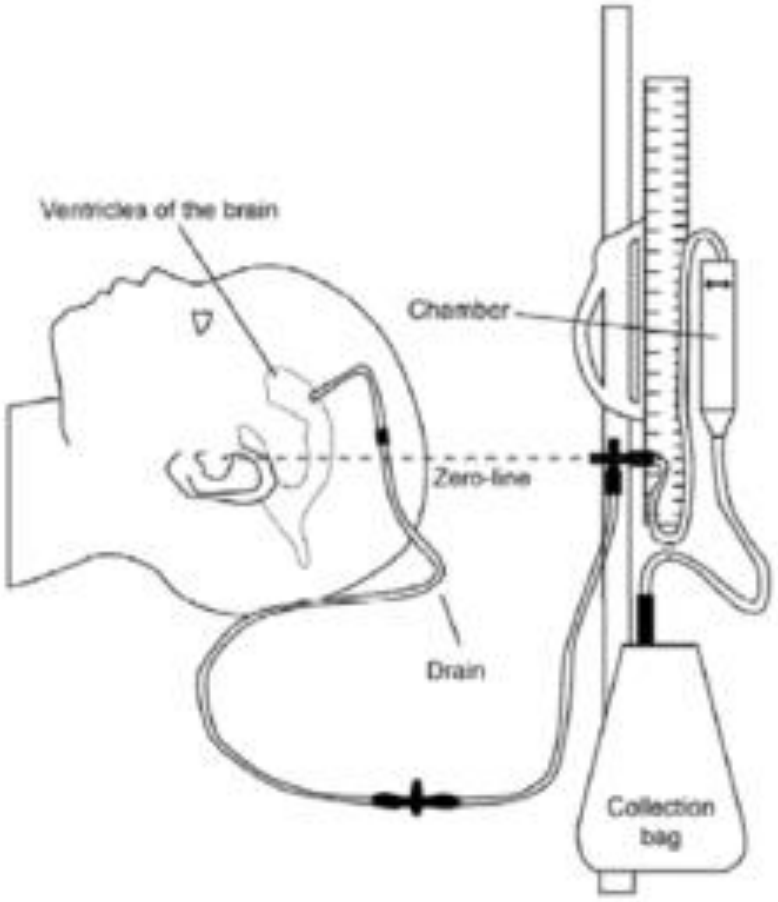


Figure 4: An external ventricular drain (EVD) is a temporary method that uses gravity to drain cerebrospinal fluid (CSF) out of compartments in the brain, called ventricles, via a thin tube that goes out of the head into a chamber and bag. The tube is inserted into the brain while your child is under a general anesthetic in the operating theatre. The tube is stitched in, and the insertion site is covered with a dressing.

In addition to monitoring ICP, the placement of an EVD has other benefits such as aiding therapeutic CSF drainage, intrathecal drug administration such as antibiotics in the case of ventriculitis, or the injection of thrombolytics in case of intraventricular hemorrhage or clotting at the proximal catheter. Additionally, the implantation of an EVD may be necessary to drain posttraumatic hemorrhage.

However, this method offers a unique set of drawbacks. Even though it seems like a routine surgical procedure, hemorrhage, and infection complications are frequent. While there are varyingly high rates of hemorrhage in different case series, hemorrhage was more frequently detected in hospitals that routinely performed CT scans following the procedure.[15] Another study [16] with a total of 188 EVD patients reported "postoperative hemorrhages" in 41% of cases, after being scanned by CT postoperatively, however only 10.6% had hemorrhages larger than 15 mL or with an intraventricular component.

Bacterial colonization of the catheter and consequent retrograde infection are other complications when dealing with EVD. This covers a broad range of illnesses, from benign skin infections to meningitis, ventriculitis, and deadly septicemia.

It is the most invasive of all available techniques, as the ventriculostomy penetrates the meninges and brain, with the risk of bacterial transmission through fluid coupling.[17, 18] The documented risk of infection varies between <1% and 27% in various studies, the mean EVD-associated infection rate is 8–9%.

Numerous techniques have been shown to lower infection rates, including the use of antibiotic- and silver-impregnated catheters, subcutaneous placement of catheters, minimal mechanical disruption of the EVD setup, limiting the duration of EVD to less than five days, and the use of sterile techniques in an operating room setting [17, 19, 20, 21] Given that there is currently insufficient data to support either prophylactic antibiotics or routine catheter changes, it would be advisable to avoid routine CSF sampling. [18, 19]

Another disadvantage of the intraventricular approach is that it can be difficult to introduce an EVD in young patients whose ventricles are narrowed or slit-like due to cerebral edema.[22] In these situations, the ICP waveform may be dropped, and the recorded values may be low due to the artifact effect.

The ipsilateral lateral ventricle anterior to the foramen of Monro or the top of the third ventricle are the best locations for EVD. However, the choroid plexus near the bottom of the third ventricle should be avoided. The preferred site is the right hemisphere, which is non-dominant in 90% of the population. Many retrospective studies have detected misplacements, either intraparenchymal or extraventricular.[23] When ventricular cannulation is attempted improperly or enthusiastically, the basal ganglia may be damaged. The catheter should be carefully examined for kinks, and the drainage tube

should be checked for air bubbles, blood clots, or debris that could obstruct the free passage of CSF or result in a dampened waveform.[24,25]

Subarachnoid devices

Another fluid-coupled device, this one-use saline-filled tubing to connect the intracranial space to an external transducer at the patient's bedside. The burr hole used to insert the subarachnoid bolt serves as a hollow screw. A spinal needle is used to puncture the dura at the base of the bolt, allowing the subarachnoid CSF to fill the bolt.[26] After that, pressure tubing is linked to communicate with a pressure monitoring system. It is no longer typical practice to monitor ICP using this technique. The benefits include little invasiveness and a reduced risk of infection. However, they are prone to errors such as ICP underestimation, screw positioning problems, and obstruction by debris.[27]

Epidural/subdural devices

They are an attractive choice because they are the least invasive and can be installed fast and easily. However, compared to intraventricular or intraparenchymal devices, they are less preferred options because of their doubtful accuracy and reliability as well as a baseline drift, which after more than a few days of use, can surpass 5 ± 10mmHg.[28]

Other invasive methods

In the current era of neurosciences, another method to directly monitor ICP is the use of enormous advancements in micro-transducer technology. These ICP micro-transducers can be used at any location – intraventricular, epidural, subdural, or intraparenchymal. The right frontal cortex parenchyma is the most typical location for micro-transducer installation in routine practice, while other sites may also be chosen in the brain parenchyma based on loco-regional pathology.[29]

Micro-transducers and intraventricular devices have shown a strong association. They have an advantage over EVD in terms of ease of use and the fact that readings are unaffected by patient postures. The lack of a fluid-coupled system reduces the risk of infection, and the ease of the placement of surgical maneuvers results in fewer hemorrhagic consequences. Additionally, compared to fluid-coupled devices like the EVD, the incidence of pressure waveform damping, and measurement artifacts is lower.[29,30]

The disadvantages of intraparenchymal transducer technology include the inability to recalibrate, therapeutic CSF drainage is not possible, inability to predict global ICP in addition to the drift in the system that develops with continued use.[30]

Fiberoptic catheter tip transducers (Camino intracranial pressure monitor)

This comprises a fiberoptic transducer that calculates ICP and represents it as both a waveform and a number by detecting changes in light signal intensity using a diaphragm and microprocessor-driven amplifier.[31] Typically, a daily baseline drift of 0.3 mm Hg takes place.[31, 32, 33] Available research indicates that the substantial infectious and hemorrhagic signs are negligible.[32, 33, 34] Ineffective fiberoptic cables have been primarily attributable to technical errors.[31, 32]

Strain Gauge Micro-Transducer ICP Monitoring Devices

Diffuse piezoelectric strain gauges are located on a silicon microchip at the transducer tip. The microsensor measures ICP at the intraparenchymal, intraventricular, or subdural source, and transmits the data electronically rather than through a hydrostatic system or fiberoptics. Extensive research has proven the Codman microsensor to be a reliable, stable, and accurate ICP monitoring system that, when used in conjunction with the ventricular catheter, provides therapeutic alternatives for CSF drainage.[30] Due to its small size, it can be used at various anatomical sites and in the pediatric age range. Alignment and zeroing are unnecessary, and most critically, infection and hemorrhagic consequences are minimal.[35, 36, 37]

Pneumatic Sensor (Spiegelberg Brain Pressure Monitor)

These ICP monitors primarily measure ICP at subdural or epidural locations[38] by using pneumatic strain gauze technology in a balloon-tipped catheter device. With minimal infections and hemorrhagic consequences, the available evidence has demonstrated results that are comparable to the gold standard intraventricular and intraparenchymal EVD-based monitors.[38, 39, 40] In addition to being less expensive than micro transducers, recent versions of these compliance monitors also feature facilities for periodic automatic drift correction, which has made them quite popular in neurocritical care setups.[30]

Non-Invasive Methods in ICP Monitoring

An invasive intracranial ICP monitor used in a direct measuring strategy is the most reliable way to properly diagnose increased ICP. However, invasive monitoring may not always be used due to the invasiveness of these monitoring techniques (which request inserting an ICP sensor into the ventricles or brain parenchyma), additional risks to the patient may present such as hemorrhage and infection, high costs associated with ICP sensor implantation, and limited access to trained personnel, i.e., a neurosurgeon/neuro-intensivist in suburban areas. Alternative methods to assess ICP

non-invasively have, therefore been sought. All ICP monitoring procedures are based on a thorough clinical evaluation together with imaging modalities (CT head and MRI).

Computerized Tomography

Several attempts have been made to develop ICP and mortality prediction models based on CT abnormalities such as loss of gray and white matter distinction, midline shift, and basal cistern and ventricular effacement.[41, 42, 3] Current data, however, suggests that CT is not a very sensitive instrument because CT remains normal even when ICP is elevated.[44]

Magnetic Resonance Imaging

The MRI-ICP method is a novel approach that predicts ICP by combining advancements in MRI technology with neurophysiological principles.[45] To estimate the mean ICP, it measures the pulsatile variations in intracranial volume and pressure.

Additionally, MRI has been utilized to assess the optic nerve and estimate the diameter of the optic nerve sheath 3 mm posterior to the globe.[46] However, MRI-based approaches have an obvious gap in that they only provide an image of ICP at a specific moment. Additionally, bedside operations are not convenient when using MRI-based techniques, which subject the patient to the logistics of transportation.[47]

Transcranial Doppler Ultrasonography

Using ultrasound, this method measures the blood flow velocity through the main intracranial vessels, most frequently the middle cerebral artery. Transcranial Doppler (TCD) tests can estimate elevated ICP since it interferes with CBF and lowers blood flow velocity as a result. In addition to the mean velocity, the slopes of the TCD waveforms and the pulsatility index have been linked to ICP. The pulsatility index is calculated as the difference between the peak systolic and end diastolic velocity, divided by mean flow velocity.[48–50] However, there is a 10 to 15 mm Hg range of error in the estimates.[51] Additionally, the approach needs practice, and variances between and within observers are possible.[52] Additionally, it could be challenging for the 10-15% of patients who don't have a sufficient bone window.

Tympanic Membrane Displacement

The method takes advantage of the perilymphatic duct's role as a conduit for CSF and perilymph communication. Tympanic membrane movement brought on by stimulation of the stapedial reflex has been correlated to ICP.[53, 54] Stapes are perched on the membrane-covered oval window. This membrane is flexible, which means that its location and movement are influenced by the pressure of the fluid within the cochlea.

