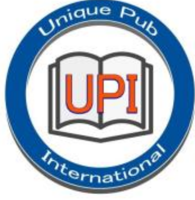

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MIGRAINE: A REVIEW ON ITS HISTORY, SYMPTOMS, AND ITS TREATMENT

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Abstract

Migraine is a prevalent and disabling neurological disorder characterized by recurrent episodes of moderate to severe headache, often accompanied by nausea, vomiting, photophobia, and phonophobia. Historically documented in Egyptian, Greek, and Roman medical texts, the understanding of migraine has evolved from humoral theories to modern neurovascular models. Migraine is classified into several subtypes, with migraine without aura being the most common. Clinical presentation often follows a multi-phase pattern including prodrome, aura, headache, and postdrome. The pathophysiology involves cortical spreading depression, activation of the trigeminovascular system, release of inflammatory neuropeptides like CGRP, serotonin dysregulation, and genetic predisposition. Diagnosis is guided by the ICHD-3 criteria and requires differentiation from other headache types such as tension-type and cluster headaches. Treatment includes both acute therapies (e.g., triptans, NSAIDs, gepants) and preventive approaches (e.g., beta-blockers, CGRP monoclonal antibodies). Non-pharmacological interventions such as cognitive behavioral therapy, neuromodulation devices, and dietary supplements offer additional benefits. Recent advances include CGRP-targeted drugs, wearable technologies, and personalized medicine strategies. This review emphasizes the need for early diagnosis, individualized treatment, and multidisciplinary care to improve outcomes. Continued research on biomarkers and new therapeutic targets holds promise for better prevention and management of migraine.

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Introduction

Migraine is a chronic, episodic neurological disorder characterized by recurrent attacks of moderate to severe headache, often accompanied by a range of autonomic and sensory disturbances [1]. It is more than just a headache; migraine involves a complex interplay of genetic, environmental, and neurovascular factors that affect the brain's pain-processing pathways. Typically presenting as a unilateral, throbbing pain that may last from 4 to 72 hours, migraine can be aggravated by routine physical activity and is commonly associated with symptoms such as nausea, photophobia (sensitivity to light), phonophobia (sensitivity to sound), and, in some cases, visual or sensory aura [2,3].

Globally, migraine affects over one billion people and is considered the second leading cause of years lived with disability (YLDs), particularly among individuals aged 15–49 years. Women are disproportionately affected due to hormonal influences, with a threefold higher prevalence compared to men. The economic and societal burden of migraine is profound, not only due to direct healthcare costs but also because of lost productivity, absenteeism, and decreased quality of life. Repeated attacks can significantly impair daily functioning, social engagement, and mental well-being, making migraine a substantial public health challenge[4-7].This review aims to provide a comprehensive overview of migraine by exploring its historical background, clinical manifestations, underlying pathophysiological mechanisms, diagnostic criteria, and evolving treatment modalities. Special emphasis is placed on both conventional pharmacological therapies and recent advances such as CGRP-targeted treatments and neuromodulation techniques. By synthesizing current evidence, the review seeks to offer insights that support improved diagnosis, management, and future research directions in migraine care.

Historical Background

The recognition of migraine as a distinct medical condition dates back to ancient civilizations, with detailed descriptions found in Egyptian, Greek, and Roman medical texts. One of the earliest accounts appears in the Ebers Papyrus (circa 1500 BCE), where headache remedies involving herbal applications and rituals were recorded. The Greek physician Aretaeus of Cappadocia (2nd century CE) described a condition he termed *heterocrania*, characterized by one-sided head pain, which closely resembles the modern clinical presentation of migraine. Similarly, Galen (129–200 CE) coined the term *hemicrania*, meaning pain in one half of the head, which eventually evolved into the modern word "migraine," derived from the French *migraigne* and Latin *hemicrania*[8,9].

Early interpretations of migraine were rooted in the humoral theory, where imbalances in bodily fluids—blood, phlegm, yellow bile, and black bile—were believed to cause disease. Headaches were often attributed to an excess of bile or blood, leading to treatments such as bloodletting, purging, and application of herbal poultices. With the advent of modern medicine, these theories gave way to vascular hypotheses, particularly the idea that migraine was caused by vasodilation of intracranial arteries following a period of vasoconstriction[10,11].

