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A Detail Review on Migraine: Pathophysiology, Diagnosis and Current Therapeutic Approaches

Prof. Pallavi T Jadhav[1], Dr. Abhishek Kumar Sen[2], Mr. Utkarsh Sudhakar Ghodke[3]
[1]Associate Professor, [2]Principal, [3]Student
Pratibhatai Pawar College of Pharmacy, Shrirampur, Ahilyanagar, Maharashtra, India

Abstract: *Migraine is a long-standing and repeatedly occurring neurological condition that contributes significantly to global disability. It presents as episodic attacks from mild to intense headache, frequently associated with vomiting, feeling sick, and increased sensitivity to both sound and light. The underlying mechanisms of migraine are multifactorial lincluding neuropeptide release, trigeminovascular system activation, and cortical spreading depression such as CGRP (calcitonin gene-related peptide), and the development of central sensitization. Diagnosis is mainly clinical, based on the criteria outlined In The third edition of the International Classification of Headache Disorders while imaging studies are used primarily to rule out secondary causes. Therapeutic management is broadly categorized into acute and preventive interventions. Acute care typically includes NSAIDs, triptans, gepants, and ditans, whereas preventive management may involve beta-blockers, anticonvulsants, antidepressants, botulinum toxin, and monoclonal antibodies targeting CGRP pathways. Alongside these treatments, lifestyle changes, behavioral interventions, and neuromodulation methods are increasingly being recognized as valuable supportive therapies. Despite remarkable advancements, migraine continues to be frequently underdiagnosed and inadequately treated, emphasizing the importance of individualized therapy and ongoing research to discover new therapeutic possibilities.*

Keywords*:* Migraine, Pathophysiology, Diagnosis, Triptans, Preventive therapy

I. INTRODUCTION

A widespread, chronic, and incapacitating neurovascular condition, migraines are characterized by recurrent bouts of moderate to severe headaches that often affect one side of the head. Nausea, vomiting, and increased sensitivity to light (photophobia) and sound (phonophobia) are common side effects of these attacks. In many cases, the attacks last between 4 and 72 hours, and some individuals experience a transient neurological phase known as aura before the headache begins [1,2]. Globally, millions of people are affected by migraine, making it one of the most burdensome neurological disorders. It is particularly significant among young women, where it represents a leading cause of disability due to its profound impact on everyday activities and general well-being [3]. Typically, this condition includes recurrent episodes of intense head pain and autonomic symptoms such as nausea, vomiting, intolerance to physical activity, and heightened sensitivity to sensory stimuli [4]. Migraine management focuses on reducing attack frequency and severity, avoiding known triggers, and making appropriate lifestyle adjustments. Preventive pharmacotherapy is also commonly employed to decrease the likelihood of future episodes [5]. Until a few years ago, preventive therapies mainly consisted of repurposed drugs sometimes referred to as "repositioned medications" originally developed for unrelated conditions but later found to provide some benefit in migraine prevention. These included calcium channel blockers, antiepileptic agents, β-blockers, and antidepressants. However, issues with tolerability often led to poor long-term adherence [6]. Growing understanding of migraine biology has helped identify more specific therapeutic targets, such as the CGRP, or calcitonin gene-related peptide, pathway, which plays a pivotal function in the pathophysiology of migraines [7,8]. The arrival of CGRP-monoclonal antibodies (CGRP-mAbs) and, more recently, gepants, has introduced the first migraine-specific preventive strategy directly aimed at blocking neuropeptides involved in attack generation. Due to their strong efficacy, favorable safety profile, and improved