The core of this method is a quantitative measurement of this movement. According to available research, tympanic membrane infrasonic emissions and TMD are reliable screening tools that can be used to evaluate and monitor individuals with elevated ICP. They do not, however, provide the measurement of precise ICP levels, and the test has some requirements, including intact stapedial reflexes, normal middle ear pressure, and a patent cochlear aqueduct.[54–57]

Optic Nerve Sheath Diameter (ONSD)

Since the optic nerve is a component of the central nervous system, the dural sheath surrounds it. A tiny 0,1-0,2 mm subarachnoid space exists between the sheath and the white matter and connects to the subarachnoid space enclosing the brain. The sheath enlarges when ICP is elevated. Using transocular ultrasound, the diameter of the nerve sheath can be seen to change (**Figure 5**).[58] Numerous research [46, 59–61] have looked into the relationship between invasively determined ICP and nerve sheath diameter. It was discovered that the correlation coefficient ranged from 0,59 to 0,73. This method is inexpensive and effective; each patient's evaluation lasts around 5 minutes.[59] In multiple investigations, it has been proven to be a reliable screening technique for identifying patients with elevated ICP who require treatment and whose optic nerve sheath diameter (ONSD) is greater> 5 mm, which corresponds to an ICP of 20 mm Hg or above.[60,61] Sonographic ONSD assessment has certain restrictions even though it's uncomplicated. It is not recommended for patients with lesions that are clinically frequent, such as tumors of the orbit, ocular inflammation, Graves' disease, sarcoidosis, disorders that alter the optic nerve sheath diameter, and people with optic nerve lesions.[29]

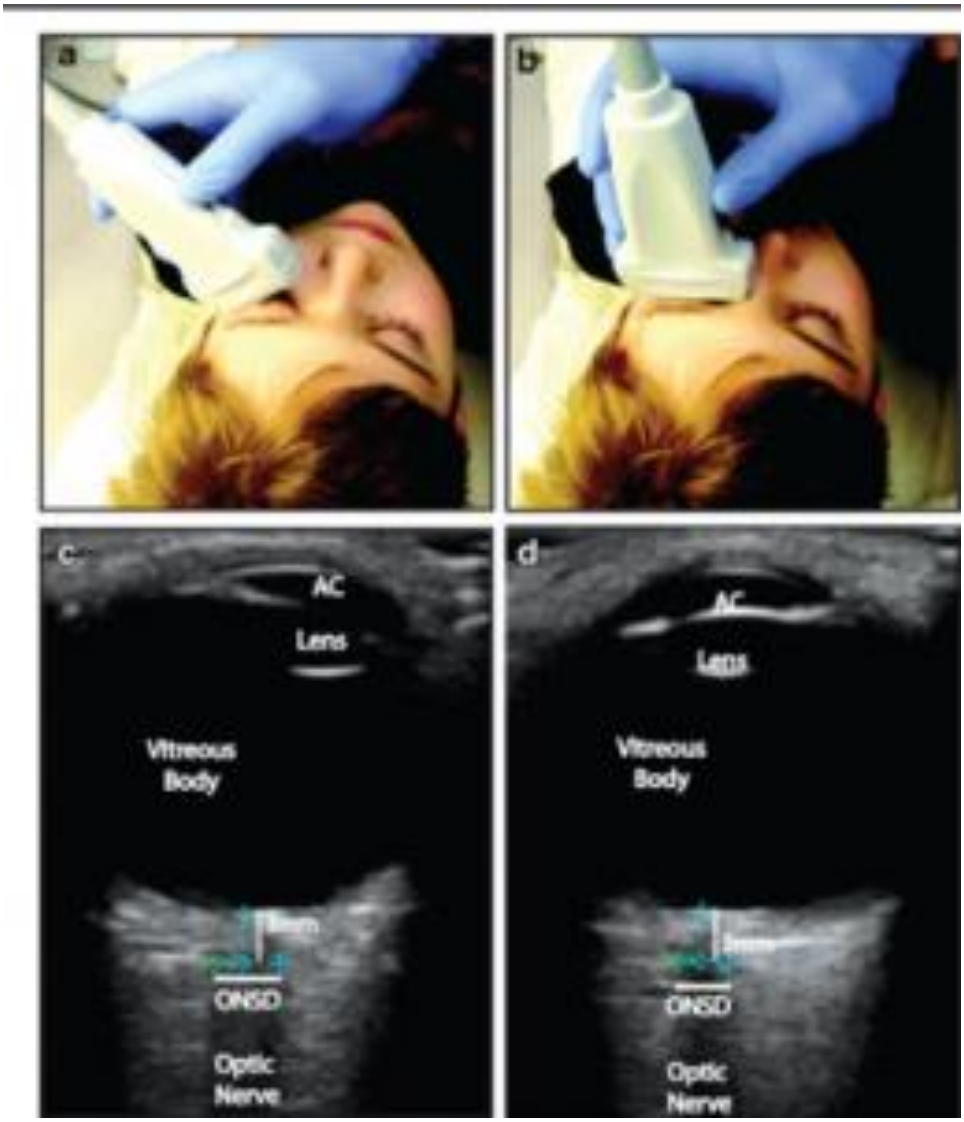


Figure 5: The evolution of ultrasound technology and the development of high-frequency (> 7.5 MHz) linear probes with improved spatial resolution has enabled excellent views of the optic nerve sheath.

In situations where invasive ICP monitoring techniques are either not practical (patients with severe coagulopathy) or not available, ONSD is a potential technique for screening patients with high ICP, setups without access to a neurosurgeon.

Conclusion

The article exposed and demonstrated the importance of using ICP monitoring systems and their indications in clinical practice and why it is important to keep monitoring this parameter in patients with high ICP to confirm and initiate ICP lowering measures as soon as possible and to assess if these interventions are effective or to avoid unnecessary treatment in patients with normal ICP. These monitoring systems are especially

important when the patients are sedated and paralyzed and neurological assessment and examination cannot be performed by the clinician. There also had been evidence, mainly from retrospective cohorts of patients with brain injury, that the outcome in patients was better if the ICP was maintained at adequate levels well below those that compromise cerebral perfusion which can be precisely achieved by using the ICP monitoring systems.

References

[1] Pressure-volume curve for ICP. The pressure-volume curve has four... | Download Scientific Diagram, (n.d.). https://www.researchgate.net/figure/Pressure-volume-curve-for-ICP-The-pressure-volume-curve-has-four-zones-1-baseline_fig2_322946615 (accessed January 20, 2023).

[2] Adams and Victor's Principles of Neurology, 11e | AccessMedicine | McGraw Hill Medical, (n.d.). https://accessmedicine.mhmedical.com/book.aspx?bookID=1477 (accessed January 20, 2023).

[3] Lundberg waves. Lundberg A waves are ICP increases for 5 to 10 minutes.... | Download Scientific Diagram, (n.d.). https://www.researchgate.net/figure/Lundberg-waves-Lundberg-A-waves-are-ICP-increases-for-5-to-10-minutes-They-reflect_fig2_311525129 (accessed January 20, 2023).

[4] P.H. Chapman, E.R. Cosman, M.A. Arnold, The relationship between ventricular fluid pressure and body position in normal subjects and subjects with shunts: a telemetric study, Neurosurgery. 26 (1990) 181. https://doi.org/10.1097/00006123-199002000-00001.

[5] R. Chawla, R. Senthilkumar, N. Ramakrishnan, Intracranial Pressure Monitoring and Management, ICU Protocols: A Step-Wise Approach, Vol I. (2016) 327–338. https://doi.org/10.1007/978-981-15-0898-1_33.

[6] N. Carney, A.M. Totten, C. O'Reilly, J.S. Ullman, G.W.J. Hawryluk, M.J. Bell, S.L. Bratton, R. Chesnut, O.A. Harris, N. Kissoon, A.M. Rubiano, L. Shutter, R.C. Tasker, M.S. Vavilala, J. Wilberger, D.W. Wright, J. Ghajar, Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition, Neurosurgery. 80 (2017) 6–15. https://doi.org/10.1227/NEU.0000000000001432.

[7] R.M. Chesnut, N. Temkin, N. Carney, S. Dikmen, C. Rondina, W. Videtta, G. Petroni, S. Lujan, J. Pridgeon, J. Barber, J. Machamer, K. Chaddock, J.M. Celix, M. Cherner, T. Hendrix, A trial of intracranial-pressure monitoring in traumatic brain injury, N Engl J Med. 367 (2012) 2471–2481. https://doi.org/10.1056/NEJMOA1207363.

[8] P. le Roux, D.K. Menon, G. Citerio, P. Vespa, M.K. Bader, G. Brophy, M.N. Diringer, N. Stocchetti, W. Videtta, R. Armonda, N. Badjatia, J. Bösel, R. Chesnut, S. Chou, J. Claassen, M. Czosnyka, M. de Georgia, A. Figaji, J. Fugate, R. Helbok, D. Horowitz, P. Hutchinson, M. Kumar, M. McNett, C. Miller, A. Naidech, M. Oddo, D.W. Olson, K. O'Phelan, J.J. Provencio, C. Puppo, R. Riker, C. Roberson, M. Schmidt, F. Taccone, The International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a list of recommendations and additional conclusions: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine, Neurocrit Care. 21 Suppl 2 (2014) 282–296. https://doi.org/10.1007/S12028-014-0077-6.

[9] Sites for invasive ICP monitoring. These sites represent actual and... | Download Scientific Diagram, (n.d.). https://www.researchgate.net/figure/Sites-for-invasive-ICP-monitoring-These-sites-represent-actual-and-potential-spaces-in_fig4_322946615 (accessed January 20, 2023).

[10] J. Zhong, M. Dujovny, H.K. Park, E. Perez, A.R. Perlin, F.G. Diaz, Advances in ICP monitoring techniques, Neurol Res. 25 (2003) 339–350. https://doi.org/10.1179/016164103101201661.

[11] Intracranial Pressure Monitoring | AACN Advanced Critical Care | American Association of Critical-Care Nurses, (n.d.). https://aacnjournals.org/aacnacconline/article-abstract/16/4/456/14163/Intracranial-Pressure-MonitoringWhy-Monitor (accessed January 18, 2023).

[12] L.A. Steiner, P.J.D. Andrews, Monitoring the injured brain: ICP and CBF, Br J Anaesth. 97 (2006) 26–38. https://doi.org/10.1093/BJA/AEL110.

[13] M. Smith, Monitoring intracranial pressure in traumatic brain injury, Anesth Analg. 106 (2008) 240–248. https://doi.org/10.1213/01.ANE.0000297296.52006.8E.

[14] External-ventricular-drain-diagram.png (472×433), (n.d.). https://www.childrens.health.qld.gov.au/wp-content/uploads/images/fact-sheets/External-ventricular-drain-diagram.png (accessed January 20, 2023).

[15] D.D. Binz, L.G. Toussaint, J.A. Friedman, Hemorrhagic complications of ventriculostomy placement: A meta-analysis, Neurocrit Care. 10 (2009) 253–256. https://doi.org/10.1007/S12028-009-9193-0/METRICS.

[16] P.A. Gardner, J. Engh, D. Atteberry, J.J. Moossy, Hemorrhage rates after external ventricular drain placement: Clinical article, J Neurosurg. 110 (2009) 1021–1025. https://doi.org/10.3171/2008.9.JNS17661.