Significant milestones in migraine research emerged during the 20th century, notably the serotonin (5-HT) theory, which linked migraine pathophysiology to fluctuations in serotonin levels. This discovery led to the development of triptans, the first class of drugs specifically designed to abort migraine attacks by targeting 5-HT1B/1D receptors. In recent years, the identification of calcitonin gene-related peptide (CGRP) as a key mediator in migraine has revolutionized treatment strategies, ushering in the era of CGRP antagonists and monoclonal antibodies. These scientific advancements have not only deepened our understanding of migraine but have also transformed it from an enigmatic ailment into a treatable neurological disorder [12-14].

Types of Migraine

Migraine is a heterogeneous disorder with several clinically recognized subtypes. The most common type is migraine without aura, characterized by recurrent headaches without preceding neurological disturbances. Migraine with aura, also known as classic migraine, involves transient visual, sensory, or speech disturbances that precede the headache. Chronic migraine is defined as headaches occurring on 15 or more days per month for more than 3 months, with migraine features on at least 8 of those days. Other less common forms include hemiplegic migraine, which presents with motor weakness, vestibular migraine, characterized by episodic vertigo, and menstrual-related migraine, which is linked to hormonal fluctuations around menstruation[15-19].

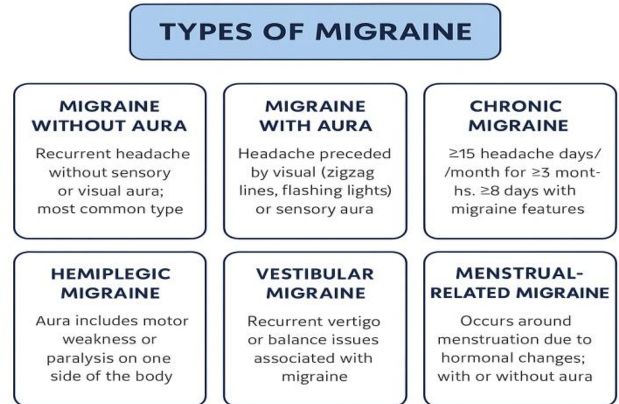

Fig.1: Types of Migraine

Symptoms and Clinical Features

Migraine is a complex neurological condition that typically progresses through a series of phases, though not all individuals experience every phase in every attack. The clinical presentation varies significantly among patients and even across different episodes in the same patient. Understanding these phases is essential for accurate diagnosis and effective management [20-23].

Table 1: Phases and Symptoms of Migraine

Phase	Timing	Key Symptoms
Prodrome	Hours to 1–2 days before	Fatigue, mood changes, food cravings, yawning, neck stiffness
Aura	Before or with headache onset	Visual: flashes, zigzags; Sensory: tingling; Aphasia; Motor weakness (rare)
Headache	4 to 72 hours	Unilateral, pulsatile pain; nausea, vomiting, photophobia, phonophobia
Postdrome	Up to 48 hours post-headache	Fatigue, cognitive fog, depression, neck pain, dizziness

Pathophysiology

The pathophysiology of migraine is multifactorial and not yet fully understood. However, advances in neuroimaging, molecular biology, and pharmacology have significantly improved our understanding of the neurovascular and neuroinflammatory mechanisms underlying migraine attacks [24-29].

Cortical Spreading Depression (CSD)

Cortical Spreading Depression is a slow-moving wave of neuronal and glial depolarization that travels across the cerebral cortex, followed by a period of neural suppression. It is strongly associated with migraine with aura, as it corresponds to the transient neurological

symptoms experienced during the aura phase. CSD is believed to trigger the activation of the trigeminovascular system and release of inflammatory mediators.

Activation of the Trigeminovascular System

A central mechanism in migraine is the activation of the trigeminal nerve fibers, which innervate the meninges and cerebral blood vessels. This activation leads to the release of vasoactive neuropeptides, causing neurogenic inflammation, vasodilation, and sensitization of pain pathways. These processes contribute to the development of headache and associated symptoms.

Inflammatory Neuropeptides (e.g., CGRP)

Calcitonin Gene-Related Peptide (CGRP) is one of the most studied neuropeptides in migraine pathophysiology. During migraine attacks, CGRP is released from trigeminal nerve endings, promoting vasodilation, mast cell degranulation, and enhanced transmission of nociceptive signals. Elevated CGRP levels have been consistently observed during attacks, making it a key therapeutic target in modern migraine management.

Role of Serotonin and Other Neurotransmitters

Serotonin (5-HT) plays a crucial role in modulating vascular tone and pain perception. Fluctuations in serotonin levels are associated with the initiation and resolution of migraine attacks. The efficacy of triptans, which are 5-HT1B/1D receptor agonists, underscores serotonin's involvement. Other neurotransmitters implicated include dopamine, glutamate, and GABA, all contributing to different aspects of the migraine cascade.