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tolerability, these therapies represent a major advancement in migraine prevention [9]. Migraine remains a widespread neurological condition affecting a large proportion of the global population and imposing significant personal and socioeconomic challenges. It is typified by recurrent episodes of moderate to severe headaches along with gastrointestinal and neurological symptoms. Activation of the trigeminovascular system and the release of vasoactive peptides, especially CGRP, are thought to be key factors in migraine development, even though the precise etiology is yet unknown [10]. Over time, migraine pharmacotherapy has evolved with the development of both acute and preventive treatment approaches. Acute therapy aims to provide immediate relief during an attack, whereas preventive therapy focuses on reducing attack frequency and long-term burden. Historically, treatment options were limited to NSAIDs, triptans, and orally administered preventives originally developed for hypertension, depression, or epilepsy [11]. Recent research, however, has emphasized the development of agents specifically targeting the CGRP pathway. CGRP, a key neuropeptide involved in vasodilation, inflammation, and nociceptive transmission, has become a major focus for new migraine treatments [12]. As a result, new medication classes were introduced, such as gepants and monoclonal antibodies that block CGRP or its receptor. CGRPmAbs work by binding to CGRP or its receptor, thereby preventing its interaction with trigeminal pain pathways and reducing neurogenic inflammation and headache frequency [13]. Gepants, on the other hand, are smallmolecule CGRP receptor antagonists taken orally that inhibit CGRPmediated vasodilation and trigeminal activation, offering effective pain relief [14]. Chronic migraine (CM) and episodic migraine (EM) are the two main types of migraine. Less than 15 headache days per month is referred to be EM, while 15 or more headache days per month for at least three consecutive months is referred to as CM. Additionally, women experience migraines more frequently than males do [15]. Approximately one-third of individuals with migraine experience aura, which consists of short-lasting sensory, motor, or visual disturbances [16]. Current ideas highlight stimulation of the trigeminovascular system (TGVS), which comprises the cranial vasculature, trigeminal nerve, and trigeminal nucleus caudalis (TNC), even if the full processes underlying migraine remain unclear. The TGVS not only regulates cerebral blood flow but also plays a central role in transmitting pain signals. Stimulation of trigeminal sensory fibers leads to the release of vasoactive mediators including substance P, neurokinin A, and CGRP which promote vasodilation and dural plasma extravasation, ultimately causing neurogenic inflammation and head pain [17]. Mild migraine attacks are typically treated with acetaminophen or aspirin, while moderate to severe episodes may require triptans or dihydroergotamine (DHE) [18,19]. About 15% of people worldwide suffer from migraines, which are a major source of impairment for those between the ages of 15 and 49 [20]. Its development involves genetic predisposition along with vascular and neurochemical factors that influence the trigeminovascular system [21]. Migraines are broadly separated into migraine with aura and migraine without aura. Common migraine or migraine without aura, represents nearly 70–80% of all cases and is characterized by unilateral throbbing pain aggravated by daily physical activities, accompanied by symptoms such as nausea, photophobia, and phonophobia [22]. Migraine with aura (classic migraine) includes transient neurological disturbances that appear before the headache phase. These disturbances may manifest as visual changes, sensory alterations, or speech difficulties lasting 5–60 minutes [23]. Additional migraine subtypes include hemiplegic migraine with a brief loss of strength on one side of the body [24] retinal migraine, characterized by temporary visual impairment in one eye [25], menstrual migraine triggered by hormonal fluctuations, and Frequent headaches that occur 15 or more days a month are indicative of chronic migraine [26]. Correct classification of migraine type is essential for accurate diagnosis and customized treatment selection [27]. Ongoing research into migraine mechanisms and classification continues to support the development of targeted therapies and improved patient outcomes, thereby reducing global migraine-related disability [28]. Migraine affects nearly 15% of the global population and is among the main reasons for disability among young and middle-aged adults [29]. Its origins involve interconnected genetic, vascular, and neurochemical pathways that contribute to abnormal brain signaling. Neuropeptides such CGRP, substance P, and neurokinin A are released when the trigeminovascular system is activated, which is the main mechanism [30]. Pain results from these chemicals' promotion of neurogenic inflammation and vasodilation. Aura symptoms are thought to be caused by another important process called cortical spreading depression (CSD), a gradual wave of neuronal and glial depolarization that activates trigeminal nociceptors