[17] R. Beer, P. Lackner, B. Pfausler, E. Schmutzhard, Nosocomial ventriculitis and meningitis in neurocritical care patients, J Neurol. 255 (2008) 1617–1624. https://doi.org/10.1007/S00415-008-0059-8/METRICS.

[18] A.P. Lozier, R.R. Sciacca, M.F. Romagnoli, E.S. Connolly, J.G. McComb, A.R. Cohen, J.P. Rock, Ventriculostomy-related infections: a critical review of the literature, Neurosurgery. 51 (2002) 170–182. https://doi.org/10.1097/00006123-200207000-00024.

[19] D. Dasic, S.J. Hanna, S. Bojanic, R.S.C. Kerr, External ventricular drain infection: the effect of a strict protocol on infection rates and a review of the literature, Br J Neurosurg. 20 (2006) 296–300. https://doi.org/10.1080/02688690600999901.
[20] J. Fichtner, E. Güresir, V. Seifert, A. Raabe, Efficacy of silver-bearing external ventricular drainage catheters: a retrospective analysis, J Neurosurg. 112 (2010) 840–846. https://doi.org/10.3171/2009.8.JNS091297.
[21] F. Furno, K.S. Morley, B. Wong, B.L. Sharp, P.L. Arnold, S.M. Howdle, R. Bayston, P.D. Brown, P.D. Winship, H.J. Reid, Silver nanoparticles and polymeric medical devices: a new approach to prevention of infection?, J Antimicrob Chemother. 54 (2004) 1019–1024. https://doi.org/10.1093/JAC/DKH478.
[22] L. N., Continuous recording and control of ventricular fluid pressure in neurosurgical practice, Acta Psychiat. Scand. 36 (1960) 1–193. https://cir.nii.ac.jp/crid/1572543024544910464 (accessed January 19, 2023).
[23] A. Saladino, J.B. White, E.F.M. Wijdicks, G. Lanzino, Malplacement of ventricular catheters by neurosurgeons: a single institution experience, Neurocrit Care. 10 (2009) 248–252. https://doi.org/10.1007/S12028-008-9154-Z.
[24] Ventriculostomy for treatment of hydrocephalus - PubMed, (n.d.). https://pubmed.ncbi.nlm.nih.gov/8241788/ (accessed January 19, 2023).
[25] B. SL, C. RM, G. J, M.H. FF, H. OA, H. R, M. GT, N. A, N. DW, R. G, S. J, S. L, T. SD, U. JS, V. W, W. JE, W. DW, Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds, J Neurotrauma. 24 Suppl 1 (2007). https://doi.org/10.1089/NEU.2007.9987.
[26] J.K. Vries, D.P. Becker, H.F. Young, A subarachnoid screw for monitoring intracranial pressure: Technical note, J Neurosurg. 39 (1973) 416–419. https://doi.org/10.3171/JNS.1973.39.3.0416.
[27] J.D. Miller, H. Bobo, J.P. Kapp, Inaccurate pressure readings for subarachnoid bolts, Neurosurgery. 19 (1986) 253–255. https://doi.org/10.1227/00006123-198608000-00012.
[28] A.K. Ream, G.D. Silverberg, S.D. Corbin, E. v. Schmidt, T.B. Fryer, Epidural measurement of intracranial pressure, Neurosurgery. 5 (1979) 36–43. https://doi.org/10.1227/00006123-197907010-00006.
[29] P.H. Raboel, J. Bartek, M. Andresen, B.M. Bellander, B. Romner, Intracranial Pressure Monitoring: Invasive versus Non-Invasive Methods-A Review, Crit Care Res Pract. 2012 (2012). https://doi.org/10.1155/2012/950393.
[30] B.P. Chitnavis, C.E. Polkey, Intracranial pressure monitoring, Care of the Critically Ill. 14 (1998) 80–84. https://doi.org/10.4103/2348-0548.165039/ID/JR_71.
[31] I. Piper, A. Barnes, D. Smith, L. Dunn, The Camino intracranial pressure sensor: is it optimal technology? An internal audit with a review of current intracranial pressure monitoring technologies, Neurosurgery. 49 (2001) 1158–1165. https://doi.org/10.1097/00006123-200111000-00026.
[32] A. Bekar, Ş. Doğan, F. Abaş, B. Caner, G. Korfali, H. Kocaeli, S. Yilmazlar, E. Korfali, Risk factors and complications of intracranial pressure monitoring with a fiberoptic device, J Clin Neurosci. 16 (2009) 236–240. https://doi.org/10.1016/J.JOCN.2008.02.008.
[33] D.S. Nag, S. Sahu, A. Swain, S. Kant, Intracranial pressure monitoring: Gold standard and recent innovations, World J Clin Cases. 7 (2019) 1535. https://doi.org/10.12998/WJCC.V7.I13.1535.
[34] M. Gelabert-González, V. Ginesta-Galan, R. Sernamito-García, A.G. Allut, J. Bandin-Diéguez, R.M. Rumbo, The Camino intracranial pressure device in clinical practice. Assessment in a 1000 cases, Acta Neurochir (Wien). 148 (2006) 435–441. https://doi.org/10.1007/S00701-005-0683-3/METRICS.
[35] W.C. Hong, Y.K. Tu, Y.S. Chen, L.M. Lien, S.J. Huang, Subdural intracranial pressure monitoring in severe head injury: clinical experience with the Codman MicroSensor, Surg Neurol. 66 (2006) S8–S13. https://doi.org/10.1016/J.SURNEU.2006.07.006.
[36] L.O.D. Koskinen, M. Olivecrona, Clinical experience with the intraparenchymal intracranial pressure monitoring Codman MicroSensor system, Neurosurgery. 56 (2005) 693–697. https://doi.org/10.1227/01.NEU.0000156609.95596.24.
[37] H.M. Fernandes, K. Bingham, I.R. Chambers, A.D. Mendelow, Clinical evaluation of the Codman microsensor intracranial pressure monitoring system, Acta Neurochir Suppl. 71 (1998) 44–46. https://doi.org/10.1007/978-3-7091-6475-4_14.
[38] J.M. Lang, J. Beck, M. Zimmermann, V. Seifert, A. Raabe, D.F. Kelly, M. Bergsneider, R.G. Grossman, T.H. Milhorat, M. Czosnyka, Clinical evaluation of intraparenchymal Spiegelberg pressure sensor, Neurosurgery. 52 (2003) 1455–1459. https://doi.org/10.1227/01.NEU.0000065136.70455.6F.
[39] K.L. Kiening, W.N. Schoening, J.F. Stover, A.W. Unterberg, Continuous monitoring of intracranial compliance after severe head injury: relation to data quality, intracranial pressure and brain tissue PO2, Br J Neurosurg. 17 (2003) 311–318. https://doi.org/10.1080/02688690310001601199.
[40] K.L. Kiening, W. Schoening, A.W. Unterberg, J.F. Stover, G. Citerio, P. Enblad, P. Nilsson, Assessment of the relationship between age and continuous intracranial compliance, Acta Neurochir Suppl. 95 (2005) 293–297. https://doi.org/10.1007/3-211-32318-X_60.
[41] M.T. Miller, M. Pasquale, S. Kurek, J. White, P. Martin, K. Bannon, T. Wasser, M. Li, D. Wang, J.D. Hoyt, G.J. Jurkovich, Initial head computed tomographic scan characteristics have a linear relationship with initial intracranial pressure after trauma, J Trauma. 56 (2004) 967–973. https://doi.org/10.1097/01.TA.0000123699.16465.8B.
[42] T. Mizutani, S. Manaka, H. Tsutsumi, Estimation of intracranial pressure using computed tomography scan findings in patients with severe head injury, Surg Neurol. 33 (1990) 178–184. https://doi.org/10.1016/0090-3019(90)90181-N.
[43] L.F. Marshall, S.B. Marshall, M.R. Klauber, M. van Berkum Clark, H.M. Eisenberg, J.A. Jane, T.G. Luerssen, A. Marmarou, M.A. Foulkes, A new classification of head injury based on computerized tomography, J Neurosurg. 75 (1991) S14–S20. https://doi.org/10.3171/SUP.1991.75.1S.0S14.
[44] J.B. Rosenberg, A.L. Shiloh, R.H. Savel, L.A. Eisen, Non-invasive methods of estimating intracranial pressure, Neurocrit Care. 15 (2011) 599–608. https://doi.org/10.1007/S12028-011-9545-4.
[45] N. Alperin, M. Mazda, T. Lichtor, S.H. Lee, From Cerebrospinal Fluid Pulsation to Noninvasive Intracranial Compliance and Pressure Measured by MRI Flow Studies, (n.d.).

[46] T. Geeraerts, V.F.J. Newcombe, J.P. Coles, M.G. Abate, I.E. Perkes, P.J.A. Hutchinson, J.G. Outtrim, D.A. Chatfield, D.K. Menon, Use of T2-weighted magnetic resonance imaging of the optic nerve sheath to detect raised intracranial pressure, Crit Care. 12 (2008) R114. https://doi.org/10.1186/CC7006.
[47] H.H. Kimberly, V.E. Noble, Using MRI of the optic nerve sheath to detect elevated intracranial pressure., Crit Care. 12 (2008) 181. https://doi.org/10.1186/CC7008/METRICS.
[48] J. Bellner, B. Romner, P. Reinstrup, K.A. Kristiansson, E. Ryding, L. Brandt, Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP), Surg Neurol. 62 (2004) 45–51. https://doi.org/10.1016/j.surneu.2003.12.007.
[49] S.G. Voulgaris, M. Partheni, H. Kaliora, N. Haftouras, I.S. Pessach, K.S. Polyzoidis, Early cerebral monitoring using the transcranial Doppler pulsatility index in patients with severe brain trauma., Med Sci Monit. 11 (2005) CR49-52. https://europepmc.org/article/med/15668630 (accessed January 19, 2023).
[50] J.A. Moreno, E. Mesalles, J. Gener, A. Tomasa, A. Ley, J. Roca, J. Fernández-Llamazares, Evaluating the outcome of severe head injury with transcranial Doppler ultrasonography, Neurosurg Focus. 8 (2000) 1–7. https://doi.org/10.3171/FOC.2000.8.1.1702.
[51] A. Behrens, N. Lenfeldt, K. Ambarki, J. Malm, A. Eklund, L.O. Koskinen, Transcranial Doppler pulsatility index: not an accurate method to assess intracranial pressure, Neurosurgery. 66 (2010) 1050–1057. https://doi.org/10.1227/01.NEU.0000369519.35932.F2.
[52] Q. Shen, J. Stuart, B. Venkatesh, J. Wallace, J. Lipman, Inter observer variability of the transcranial Doppler ultrasound technique: impact of lack of practice on the accuracy of measurement, J Clin Monit Comput. 15 (1999) 179–184. https://doi.org/10.1023/A:1009925811965.
[53] E.W. Lang, K. Paulat, C. Witte, J. Zolondz, H. Maximilian Mehdorn, Noninvasive intracranial compliance monitoring. Technical note and clinical results, J Neurosurg. 98 (2003) 214–218. https://doi.org/10.3171/JNS.2003.98.1.0214.
[54] R. A, M. RJ, B. DM, M. AM, B. DE, P. JD, B. AP, The relationship between intracranial pressure and tympanic membrane displacement, Br J Audiol. 24 (1990) 123–129. https://doi.org/10.3109/03005369009077853.
[55] H. Kristiansson, E. Nissborg, J. Bartek, M. Andresen, P. Reinstrup, B. Romner, Measuring elevated intracranial pressure through noninvasive methods: a review of the literature, J Neurosurg Anesthesiol. 25 (2013) 372–385. https://doi.org/10.1097/ANA.0B013E31829795CE.
[56] M. Samuel, D.M. Burge, R.J. Marchbanks, Tympanic membrane displacement testing in regular assessment of intracranial pressure in eight children with shunted hydrocephalus, J Neurosurg. 88 (1998) 983–995. https://doi.org/10.3171/JNS.1998.88.6.0983.
[57] E. Stettin, K. Paulat, C. Schulz, U. Kunz, U.M. Mauer, Noninvasive intracranial pressure measurement using infrasonic emissions from the tympanic membrane, J Clin Monit Comput. 25 (2011) 203–210. https://doi.org/10.1007/S10877-011-9297-X.
[58] optic_nerve_sheath_diameter_ultrasonography.png [Operative Neurosurgery], (n.d.). https://operativeneurosurgery.com/lib/exe/detail.php?id=optic_nerve_sheath_diameter_ultrasonography&media=optic_nerve_sheath_diameter_ultrasonography.png (accessed January 20, 2023).
[59] H.H. Kimberly, S. Shah, K. Marill, V. Noble, Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure, Acad Emerg Med. 15 (2008) 201–204. https://doi.org/10.1111/J.1553-2712.2007.00031.X.
[60] T. Soldatos, D. Karakitsos, K. Chatzimichail, M. Papathanasiou, A. Gouliamos, A. Karabinis, Optic nerve sonography in the diagnostic evaluation of adult brain injury, Crit Care. 12 (2008) R67. https://doi.org/10.1186/CC6897.
[61] V. Rajajee, M. Vanaman, J.J. Fletcher, T.L. Jacobs, Optic nerve ultrasound for the detection of raised intracranial pressure, Neurocrit Care. 15 (2011) 506–515. https://doi.org/10.1007/S12028-011-9606-8.
[62] Hirzallah MO, Choi HA. The Monitoring of Brain Edema and Intracranial Hypertension. J Neurocit Care 2016;9:92–104.