Genetic Predisposition and Channelopathies

Migraine has a strong genetic component, particularly in cases of familial hemiplegic migraine (FHM), which is linked to mutations in genes encoding ion channels (e.g., CACNA1A, ATP1A2, SCN1A). These channelopathies result in neuronal hyperexcitability, making individuals more susceptible to triggers that can initiate CSD and downstream migraine mechanisms.

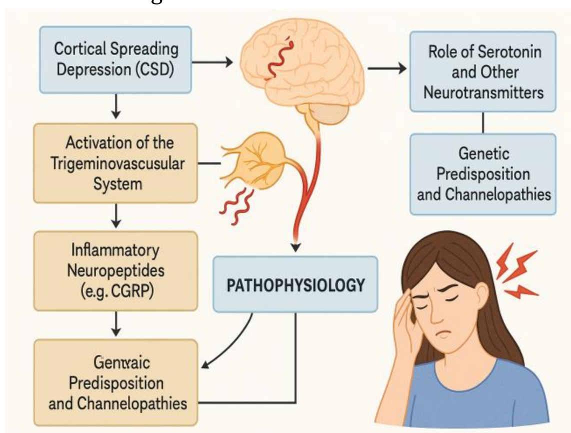

Fig.2: Pathophysiological Mechanisms of Migraine.

Diagnosis and Differential Diagnosis

The diagnosis of migraine is primarily clinical, based on patient history and the exclusion of secondary causes. The International Classification of Headache Disorders, 3rd edition (ICHD-3) provides standardized criteria to aid in the diagnosis of various headache types, including migraine. According to ICHD-3, a diagnosis of migraine without aura requires at least five attacks fulfilling the following characteristics: headache lasting 4–72 hours, with at least two of the following—unilateral location, pulsating quality, moderate to severe intensity, aggravation by physical activity—and at least one associated symptom such as nausea/vomiting or photophobia/phonophobia[30,31].

Migraine with aura is diagnosed when the patient experiences at least two attacks involving fully reversible aura symptoms (e.g., visual, sensory, speech) that develop gradually over ≥5 minutes and last between 5–60 minutes, followed or accompanied by headache [32].

It is essential to assess the duration, frequency, intensity, and characteristics of the headache, as well as associated symptoms and any aura phenomena. A thorough clinical examination and history should be complemented with investigations only when secondary headache is suspected, such as in cases with red flags like sudden-onset headache, neurological deficits, or new headache in older adults. Conditions such as brain tumors, stroke, intracranial hemorrhage, or meningitis must be ruled out when indicated [33].

Differential Diagnosis

Migraine must be distinguished from other primary headache disorders:

- **Tension-Type Headache**: Bilateral, non-pulsatile, mild to moderate intensity, not worsened by activity, and lacking nausea or aura.
- **Cluster Headache**: Severe, unilateral periorbital pain with autonomic features (e.g., lacrimation, nasal congestion); occurs in bouts.
- **Medication-Overuse Headache**: Occurs in patients using analgesics frequently; presents as a dull, daily headache often overlapping with migraine.

Early and accurate diagnosis of migraine is crucial to initiate appropriate treatment, improve outcomes, and prevent progression to chronic migraine.

Treatment Approaches

Migraine treatment involves both acute (abortive) and preventive (prophylactic) strategies, aimed at controlling symptoms, reducing attack frequency, and improving quality of life. Acute therapies are used during attacks to relieve pain and associated symptoms, while preventive treatments aim to reduce the severity and frequency of attacks over time. Non-pharmacological and complementary interventions also play a significant role, especially in patients who cannot tolerate or prefer to avoid medications [34-37].