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[31]. Altered serotonin levels and ion- channel dysregulation also contribute to neuronal hyperexcitability and pain transmission. Diagnosis of migraine is primarily clinical and follows ICHD-3 criteria [32]. A thorough patient history helps differentiate migraine from secondary causes, while neuroimaging such as MRI is reserved for atypical cases. Early diagnosis plays a crucial role in preventing progression to chronic migraine. Therapeutic options are divided into acute and preventive categories. Acute treatment includes NSAIDs, triptans, and antiemetics, while preventive strategies involve β-blockers, antidepressants, antiepileptic drugs, and the newer CGRP monoclonal antibodies [33]. Mi ain most commonly affects the frontal, temporal, or orbital regions and may radiate to the neck or occipital region as the attack evolves [34]. Because the trigeminal vascular system, which supplies sensory innervation to the face, scalp, and meninges, is involved in classic migraine, pain typically starts around the eye or temple and progresses across one side of the head [35]. Neuropeptides such CGRP and substance P are released during an attack, causing cranial blood vessels to dilate and become inflamed, resulting in a throbbing or pulsating feeling [36]. Central sensitization within b structures such as the trigeminal nucleus caudalis further contributes to pain amplification and persistence. Recognizing the typical features and distribution of migraine pain assists clinicians in distinguishing it from other headache disorders such as tension-type or cluster headaches. Migraine pain is often described as pulsatile or throbbing and is worsened by physical activity. Some individuals may also report pain spreading to the jaw, ears, or neck due to variations in nerve involvement [37].

Epidemiology of Migraine

Migraine is one of the most widespread and disabling primary headache conditions across the world. It affects millions of people and is a major contributor to the global neurological disease burden. Findings from the Global Burden of Disease Report (2019) identified migraine as the second most common cause of years lived with disability (YLDs), ranking just after lower back pain [38]. Globally, its estimated prevalence is around 14–15%, though this percentage differs by demographic and geographical groups [39]. According to the World Health Organization, nearly one out of every seven individual's experiences migraine at some point in life [40]. Th ondition Is significantly more common in women, with a prevalence of 18–25%, compared to 6–8% in men largely attributed to hormonal fluctuations, particularly changes in estrogen levels [41]. Prevalence rises after puberty, reaches its highest occurrence between 30 and 40 years, and gradually decreases with age [42]. In children, migraine affects around 3–5%, but the rate rises sharply during adolescence, especially among girls [43].

• Epidemiology in India

In India, migraine has emerged as a significant public health concern. Research from several states shows prevalence rates between 10% and 25% among adults [44]. A large multicenter study in South India reported a prevalence of 22.4%, with women and individuals from economically weaker backgrounds showing higher rates [45]. A North Indian population- based survey recorded a prevalence of 14.1%, highlighting the issues of underdiagnosis and under treatment due to low awareness and limited specialized care facilities [46]. Indian migraine cases are strongly influenced by environmental and lifestyle factors. Urban residents report higher rates of migraine due to chronic stress, disrupted sleep cycles, long working hours, and increased exposure to pollution [47]. However, rural areas have also seen a rise in migraine cases as lifestyles change due to urbanization and growing psychological stressors [48].

• Global Trends and Burden

Worldwide, migraine consistently affects more women than men across all ethnicities and regions. In Europe, its lifetime prevalence is around 16%, while Asian countries report rates between 9% and 21% [49]. Beyond personal discomfort, migraine imposes a significant socioeconomic burden causing productivity loss, reduced work performance, and frequent absenteeism. In the United States alone, the American Migraine Foundation estimates over 113 million workdays are lost each year due to migraine-related disability [50].

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Classification of Migraine

Migraine presents in multiple clinical forms, and The International Headache Society created the International Classification of Headache Disorders (ICHD-3), provides a standardized method of categorizing these forms. The classification is mainly based on aura, symptom profile, and attack frequency [51].

• Migraine Without Aura

Migraine without aura previously termed common migraine is the most frequently observed type, accounting for 70–75% of all cases.