Article Topic: The use of stem cell therapy in the treatment of neurological disorders.

Author: Loay B. Zamil.

Editors: Peter Bael, Hamid Ghanem.

Reviewer: Ethar Hazaimeh.

Keywords: stem cell therapy, neurological disorders, neurodegenerative diseases, nervous system, regenerative medicine.

Introduction

Nervous tissues have a special feature that other tissues do not have; the inability to regenerate their cells. You develop a nervous system, and it remains with you throughout your life, except for some specific areas within the brain that are characterized by neurogenesis during adulthood which are the subgranular zone of the hippocampus (SGZ), and subventricular zone of the lateral ventricle (SVZ) [1].

There is a limited ultimate cure window for neurodegenerative diseases such as Alzheimer's disease (AD), Cerebral palsy (CP), Multiple sclerosis (MS), and Parkinson's disease (PD), which occurs due to progressive loss of structure, function, or number of neurons [2]. Besides that, the limitation for most drugs regarding crossing the blood-brain barrier (BBB) makes the process of treatment more difficult [3].

Stem cell therapy looks like a golden solution for such disorders. It is a branch of regenerative medicine that focuses on the use of stem cells [4], which can achieve self-renewal and differentiate, to regenerate damaged cells of other types of tissue cells to replace damaged tissues that could not regenerate again for any reason [2]. This gives us novel and effective treatments for neurodegenerative diseases with wider therapeutic windows than the currently limited treatment, and clinicians are solving the problem, not just supportive care, and rehabilitation.

The problem that we struggle with

- Alzheimer's disease (AD) is the most common type of dementia accounting for 60–70% of cases. Currently, more than 55 million people have dementia worldwide which is expected to rise to 139 million in 2050, and approximately 10 million new cases every year [5]. It is a multi-factorial disorder; the main reasons are age, environmental factors, such as chronic stress, traumatic brain injury, and several genetic factors.

Clinically, these patients are characterized by an impairment of short-term memory, later they are followed by impairment in other cognitive functions, such as logical understanding, language, and executive function. These characteristics are associated with a significant reduction in brain volume [6]. This reduction results from the degeneration of neurons and synapses, particularly in the hippocampus [1], which is a region of the brain responsible for memory and spatial orientation. The hippocampus is one of the first regions of the brain to suffer from damage.

Current pharmacological interventions in dementia are symptomatic relief drugs, which aim to treat some of the symptoms of dementia itself or other reflected symptoms. Currently, there are two drugs available for these patients, **cholinesterase inhibitors**, which function to prevent the **acetylcholinesterase** from breaking down acetylcholine, which helps in contact between nerve cells. The other drug is the **N-methyl-D-aspartate (NMDA) receptor**, which tries to block the effects of glutamate, which is excessively released in the brains of Alzheimer's patients and causes damage to their brain cells [7][8].

- Multiple sclerosis (MS) is a central nervous system disorder characterized by damage to the myelin sheaths surrounding the axons of neurons, caused by an autoimmune or persistent infection. Damaged myelin sheaths disrupt the conduction of action potentials along these axons, which is thought to cause many of the symptoms, and can also lead to the deterioration of axons, which can be detected as plaques or lesions visible with neuroimaging [9][24].

- Cerebral palsy (CP) is considered a neurodevelopmental disease, caused by multifactor that cause failure of the development of some brain areas during fetal life or post-neonatal onset, such factors are infection, hypoxia, and genetic mutation [10].

- Parkinson's disease (PD) is a neurodegenerative brain disorder characterized by unintended or uncontrollable movements, that are caused by low levels of dopamine in the basal ganglia, a group of structures involved with the movement. These low dopamine levels in the basal ganglia are caused by the death of dopamine neurons in a region of the basal ganglia called the substantia nigra [11].

Such disorders and others have in common a characteristic of neurodegenerative disorder, which here in the nervous system causes a struggling issue that is distinct from other systems because the nervous tissues cannot regenerate their cells.

The Golden Solution for this problem

"This problem" is the lack of the ability to regenerate cells in the nervous tissue, and to solve it we have to replace or regenerate neuron cells. **Stem cell therapy,** which has been developed relatively recently, gives hope for doing that, an important branch of

regenerative medicine, that focuses on the use of stem cells which can self-renewal and differentiate, to regenerate damaged cells of other types of tissue cells to replace damaged tissues that couldn't regenerate again for any reason[2,3]. Stem cells as a treatment option have been increasingly popular due to their capacity to target specific pathways and improve patient outcomes [23].

Stem cell therapy enhances the level of functional recovery in the nervous system after the degeneration of its tissue and cells, by implementing exogenous stem cells, the degenerated neuronal circuitry could be regenerated [11]. Stem cell therapy offers amazing possibilities. The treatment aims to repair, replace, or at least prevent future deterioration, whereas, at present, we mainly provide supportive care to prevent such situations from becoming worse.

The Therapeutic Strategies:

Stem cell transplantation is mainly done by two methods. One is the transplantation of proper stem cells directly into the desired location, beside of internal environment and specific signal molecules they will be guided towards differentiation into a particular mature cell, thus exerting the necessary functions. The other method is done in vitro, by isolating, purifying, and amplifying a certain type of stem cell, and inducing it to differentiate into the cells with desired functions. Then, these mature, differentiated cells can be implanted into the damaged area. An appropriate combination of both methods may produce better effects for patients [12][21].

From where can I get it?

Stem cells can be classified into three types according to their abilities to differentiate and the range of the types of cells that can be generated. The first type is **totipotent stem cells,** which can give rise to all the cell types in a body, plus the placental cells. The second type is **pluripotent stem cells,** which can give rise to the three embryonic layers (endoderm, mesoderm, and ectoderm). Such as embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC). The third type is **multipotent stem cells,** which are adult stem cells and can only generate specific lineages of cells. Such as neural stem cells (NSCs) which are derived from neural tissues and can give rise to all cell types (neurons, astrocytes, and oligodendrocytes) of the nervous system [13][22].

Endogenous Regeneration

Mainly for AD, because this process depends on the principle of powering the neurogenesis ability of hippocampus tissue that has been weakened with age or other reasons [5][21].

The treatment aimed to return the ability of neurogenesis of such these areas and power it furthermore to recompensate that weakens. Which can be stimulated through extrinsic administration of chemical agents and growth factors, such as Erythropoietin, fluoxetine, granulocyte colony-stimulating factor, nerve growth factor (NGF), insulin growth factor-1 (IGF-1), and brain-derived neurotrophic factor (BDNF) [14].

Engrafted Regeneration

In contrast, this is concerned with implanting stem cells from outside the concerned tissue. Several major groups of stem cells are used for therapeutic purposes. Mostly, embryonic stem cells (ESCs), neural stem cells (NSCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) are applied in this context. Other types, such as olfactory ensheathing cells and hematopoietic stem cells, may as well be applied [14][20].

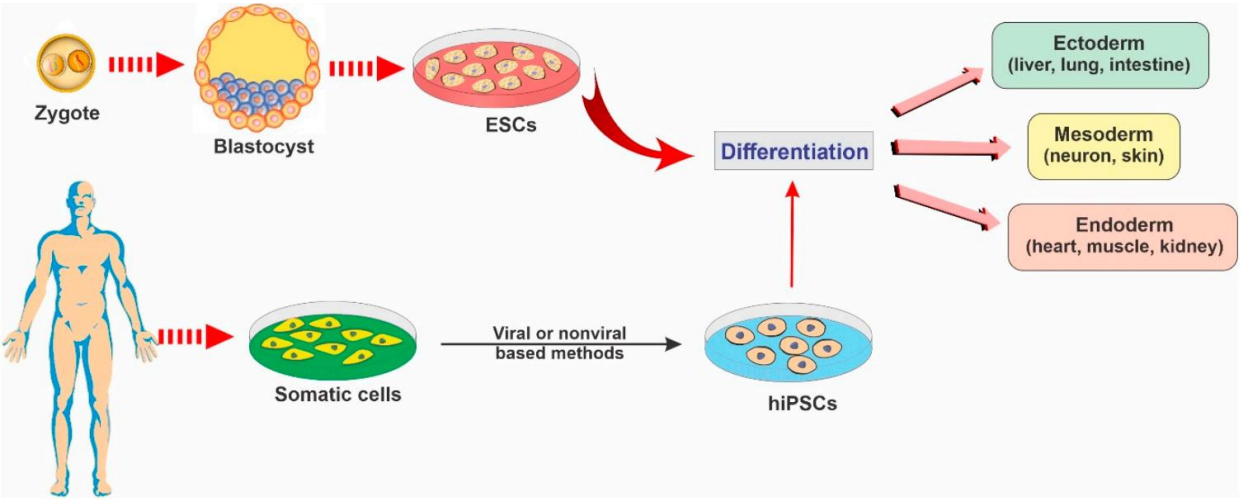


Figure (1): Representative diagram depicting the main types of stem cells and their potential to differentiate into various lineages.

Embryonic stem cells (ESCs)

They are pluripotency stem cells, incredibly attractive candidates for therapeutic use. They are derived from the inner cell mass of a developing blastocyst at embryonic days 5-6. Pluripotency is one of the biggest advantages, however, it is one of their main drawbacks, as their differentiation can occur in any direction, and lead to neoplasia or teratoms [15].