Table 2: Treatment Approaches for Migraine

Category	Treatment Option	Mechanism/Use
Acute/Abortive Treatment		
NSAIDs & Analgesics	Ibuprofen, Naproxen, Aspirin	First-line for mild-to-moderate migraine pain relief
Triptans	Sumatriptan, Rizatriptan	5-HT1B/1D receptor agonists; abort moderate-to-severe attacks
Ergot Alkaloids	Ergotamine, Dihydroergotamine	Vasoconstrictive agents for acute treatment, less preferred due to side effects
Gepants (CGRP antagonists)	Ubrogepant, Rimegepant	New class targeting CGRP pathway; effective and well-tolerated
Lasmiditan	5-HT1F receptor agonist	Acute treatment without vasoconstrictive effect; suitable for cardiovascular risk
Preventive/Prophylactic		
Beta-Blockers	Propranolol, Metoprolol	Reduce migraine frequency by modulating adrenergic tone
Anticonvulsants	Topiramate, Valproate	Stabilize neuronal excitability; effective in chronic migraine
Tricyclic Antidepressants	Amitriptyline	Useful for migraine with comorbid depression or insomnia
CGRP Monoclonal Antibodies	Erenumab, Fremanezumab	Long-acting injectable biologics targeting CGRP or its receptor
Lifestyle Adjustments	Sleep hygiene, hydration, regular meals	Avoidance of known triggers (e.g., stress, alcohol, certain foods)
Non-Pharmacological & Complementary		
Behavioral Therapy/CBT	Cognitive Behavioral Therapy	Helps manage stress, anxiety, and pain perception
Biofeedback	EMG or thermal biofeedback	Teaches control over physiological responses to reduce migraine
Acupuncture	Traditional Chinese medicine technique	May reduce frequency and severity through neuromodulation
Neuromodulation Devices	Cefaly (transcranial), gammaCore (vagal stimulator)	Non-invasive devices for acute and preventive treatment
Dietary Supplements	Magnesium, Riboflavin, Coenzyme Q10	Support mitochondrial function and reduce attack frequency

Recent Advances in Migraine Therapy

In recent years, migraine management has undergone a paradigm shift with the emergence of targeted therapies and technological innovations. One of the most significant developments is the introduction of CGRP-based drugs, including both gepants (CGRP receptor antagonists such as ubrogepant and rimegepant) and monoclonal antibodies (e.g., erenumab, fremanezumab, galcanezumab) that target either the CGRP ligand or receptor. These agents have shown high efficacy with favorable tolerability and are particularly valuable for patients who are refractory to traditional treatments or have cardiovascular contraindications to triptans.

Neuromodulation technologies have also gained traction as non-pharmacological options. Devices like Cefaly (transcranial electrical stimulation), gammaCore (non-invasive vagus nerve stimulation), and Nerivio (remote electrical neuromodulation) offer acute and preventive relief, often without systemic side effects. These are especially beneficial for patients who prefer non-drug interventions or have medication overuse issues [38,39].

The era of personalized medicine is taking shape in migraine care through genetic profiling, identification of individual triggers, and biomarker discovery, which aim to predict treatment response and tailor therapy. Research into pharmacogenomics may further enable selection of the most effective drug with minimal trial and error [40]. Ongoing clinical trials continue to expand the migraine drug pipeline, investigating novel targets beyond CGRP, such as PACAP (pituitary adenylate cyclase-activating polypeptide) and orexin pathways. Emphasis is also placed on early diagnosis, individualized treatment plans, and multidisciplinary care integrating neurologists, psychologists, and pain specialists [41]. Future research should prioritize biomarker discovery, neuroimaging-based diagnostics, and preventive strategies to reduce the

burden of migraine and improve patient outcomes through more precise and proactive care [42].

Conclusion

Migraine is a complex, multifactorial neurological disorder with a significant impact on global health and quality of life. A deeper understanding of its pathophysiological mechanisms has led to significant therapeutic innovations, particularly CGRP-targeted agents and neuromodulation devices. Effective migraine management requires a multifaceted approach that includes early diagnosis, individualized pharmacologic and non-pharmacologic therapies, and lifestyle modifications. While current treatments offer substantial relief for many, a subset of patients remains refractory, highlighting the importance of continued clinical research and innovation. The future of migraine therapy lies in personalized medicine, genetic profiling, and the identification of reliable biomarkers to guide targeted interventions. Multidisciplinary care and increased awareness are essential to reduce the societal and personal burden of this disabling condition.

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Conflict Of Interest

Authors are declared that no conflict of interest.