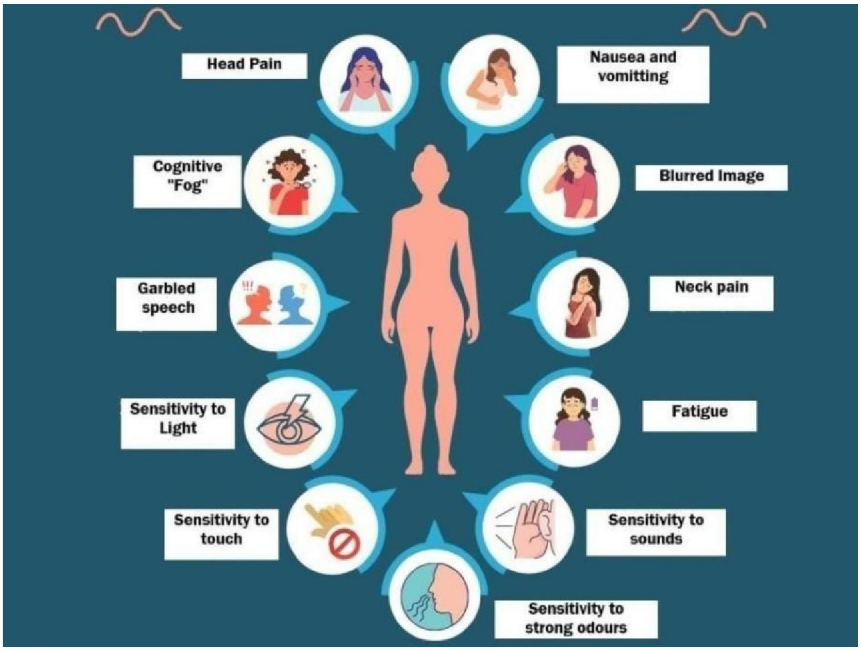

Fig 1. Migraine without aura

Attacks typically last 4–72 hours and feature unilateral, pulsating headaches that worsen with routine physical activity. light sensitivity, nausea, and vomiting intolerance to sound are common accompanying symptoms [52].

• Migraine With Aura

This type, earlier known as classic migraine, involves temporary and reversible neurological disturbances that appear before or together with the headache. Auras usually develop over 5-20 minutes and resolve within an hour. Visual auras such as flashing lights, zigzag patterns, or blind spots are most common, though sensory changes and speech disturbances may also occur. The headache phase typically begins within 60 minutes after the aura.

• Chronic Migraine

Chronic migraine is diagnosed when a person has headaches at least 15 days a month for three months, with at least eight days meeting the criteria for migraines. It may evolve from episodic migraine and is often associated with medication overuse, psychological stress, or hormonal factors. This subtype causes severe disability and is frequently accompanied by anxiety or depression [53].

• Other Migraine Variants

Several less common forms of migraine also exist. Vestibular migraine is characterized by repeated episodes of vertigo along with classical migraine symptoms. Menstrual migraine is linked to hormonal changes around menstruation. Hemiplegic migraine involves temporary motor weakness during aura. Abdominal migraine, typically seen in children, presents with abdominal pain, nausea, and pallor without significant headache [54].

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Etiology and Risk Factors

Migraine arises from a mix of hereditary susceptibility, environmental influences, hormonal changes, and lifestyle behaviors. The interaction between abnormal neuronal activity and altered vascular function forms the core of its pathophysiology [55].

• Genetic Factors

Genetics plays a crucial role, with studies showing heritability estimates of 40–70%. Mutations in genes regulating ion channels such as CACNA1A, ATP1A2, and KCNK18have been associated FHM, or familial hemiplegic migraine, is an uncommon inherited subset. These mutations affect calcium and potassium channel functioning, promoting cortical spreading depression and altered neuronal excitability [56,57].

• Hormonal Influences

Hormonal fluctuations, particularly changes in estrogen, significantly influence migraine frequency. Estrogen modulates serotonin receptors and regulates the release of calcitonin generelated peptide (CGRP), both key components in pain transmission. A sudden decline in estrogen before menstruation is a common trigger in menstrual migraine [58,59].

• Environmental and Lifestyle Triggers

Multiple lifestyle and environmental factors can provoke migraine attacks. Common triggers include psychological stress, irregular sleep patterns, fasting, dehydration, caffeine withdrawal, strong smells, and weather fluctuations. Foods such as chocolate, aged cheeses, wine, and items containing MSG or nitrates may also induce attacks. Adopting consistent sleep, hydration, and dietary routines can substantially reduce the frequency of episodes [60,61].

• Psychological and Comorbid Conditions

Depression, anxiety disorders, and sleep-related issues often coexist with migraine and can intensify its severity and frequency. Shared neurochemical pathways involving serotonin, dopamine, and stress hormones link these conditions, underscoring the importance of an integrative treatment approach addressing both neurological and mental health [62].