Neural stem cells (NSCs)

Like "Engrafted Regeneration" in some way, it is a type of stem cell that is derived from the areas of the brain that have the feature of neurogenesis, such as the sub-granular zone (SGZ) of hippocampal and the subventricular zone (SVZ) of the lateral walls of the

ventricles [1]. They are multipotent stem cells that can give rise to neurons, oligodendrocytes, or astrocytes [14].

Induced pluripotent stem cells (iPSCs)

Pluripotent stem cells are produced by reprograming derived patients' cells by defined reprogramming factors back into an embryonic-like pluripotent state. Currently, there is a limited number of studies about iPSCs, due to their novelty and ethical issues.

Mesenchymal stem cells (MSCs)

They are multipotent stromal stem cells, found normally in the body's tissue that can be isolated, such as bone marrow, umbilical cord, adipose tissue, peripheral blood, amniotic fluid, muscle, and lung. Bone marrow mesenchymal stem cells can differentiate into mesodermal tissues, which differentia from ectodermal and endodermal fates to end with the ability for use with neurological disorders.

The Routes of Stem Cell Administration

To deliver stem cells to the desired location of nervous tissue there is a variety of routes that are applied in research, comprising:

- Intraventricular, intra-subarachnoid space, and intrathecal transplantation provide effective access to pass through the BBB, allowing the stem cell to migrate and implant in the injured brain tissue area via the cerebrospinal fluid (CSF).
- Intracerebrally transplantation, delivery of clusters of stem cells, impeding their further migration towards sites of the damaged tissue, which compromises the effects and limits the application.
- Intravenous transplantation of cells overcomes the above disadvantages and can afford the transfer of a large number of SCs.
- The intraarterial route is the vascular delivery of stem cells, which can be directed to the injury site, and is more effective than the intravenous route. However, occlusion and thrombosis are the biggest problems.
- Another route is intranasal administration, which will not cause secondary injury.

It is self-evident that insufficient transplanted cells do not exert therapeutic effects, whereas an excess of cells may cause multiple complications including occlusion, thrombosis, and even the increased risk of tumor formation [18][25].

The Safety of Stem Cell Therapy

Administration of stem cells may cause severe adverse reactions and complications, such as:

- Thrombosis or embolism causes occlusion of the blood vessels which can result from excessive administration of stem cells [16].
- Immune rejection is caused by transplanted stem cells [17].
- Tumorigenicity and instability [12].
- In addition, can cause also other side effects such as seizure, infection, hyperpyrexia, and even death [12].

According to the Food and Drug Administration (FDA), other safety concerns

- Administration site reactions.
- The ability of cells to move from placement sites and change into inappropriate cell types or multiply.
- Failure of cells to work as expected.
- The growth of tumors [19].

References

1. Abdissa, D., Hamba, N., & Gerbi, A. (2020). Review Article on adult neurogenesis in humans. Translational Research in Anatomy, 20, 100074. https://doi.org/10.1016/j.tria.2020.100074
2. Sivandzade, F., & Cucullo, L. (2021). Regenerative Stem Cell Therapy for Neurodegenerative Diseases: An Overview. International journal of molecular sciences, 22(4), 2153. https://doi.org/10.3390/ijms22042153
3. Kanwar, J. R., Sriramoju, B., & Kanwar, R. K. (2012). Neurological disorders and therapeutics targeted to surmount the blood-brain barrier. International journal of nanomedicine, 7, 3259–3278. https://doi.org/10.2147/IJN.S30919
4. Hoang DM, Pham PT, Bach TQ, et al. Stem cell-based therapy for human diseases. Signal Transduct Target Ther. 2022;7(1):272. Published 2022 Aug 6. doi:10.1038/s41392-022-01134-4
5. World Health Organization: WHO. (2023, March 15). https://www.who.int/news-room/fact-sheets/detail/dementia
6. Mattson, M.P. Pathways towards and away from Alzheimer's disease. Nature 2004, 430, 631–639. [CrossRef] [PubMed]
7. Alzheimer's Disease International. (2018, September 21). *World Alzheimer Report 2018: The state of the art of dementia research: New frontiers*. ADI - World Alzheimer Report 2018. https://www.alzint.org/resource/world-alzheimer-report-2018/
8. Wang, R., & Reddy, P. H. (2017). Role of Glutamate and NMDA Receptors in Alzheimer's Disease. *Journal of Alzheimer's disease: JAD*, *57*(4), 1041–1048. https://doi.org/10.3233/JAD-160763
9. Tafti, D. (2022, September 7). Multiple Sclerosis. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK499849/#:~:text=The%20pathophysiology%20of%20MS%20is,blood-brain%20barrier%20(BBB)
10. Marret, S., Vanhulle, C., & Laquerriere, A. (2013). Pathophysiology of cerebral palsy. *Handbook of clinical neurology*, *111*, 169–176. https://doi.org/10.1016/B978-0-444-52891-9.00016-6
11. Website, N. (2022, November 11). Parkinson's disease. nhs.uk. https://www.nhs.uk/conditions/parkinsons-disease/
12. Gao, L., Xu, W., Li, T., Chen, J., Shao, A., Yan, F., & Chen, G. (2018). Stem Cell Therapy: A Promising Therapeutic Method for Intracerebral Hemorrhage. *Cell transplantation*, *27*(12), 1809–1824. https://doi.org/10.1177/0963689718773363
13. Hung, C. W., Liou, Y. J., Lu, S. W., Tseng, L. M., Kao, C. L., Chen, S. J., Chiou, S. H., & Chang, C. J. (2010). Stem cell-based neuroprotective and neurorestorative strategies. *International journal of molecular sciences*, *11*(5), 2039–2055. https://doi.org/10.3390/ijms11052039
14. Vasic, V., Barth, K., & Schmidt, M. H. H. (2019). Neurodegeneration and Neuro-Regeneration-Alzheimer's Disease and Stem Cell Therapy. *International journal of molecular sciences*, *20*(17), 4272. https://doi.org/10.3390/ijms20174272
15. Fujikawa, T.; Oh, S.-H.; Pi, L.; Hatch, H.M.; Shupe, T.; Petersen, B.E. Teratoma formation leads to failure of treatment for type i diabetes using embryonic stem cell-derived insulin-producing cells. Am. J. Pathol. 2005, 166, 1781–1791. [CrossRef]

16. Banerjee S, Williamson D, Habib N, Gordon M, Chataway J. Human stem cell therapy in ischaemic stroke: a review. Age Ageing. 2011;40(1):7–13.
17. Barker RA, Widner H. Immune problems in central nervous system cell therapy. NeuroRx. 2004;1(4):472–481.
18. Rodriguez-Frutos B, Otero-Ortega L, Gutierrez-Fernandez M, Fuentes B, Ramos-Cejudo J, Diez-Tejedor E. Stem cell therapy and administration routes after stroke. Transl Stroke Res. 2016; 7(5):378–387.
19. Office of the Commissioner & Office of the Commissioner. (2019, September 3). FDA Warns About Stem Cell Therapies. U.S. Food And Drug Administration. https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies
20. Mousaei Ghasroldasht, M.; Seok, J.; Park, H.-S.; Liakath Ali, F.B.; Al-Hendy, A. Stem Cell Therapy: From Idea to Clinical Practice. Int. J. Mol. Sci. 2022, 23, 2850. https://doi.org/10.3390/ijms23052850
21. Alessandrini, M., Preynat-Seauve, O., De Bruin, K., & Pepper, M. S. (2019). Stem cell therapy for neurological disorders. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 109(8b), 70–77. https://doi.org/10.7196/SAMJ.2019.v109i8b.14009
22. Hoang, D. M., Pham, P. T., Bach, T. Q., Ngo, A. T. L., Nguyen, Q. T., Phan, T. T. K., Nguyen, G. H., Le, P. T. T., Hoang, V. T., Forsyth, N. R., Heke, M., & Nguyen, L. T. (2022). Stem cell-based therapy for human diseases. Signal transduction and targeted therapy, 7(1), 272. https://doi.org/10.1038/s41392-022-01134-4
23. Zayed, M.A.; Sultan, S.; Alsaab, H.O.; Yousof, S.M.; Alrefaei, G.I.; Alsubhi, N.H.; Alkarim, S.; Al Ghamdi, K.S.; Bagabir, S.A.; Jana, A.; Alghamdi, B.S.; Atta, H.M.; Ashraf, G.M. Stem-Cell-Based Therapy: The Celestial Weapon against Neurological Disorders. Cells 2022, 11, 3476. https://doi.org/10.3390/cells11213476
24. Oboudiyat, C., Glazer, H., Seifan, A., Greer, C., & Isaacson, R. S. (2013). Alzheimer's disease. Seminars in neurology, 33(4), 313–329. https://doi.org/10.1055/s-0033-1359319
25. Willing, A. E., Garbuzova-Davis, S., Sanberg, P. R., & Saporta, S. (2002). Routes of stem cell administration in the adult rodent. Methods in molecular biology (Clifton, N.J.), 198, 357–374. https://doi.org/10.1385/1-59259-186-8:357

Article topic: Cerebellum: The Little Brain.

Author: Abed Dhadil.

Editors: Yara Alswaiti, Rawan Hamamreh.

Reviewer: Omar B. Sanduka.

Overview

The cerebellum is a crucial part of the brain located at the posterior region of the head. Its primary functions include postural adjustment and the maintenance of balance [1]. Moreover, the cerebellum plays a pivotal role in motor skills and functions. This process typically involves a shift from "controlled" to "automatic" processing, wherein movements that initially necessitate problem-solving and focused attention become progressively more efficient, stereotypical, less responsive to real-time feedback, and notably demand reduced attention [2]. Across all vertebrates, the cerebellum develops from two bilaterally symmetrical anlagen, which are dorsally positioned at the anterior end of the rhombencephalon [3]. Dysfunction in the cerebellum is clear in various developmental disorders, including autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and developmental dyslexia. Furthermore, damage to the cerebellum during early development can have enduring impacts on motor skills, cognition, and emotional regulation [4].

Introduction

The cerebellar cortex consists of several distinct components, including granule cells, Purkinje cells, and two types of inhibitory interneurons known as Golgi cells and stellate/basket cells. This cortex receives input from three types of extracerebellar afferents: mossy fibers, climbing fibers (both of which are excitatory), as well as diffusely organized monoaminergic and cholinergic afferents.

The output of the cerebellar cortex follows a unique pattern organized into parallel longitudinal zones. These zones can span one or more lobules, with some extending across the entire rostrocaudal length of the cerebellum. It is important to note that within the vermis and hemispheres, these zones are still parallel to the long axis of the folial chains [5] (see Figure 1 for reference).