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Not Applicable

Author Contributions

Polimetla Amulya, Kakarlapudi Sahithi Varma and Tilakchand bias Rekha Singhcontributed to literature collection and drafting the manuscript. A. Suneetha provided support in organizing and refining the content. Patibandla Jahnavi conceptualized, supervised, and finalized the manuscript for submission.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211.
2. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: A disorder of sensory processing. Physiol Rev. 2017;97(2):553–622.
3. Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol. 2018;17(2):174–82.
4. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. Headache. 2015;55(1):21–34.
5. Lipton RB, Bigal ME. The epidemiology of migraine. Am J Med. 2005;118(1):3–10.
6. Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. Headache. 2004;44(9):865–72.
7. Ferrari MD. Migraine. Lancet. 1998;351(9108):1043–51.
8. Lauritzen M. Pathophysiology of the migraine aura: The spreading depression theory. Brain. 1994;117(Pt 1):199–210.
9. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annu Rev Physiol. 2013;75:365–91.
10. Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. Headache. 2017;57(Suppl 2):47–55.
11. Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of migraine. Lancet Neurol. 2010;9(3):285–98.
12. Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine: A comparative review of pharmacology, pharmacokinetics and efficacy. Drugs. 2000;60(6):1259–87.
13. Dodick DW. Migraine. Lancet. 2018;391(10127):1315–30.
14. Tepper SJ. CGRP and migraine: the role of monoclonal antibodies. Headache. 2018;58(Suppl 1):33–47.
15. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. Headache. 2015;55(Suppl 2):103–22.
16. Silberstein SD. Preventive migraine treatment. Continuum (Minneap Minn). 2015;21(4):973–89.
17. Diener HC, Charles A, Goadsby PJ, Holle D. New therapeutic approaches for the prevention and treatment of migraine. Lancet Neurol. 2015;14(10):1010–22.
18. Messina R, Goadsby PJ. CGRP monoclonal antibodies for migraine prevention. Curr Opin Neurol. 2021;34(3):376–85.
19. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine progression: a systematic review. Headache. 2019;59(3):306–38.
20. May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. Nat Rev Neurol. 2016;12(8):455–64.
21. Ashina M, Buse DC, Ashina H, Pozo-Rosich P, Peres MFP, Lee MJ, et al. Migraine: integrated approaches to clinical management and emerging treatments. Lancet. 2021;397(10283):1505–18.
22. Goadsby PJ. Neuromodulation in primary headaches. Cephalalgia. 2014;34(5):355–61.
23. Silberstein SD, Dodick DW, Pearlman SH. Headache. Med Clin North Am. 2009;93(2):215–31.

24. Lanteri-Minet M. Economic burden and costs of chronic migraine. Curr Pain Headache Rep. 2014;18(1):385.
25. Goadsby PJ. CGRP antagonists for acute migraine treatment. Lancet. 2019;394(10203):533–5.
26. Akerman S, Romero-Reyes M, Holland PR. Targeting CGRP for the treatment of migraine: pharmacological mechanisms and clinical implications. CNS Drugs. 2020;34(9):805–20.
27. Starling AJ. Personalized medicine for migraine: a future paradigm. Headache. 2018;58(Suppl 1):45–56.
28. Raffaelli B, Neeb L, Reuter U. Monoclonal antibodies for the prevention of migraine. Expert OpinBiol Ther. 2019;19(12):1307–17.
29. Brennan KC, Charles A. An update on the blood–brain barrier in migraine. Headache. 2010;50(6):1040–56.
30. Charles A. The evolution of a migraine attack—a review of recent evidence. Headache. 2013;53(2):413–9.
31. Alstadhaug KB. Migraine and the hypothalamus. Cephalalgia. 2009;29(8):809–17.
32. Olesen J. The role of nitric oxide (NO) in migraine, tension-type headache and cluster headache. Pharmacol Ther. 2008;120(2):157–71.
33. Yu S, Liu R, Zhao G, Yang X, Qiao X, Feng J, et al. The prevalence and burden of primary headaches in China: a population-based door-to-door survey. Headache. 2012;52(4):582–91.
34. Pringsheim T, Davenport W, Mackie G, Christie SN, Aubé M, Gladstone J, et al. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012;39(2 Suppl 2):S1–59.
35. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment. Headache. 2015;55(1):3–20.
36. Kelman L. Pain characteristics of migraine with and without aura. Headache. 2004;44(9):856–60.
37. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol. 1993;33(1):48–56.
38. Holland PR, Headache: pathophysiology and clinical targets for treatment. Expert Opin Ther Targets. 2014;18(8):943–53.
39. Russell MB, Olesen J. The genetics of migraine without aura and migraine with aura. Cephalalgia. 1993;13(4):245–8.
40. Sances G, Guaschino E, Ghiotto N, Allena M, Tassorelli C. Medication overuse headache: epidemiology and management. Neurol Sci. 2019;40(Suppl 1):107–13.
41. Ashina M, Hansen JM, Á Dunga BO, Olesen J. Migraine and the trigeminovascular system—40 years and counting. Lancet Neurol. 2019;18(8):795–804.
42. Ford JH, Jackson J, Milligan G, Cotton S, Ahl J, Aurora SK. A real-world analysis of migraine: a cross-sectional study of disease burden and treatment patterns. Headache. 2017;57(10):1532–44.