• Medication Overuse

Medication Overuse Headache (MOH) can result from overusing acute migraine drugs including analgesics, triptans, or derivatives of ergot. This disorder contributes significantly to the transition from episodic to chronic migraine by increasing the frequency and intensity of headaches. To prevent MOH, patients must be taught how to use medications responsibly [63].

Pathophysiology of Migraine

Migraine is a multifaceted neurological disorder in which recurrent headache episodes are accompanied by various neurological, gastrointestinal, and autonomic manifestations. The disorder develops through a complex interplay of factors, including heightened neuronal sensitivity, abnormalities in vascular regulation, and inherited genetic influences. These interconnected mechanisms collectively contribute to the initiation and progression of migraine attacks [64].

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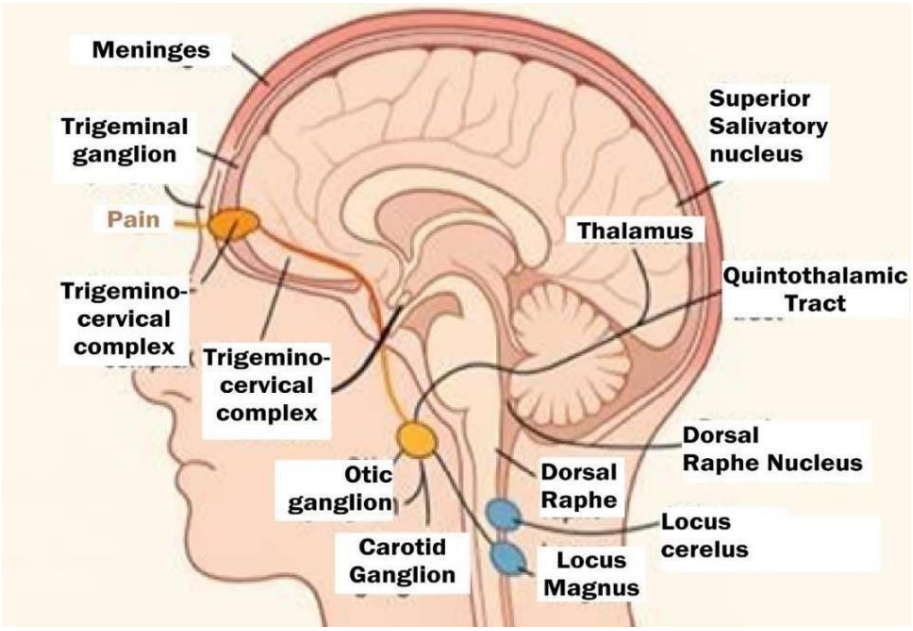

Fig 2. Pathophysiology

• Cortical Spreading Depression (CSD)

Spreading Cortically Depression is characterized by a period of decreased cortical activity after a gradually progressing wave of severe neuronal and glial depolarization. Usually starting in the occipital area, this phenomenon moves into the cerebral cortex at a rate of two to six millimeters per minute. It is generally acknowledged that CSD is the primary trigger for trigeminovascular activation and the physiological cause of migraine aura [65]. Numerous chemicals, such as potassium ions, hydrogen ions, nitric oxide, and glutamate, are released into the extracellular space during this depolarization process. These chemicals make meningeal nociceptors more sensitive, which facilitates the transmission of pain signals [66].

• Trigeminovascular System Activation

The trigeminovascular system (TGVS) forms a crucial component of migraine pathophysiology. When trigeminal sensory fibers that supply the meningeal blood vessels become activated, they release several Vasoactive neuropeptides include substance P, neurokinin A, and calcitonin gene-related peptide (CGRP) [67]. Vasodilation, plasma protein leakage, and neurogenic inflammation are all mediated by these neuropeptides. The experience of migraine pain is greatly influenced by these occurrences taken together [68].

• Role of Calcitonin Gene-Related Peptide (CGRP)

CGRP is recognized as one of the primary sources of the development of migraine. Increased concentrations of CGRP are consistently observed during an attack, and a decrease in its levels is associated with relief from symptoms [69]. CGRP causes dilation of intracranial arteries and enhances the transmission of pain signals within the trigeminal nucleus caudalis. In recent years, targeted therapies particularly monoclonal antibodies directed against CGRP or its receptor have shown substantial effectiveness in preventing migraine episodes [70].