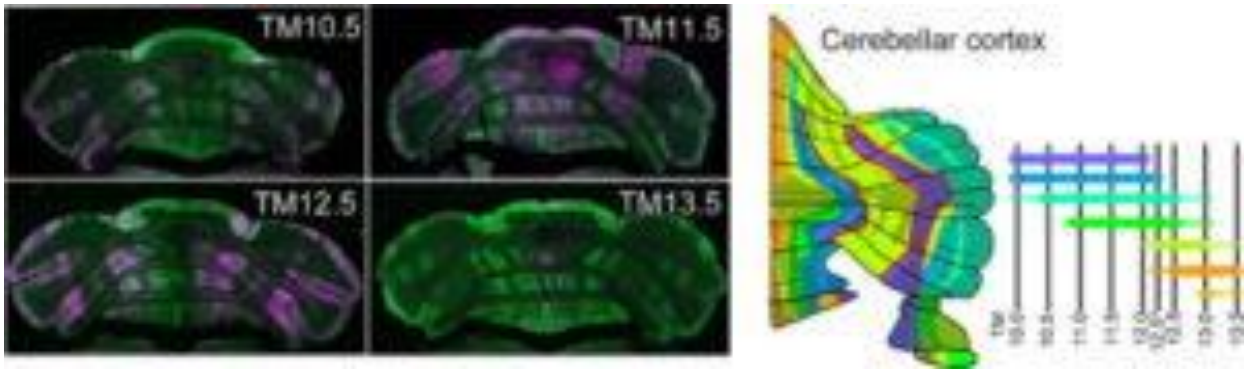


Figure 1: Striped distribution pattern of Purkinje cells of different birthdates in the mouse cerebellar cortex [6].

Physiology and Function

The primary function of the cerebellum encompasses motor control, which includes regulating movement and balance and maintaining kinesthetic homeostasis. Additionally, the cerebellum has a secondary, albeit minor, non-motor function. Mossy fibers, originating from neurons in the brainstem, synapse onto granule cells. These granule cells send out axons referred to as parallel fibers, which ascend into the higher layers and levels of the cerebellar cortex. There, they branch and establish excitatory connections with numerous Purkinje cells, often numbering in the thousands. Some of the parallel fibers also synapse on basket or stellate cells, which in turn inhibit the Purkinje cells. Additionally, certain parallel fibers synapse on the dendrites of Golgi cells, which makes inhibitory connections back to the granule cells. Mossy fiber collaterals project onto neurons located in the deep cerebellar nuclei. Climbing fibers originate in the inferior olive and ascend to the cerebellar cortex. There, they wind around one or two Purkinje cells, forming thousands of synaptic contacts with them. Climbing fibers also send their collaterals directly to neurons in the deep cerebellar nuclei [7].

Psychological function of the cerebellum

The cerebellum is thought to play a significant role in adapting general problem-solving circuitry to specific contextual demands. Prefrontal cortical regions, which are involved in complex problem-solving tasks, may develop a generalized cognitive program that is then refined through interaction with the cerebellum. This collaboration between brain regions represents a precise and coherent solution to cognitive challenges. This function can be described as attentional, particularly in the context of certain tasks that require the specific identification of relevant stimuli for processing. Error-correcting feedback mechanisms are crucial for organizing this coherence, potentially acting as a filter to determine which components of available systems are integrated into the coherent solution. For instance, if a critical stimulus is omitted from the motor or cognitive program, error correction mechanisms will ensure the inclusion of all necessary

circuitry in the coherent solution. Furthermore, the exclusive inhibitory function in the essential cortico-nuclear connection can be likened to a circuit breaker, serving as the ultimate stabilization device. It facilitates the dissolution of coherence when necessary, allowing for transitions into new behavioral modes. This includes shifts from feedback to feedforward movement phases, the release of a conditioned eye blink, or preparation for new stimuli in cognitive tasks. In light of these observations, we propose that the cerebellum actively participates in a range of psychological functions, including attention, timing, and learning [7]. Figure (2)

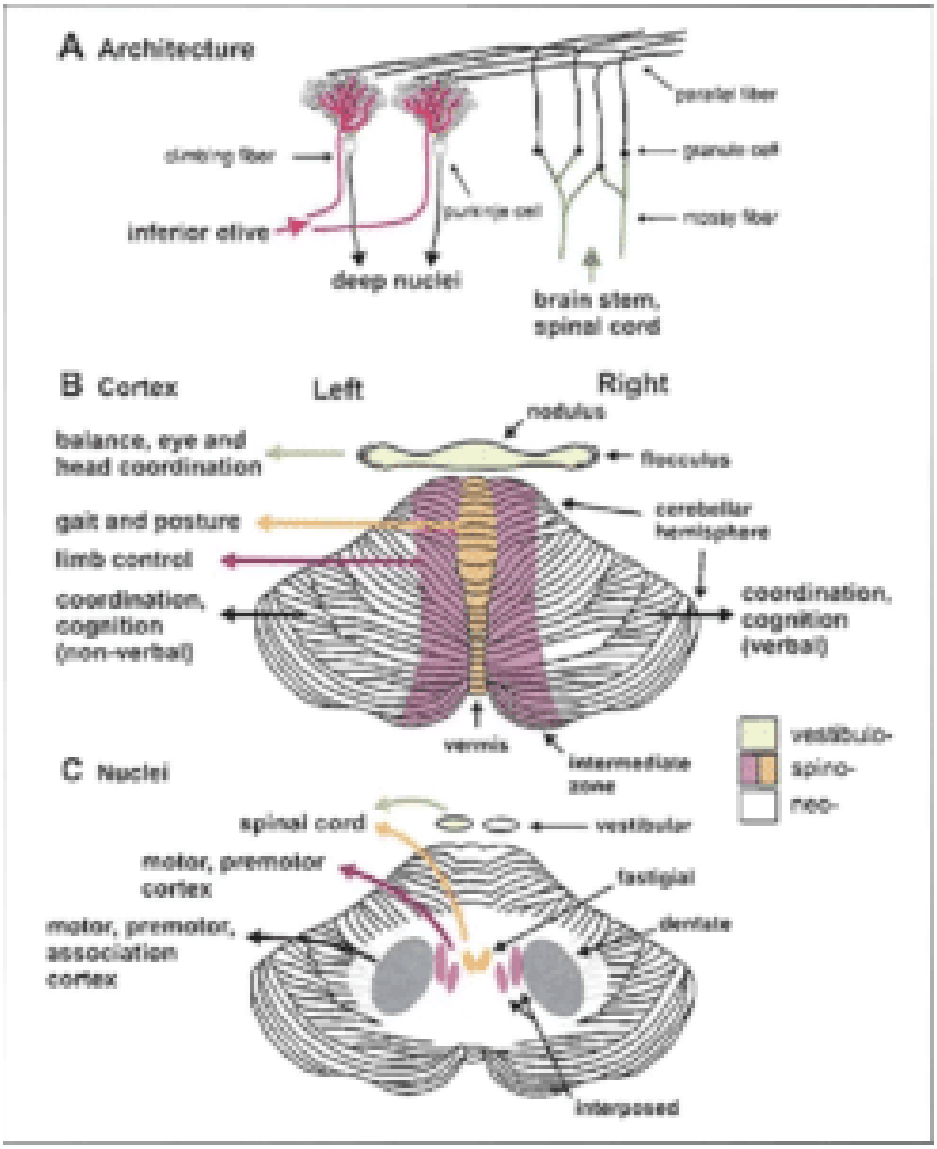


Figure 2: Anatomical and functional organization of the cerebellum [8]

Components

Grey matter –On the surface of the cerebellum. It is tightly folded, forming the cerebellar cortex. The gray matter of the cortex is divided into three layers: an external -

the molecular layer; a middle - the Purkinje cell layer; and an internal - the granular layer. The molecular layer contains two types of neurons: the outer stellate cell and the inner basket cell.

White matter – Located underneath the cerebellar cortex. There are four nuclei embedded in the white matter (the dentate, emboliform, globose, and fastigi nuclei). (Figure 3)

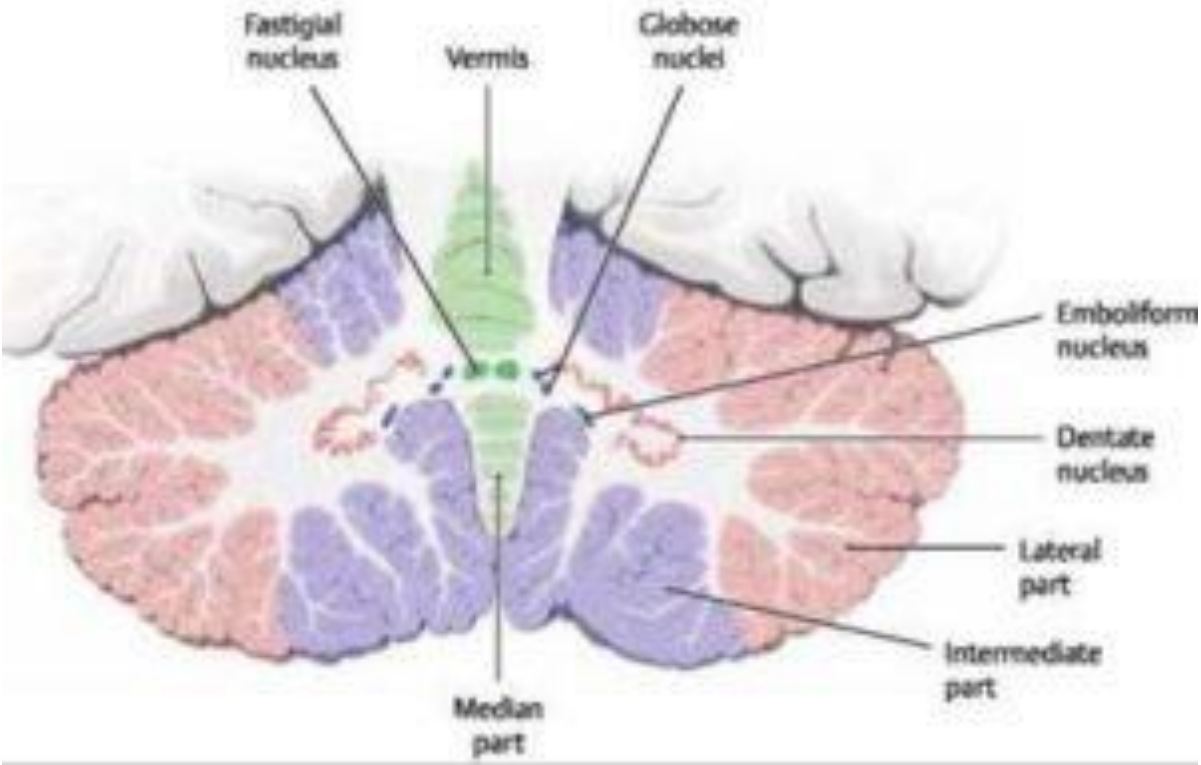


Figure 3: Nuclei of the cerebellum. [9]

The deep cerebellar nuclei

The dentate nucleus, positioned as the most lateral of the cerebellar nuclei and distinguished by its richness in iron, lives near both the cerebellar vermis and the roof of the fourth ventricle. Its pivotal role encompasses the regulation of fine control over voluntary motor movements, cognitive processes, language, and various sensory functions.

The dentate nucleus has two parts: the dorsal (motor) domain which has connections with cortical motor areas that regulate motor functions, and the ventral (non-motor) domain which has links with the cortical association areas that control major cognitive functions.

Input to the dentate nucleus

Afferent proprioceptive information synapses with dentate nucleus neurons through the spinocerebellar tract through the inferior cerebellar peduncle. Both the premotor cortex and supplementary cortex neurons also synapse with the dentate nucleus. [10]

Output to the thalamus

Utilizing the dentate-thalamic tract, the dentate nucleus sends output signals via the ipsilateral superior cerebral peduncle and then decussates to synapse the contralateral ventrolateral (VL) thalamic nucleus. VL neurons then send fibers to the precentral gyrus (primary motor cortex; M1), premotor cortex, prefrontal gyri, posterior parietal areas, and the basal ganglia – specifically the striatum and the substantia nigra. [10]

Myoclonic triangle

The myoclonic triangle, also known as the triangle of Guillain-Mollaret, comprises the dentate nucleus, the red nucleus, and the inferior olivary nucleus (ION) located within the medulla oblongata. This intricate network plays a pivotal role in the control of fine voluntary movements. Through the dentate-rural tract, the dentate nucleus sends fibers via the superior cerebellar peduncle to the contralateral red nucleus. Parvocellular red nucleus axons, in turn, establish synapses with the ipsilateral ION through the central tegmental tract. Axons originating from the ION traverse through the inferior cerebral peduncle as climbing fibers, ultimately reaching the contralateral cerebellar cortex, where they synapse on Purkinje cells. Subsequently, Purkinje cells complete the loop by synapsing with the ipsilateral dentate nucleus. [10]

Cerebellar Purkinje cells

Cerebellar Purkinje cells, which are GABA-ergic neurons located in the cerebellar cortex, synapse on deep cerebellar nuclei such as the dentate nucleus. They have an inhibitory role on the deep cerebellar nuclei. [10]

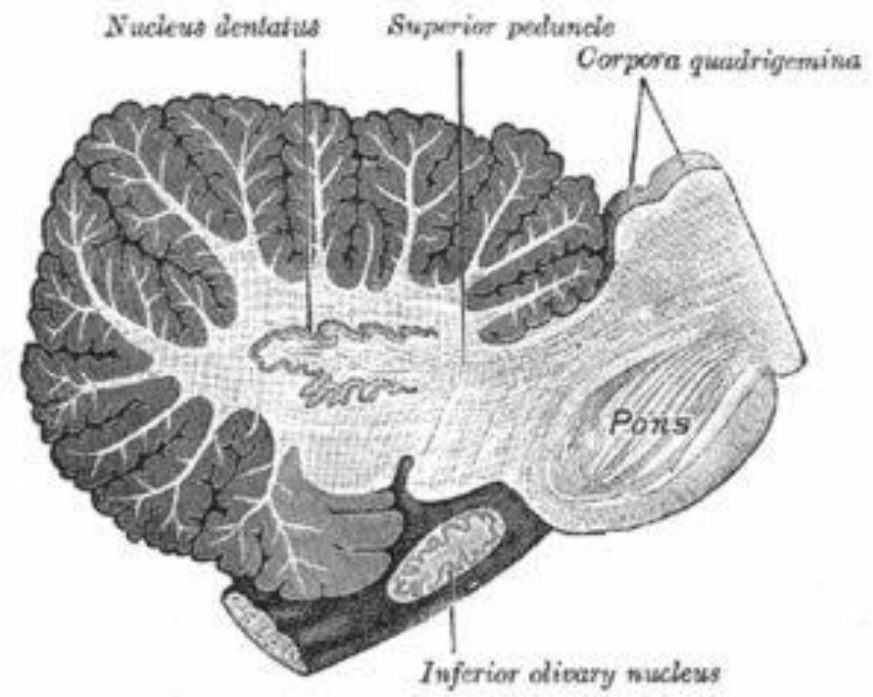


Figure 4: Dentate nucleus, case courtesy of Craig Hacking. [11]

The fastigial nucleus (medial)

The caudal fastigial nuclei (cFN) are the output nuclei by which the medio-posterior cerebellum influences the production of the visual saccades. Unilateral inactivation of the caudal fastigial nucleus results in a reduced accuracy of saccades directed toward moving targets. [12]
Similar to saccades aimed at stationary targets, interceptive saccades exhibit a hypometric pattern when directed towards the contralesional side and a hypermetric pattern when directed towards the ipsilesional side. The dysmetria depends on target velocity, but the use of accelerating or decelerating targets reveals that velocity is not the crucial parameter. [12]

The major cerebellar circuit

The ultimate destination of afferent pathways to the cerebellar cortex is a distinctive cell type called Purkinje cell. However, the input from the cerebral cortex to the Purkinje cells is indirect. Neurons in the pontine nuclei receive a projection from the cerebral cortex and then relay the information to the contralateral cerebellar cortex. The axons from the pontine nuclei and other sources are called mossy fibers (because of the appearance of their synaptic terminals). Mossy fibers then synapse on granule cells in the granule cell layer of the cerebellar cortex. The cerebellar granule cells are widely held to be the most abundant class of neurons in the brain. They give rise to specialized axons called parallel fibers that ascend to the molecular layer (external or outermost layer) of the cerebellar cortex. The parallel fibers bifurcate in the molecular layer to form

T-shaped branches that relay information via excitatory synapses onto the dendritic spines of the Purkinje cells. [13]

Cerebellar dysfunction

Cerebellar dysfunction is associated with many manifestations and alternations in cerebellar functions including, decreased muscle tone (hypotonia), eye problems, including double vision and involuntary eye movements (nystagmus), poor muscle coordination in the limbs (ataxia). As previously mentioned, it appears to have a critical role in autism spectrum disorder (ASD).

The role of cerebellar dysfunction in ASD patients

In ASD patients, there are observable increased connections between the supra-modal regions of the cerebellum and the sensorimotor cortex, as well as reciprocal connections. Furthermore, research has subdivided the temporoparietal junction, a region crucial for social cognition, into eleven subdivisions. It was noted that ASD patients display a decrease in connectivity between the right dorsal temporoparietal junction and the left cerebellar Crus II.

However, it is essential to acknowledge that different studies have reported varying findings. One study, for instance, observed an increase in functional connectivity between the left inferior parietal lobule and the right Crus I in ASD patients. These diverse outcomes underscore the ongoing debate regarding which specific regions of the cerebellum and cerebral cortex play a significant role in ASD etiology.

Additional studies have highlighted decreased resting state connectivity between the left cerebellar dentate nucleus and cortical regions associated with the theory of mind and mode networks in adults with ASD. Furthermore, hyperconnectivity was detected between the left dentate nucleus and supra-modal regions of the cerebellum in ASD patients. Lastly, one study revealed a significant decrease in the volume of the right Crus II and a reduction in connectivity between the right Crus II and the frontal, temporal, and parietal regions in individuals with ASD. [14]

Role of genetics in cerebellar dysfunction and ASD

The majority of ASD cases result from multiple genetic mutations and exhibit a high degree of heritability. To investigate the cognitive, emotional, and motor dysfunctions associated with this disorder, the creation of animal models, such as rodents, with genetic mutations linked to ASD becomes an appealing avenue of study.

Utilizing mouse models, which enables the manipulation of genetic factors, proves to be an effective method for elucidating the impacts of both distal and proximal etiological influences on cerebellar function and cerebro-cerebellar circuitry. The insights gained

from mouse models serve to validate and expand our comprehension of the neurochemical and behavioral consequences brought about by genetic changes. Furthermore, these models aid in the search for biomarkers of ASD.

Researchers can use the advantages offered by mouse genetics to explore whether cerebellar dysfunction alone can give rise to ASD-related behaviors.

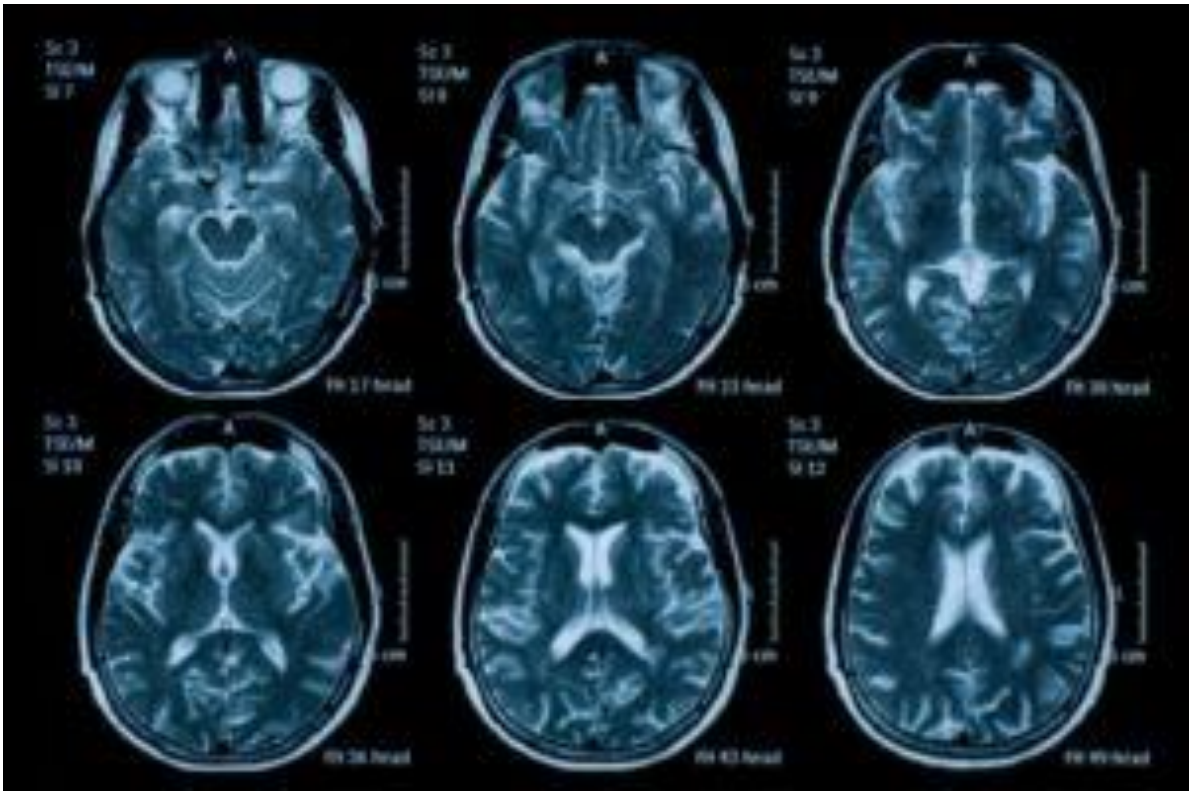


Figure 5: Brain scan of an ASD patient by Devika G. Bansal. [15]

Autosomal dominant cerebellar ataxia

Autosomal dominant cerebellar ataxias (ADCA) have traditionally been classified into ADCA types I, II, and III, as well as episodic ataxia, based on clinical criteria.

ADCA type I (linked to gait and position): In ADCA type I, individuals experience cerebellar ataxia affecting both gait and limb function. This presentation may vary and is often accompanied by a range of added features such as supranuclear ophthalmoplegia, slow saccades, optic atrophy, pyramidal and extrapyramidal symptoms (e.g., parkinsonism, dystonia, chorea), sphincteric disturbances, mild to moderate dementia, amyotrophy, and peripheral neuropathy. [16]

ADCA type II shares the same clinical phenotype as ADCA type I but is further associated with macular degeneration. ADCA type III manifests as late-onset cerebellar atrophy.

In recent years, ADCA has undergone subdivision into various types known as spinocerebellar ataxias (SCAs), encompassing numbers one through sixteen. This classification is based on the specific genes or chromosomal loci associated with the disease. The different forms of ADCA have several clinical and genetic features: (a) onset in adulthood; (b) occurrence of anticipation, i.e. earlier age at onset and increasing severity of the disease in subsequent generations; (c) cerebellar atrophy or olivopontocerebellar atrophy seen in brain imaging studies; (d) molecular defects in the cloned genes consisting of an expansion of trinucleotide or pentanucleotide repeats; and (e) presence of an inverse correlation between expansion size and the degree of clinical involvement. The majority of spinocerebellar ataxias, and the form named dentatorubral-pallidoluysian atrophy (DRPLA), are due to pathological expansions of a CAG-repeated sequence within the coding region, the part of the gene that will be eventually transcribed and translated into protein, of the corresponding genes. The mutated proteins, which carry the elongated polyglutamine tract, supposedly gain a toxic function, leading to neuronal cell death and neurodegeneration. [16]

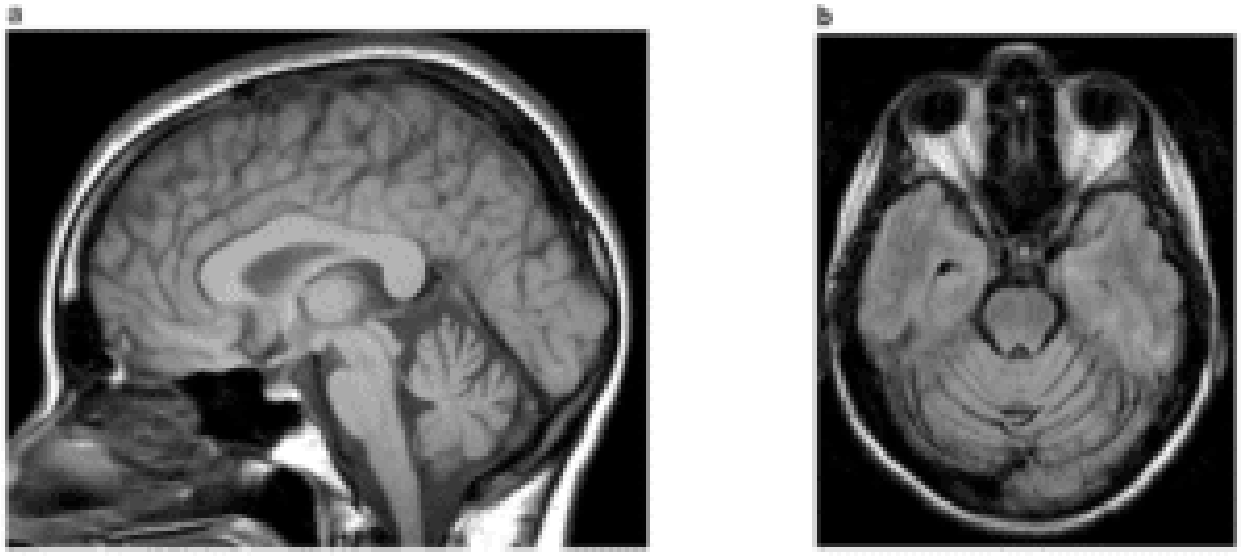


Figure 6: The MR (T1) brain (A) sagittal, (B) axial in a 54-year-old African American male with genetically confirmed SCA2 who presented with cerebellar ataxia, dysarthria, slowed saccades, and peripheral neuropathy demonstrates cerebellar and brainstem atrophy. [17]

Cerebellar tumors

The cerebellum is the most common site of presentation of CNS tumors in children, but it is extremely rare in adults. Children usually present with acute symptoms related to increased intracranial pressure that require urgent surgical intervention. The differential diagnosis is broad and includes a variety of benign and malignant entities. [18]

- **Pediatric low-grade gliomas (PLGGs)**
  Benign tumors of glial origin can arise anywhere in the central nervous system,

most commonly (one-third of tumors) in the cerebellum. The most common histology is a pilocytic astrocytoma, characterized by the presence of cells with bipolar “hair-like” processes, low mitotic index, and the presence of Rosenthal fibers on histology. Though PLGGs are often associated with genetic predisposition syndromes – most notably neurofibromatosis type 1 (15%) – the lesions in children with neurofibromatosis type 1 are located in the optic pathway, while cerebellar tumors are uncommon. [18]

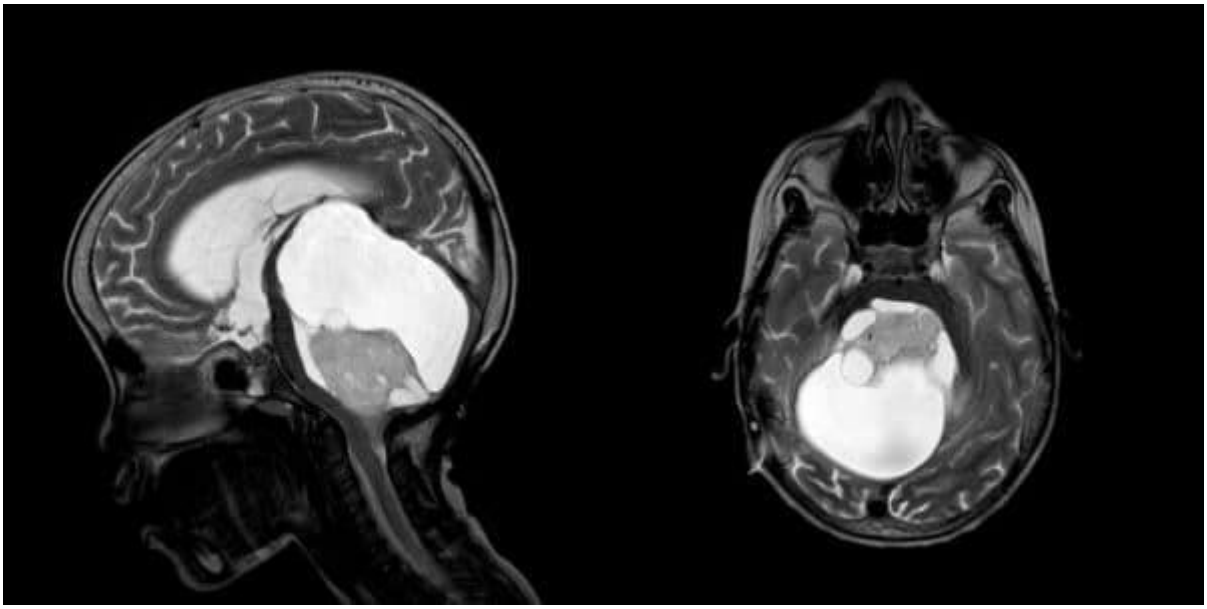


Figure 7: Sagittal & axial sections of a pilocytic astrocytoma. Case courtesy of Abiola Ayodele. [19]

- **Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos-disease)**
  Lhermitte-Duclos-disease is a slow-growing cerebellar mass. It is a matter of debate whether it represents a neoplasm or a hamartoma. Histologically, the lesion comprises dysplastic ganglion cells localized predominantly in the internal granule cell layer. Imaging characteristics may be enough for diagnosis, due to a typical striated pattern on T2-weighted sequences with a lack of contrast enhancement. It is associated with Cowden syndrome, an autosomal-dominant multiple hamartoma-neoplasia syndrome caused by germline mutations in the tumor suppressor gene (PTEN) on chromosome number 10. [18]
- **Hemangioblastoma**
  Hemangioblastomas are benign tumors that arise in the cerebellum, brainstem, and/or spinal cord/canal, that occur sporadically (often solitary) or are associated with von Hippel–Lindau disease (usually multiple lesions). [18]
- **Medulloblastoma (MB)**
  Medulloblastomas are malignant embryonal tumors of the cerebellum. Although

prevalent across the entire age spectrum, they are extremely rare in adults (< 1% of adult CNS tumors). In children aged 0–14 years, MB is the most common embryonal brain tumor with an age-adjusted incidence rate of 0.49 per 100,000. There are four molecular subgroups of MB – wing-less (WNT), sonic hedgehog (SHH), group 3, and group 4 – with distinct clinical features, cells of origin, pathogenesis, and outcome. WNT-MBs are believed to originate from dorsal brainstem progenitors of the lower rhombic lip and arise at the level of the cerebellopontine angle and cerebellar peduncle. They account for 10% of MBs and display WNT pathway activation, due to mutations in (CTNNB1) gene encoding beta-catenin. With a low propensity to metastasize and a good response to different treatment regimens (overall survival of more than 90%), WNT tumors have the best prognosis of all four subgroups. [18]

Conclusion

The cerebellum is a part of the brain that is responsible for the coordination of voluntary motor movement, balance and equilibrium, and muscle tone. It is located at the back of the brain, underlying the occipital and temporal lobes of the cerebral cortex. Damage or degeneration to cerebellar structures can lead to serious conditions and syndromes such as ASD & ataxia, among others.

References

1. James Knierim. chapter 5 : cerebellum. Neuroscience.
2. Koziol LF, Budding D, Andreasen N *et al.* Consensus paper: the cerebellum's role in movement and cognition. Cerebellum 2014; 13: 151–177.
3. Nieuwenhuys R. Comparative anatomy of the cerebellum. Prog Brain Res 1967; 25: 1–93.
4. Stoodley CJ. The Cerebellum and Neurodevelopmental Disorders. Cerebellum 2016; 15: 34–37.
5. Voogd J, Glickstein M. The anatomy of the cerebellum. Trends Neurosci 1998; 21: 370–375.
6. Zhang J, Tran-Anh K, Hirata T, Sugihara I. Striped Distribution Pattern of Purkinje Cells of Different Birthdates in the Mouse Cerebellar Cortex Studied with the Neurog2-CreER Transgenic Line. Neuroscience 2021; 462: 122–140.
7. Katz DB, Steinmetz JE. Psychological functions of the cerebellum. Behav Cogn Neurosci Rev 2002; 1: 229–241.
8. Hawkes RB. Cerebellum: Anatomy and Organization. In: Encyclopedia of Life Sciences. John Wiley & Sons, Ltd, 2001.
9. Khonsary SA. THIEME Atlas of Anatomy, Head and Neuroanatomy. Surgical Neurology International 7 2016.
10. de Leon AS, M Das J. Neuroanatomy, Dentate Nucleus. In: Treasure Island (FL), 2023.
11. Hacking C, Dentate nucleus (Gray's illustration). Case study R or. dentate nucleus. https://radiopaedia.org/cases/81788.
12. Bourrelly C, Quinet J, Goffart L. The caudal fastigial nucleus and the steering of saccades toward a moving visual J Neurophysiol 2018; 120: 421–438.
13. Purves D, Augustine GJ, Fitzpatrick D, et al. E, Associates S (MA): S. Neuroscience. 2nd edition. 2001.
14. Su L-D, Xu F-X, Wang X-T, Cai X-Y, Shen Y. Cerebellar Dysfunction, Cerebro-cerebellar Connectivity and Autism Spectrum Neuroscience 2021; 462: 320–327.
15. Devika G. Bansal. brain scan to an autism patient. UCSF.
16. Mariotti C, Di Donato S. Cerebellar/spinocerebellar syndromes. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol 2001; 22 Suppl 2: S88-92.
17. Whaley NR, Fujioka S, Wszolek ZK. Autosomal dominant cerebellar ataxia type I: A review of the phenotypic and genotypic characteristics. Orphanet J Rare Dis 2011; 6: 33.
18. Guerreiro Stucklin AS, Grotzer MA. Cerebellar tumors. Handb Clin Neurol 2018; 155: 289–299.
19. Ayodele A, Pilocytic astrocytoma. Case study R or. pilocytic astrocytoma. https://radiopaedia.org/cases/92828.

FIRST EDITION

NEUROPEDIA

FOR TRAINING AND SCIENTIFIC RESEARCH

JORDAN

WWW.NEUROPEDIA.NET

ISBN 978-9923-9419-0-4