• Brainstem Dysfunction

During migraine attacks, neuroimaging studies have shown aberrant activity patterns in important brainstem areas, such as the dorsal raphe nucleus, locus coeruleus, and periaqueductal gray (PAG) [71]. These areas are crucial for the

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modulation of vascular tone and descending pain. Increased neuronal excitability and decreased inhibitory control over trigeminal nociceptive input are two consequences of dysfunction in these areas that might prolong the migraine process [72].

• Serotonin and Neurotransmitter Imbalance

Serotonin (5-HT) signaling disruptions are another important aspect of migraine pathophysiology. Reduced serotonin levels during an attack lead to increased production of neuropeptides including substance P and CGRP and cerebral vasodilation [73]. Triptans, which function as 5-HT1B/1D receptor agonists, reduce migraine symptoms by suppressing neuropeptide release and constricting blood vessels, highlighting the significance of serotonergic pathways in migraine treatment [74].

• Genetic and Ion Channel Mechanisms

Migraine, especially familial hemiplegic migraine (FHM), is significantly influenced by genetic susceptibility. Key ion channel genes like CACNA1A (which codes for P/Q-type calcium channels), ATP1A2 (which codes for Na+/K+-ATPase), and SCN1A (which codes for voltagegated sodium channels) have been shown to have mutations that cause neuronal hyperexcitability and make the brain more susceptible to CSD [75]. Moreover, a number of other genetic loci linked to functions including glutamatergic signaling and vascular tone modulation have been found through genome-wide association studies [76].

• Neuroinflammation and Glial Activation

Recent research indicates that neuroinflammatory processes contribute significantly to the persistence and progression of migraine. Activated glial cells including microglia and astrocytes release pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6. These molecules intensify pain transmission within the trigeminal pathway and may facilitate the shift from episodic to chronic migraine by maintaining a heightened inflammatory environment [77]. This prolonged inflammatory response further reinforces neural sensitization [78].

• Central Sensitization

Central sensitization refers to an increased responsiveness of neurons within the central nervous system, particularly in structures such as caudalis trigeminal nucleus and the thalamus. Clinically, this manifests as cutaneous allodynia and exaggerated sensitivity to normally nonpainful stimuli [79]. Persistent activation of peripheral meningeal nociceptors strengthens central sensitization, which can ultimately make migraine attacks more resistant to standard therapeutic approaches [80].

Diagnosis of Migraine

• Clinical Basis of Diagnosis

Migraine is diagnosed mainly through clinical evaluation, as no blood test or imaging technique can conclusively confirm the disorder. A detailed assessment of the headache characteristics such as onset, duration, severity, and associated symptoms is essential. A typical migraine attack lasts four to seventy-two hours and manifests as throbbing or pulsating pain, usually on one side of the head. Patients may have nausea, vomiting, light or sound sensitivity, and regular physical activity seems to exacerbate the pain. Diagnosis is largely based on recognizing this specific pattern and excluding other potential causes through careful historytaking and neurological examination [81].

• Use of ICHD-3 Diagnostic Criteria

Standardized criteria for diagnosing migraines are provided by the International Classification of Headache Disorders (ICHD-3). These guidelines state that a patient is diagnosed with migraine without aura if they have at least five attacks that last between four and seventy-two hours with two of the following features: one-sided pain, a pulsing nature,

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moderate to severe intensity, or worsening after regular physical activity. Additionally, the attack must cause light and sound sensitivity or nausea/vomiting. Before the headache starts, people with migraine with aura typically have brief neurological symptoms, such as visual or sensory abnormalities [82].

• Differentiating From Secondary Headaches

A vital part of diagnosing migraine is distinguishing it from headaches caused by other underlying conditions. Secondary causes may include infections, vascular disorders, tumors, or systemic diseases. Red-flag features such as a sudden, severe "thunderclap" headache, new onset of headache after age 50, progressive worsening, fever, weight loss, or neurological deficits require further investigation. In such cases, imaging or laboratory tests are necessary.

When a patient presents with typical migraine features and a normal neurological exam, additional testing is generally not required [83].

• Importance of History and Headache Pattern Recognition

A patient's detailed history is one of the most reliable tools for diagnosing migraine. Clinicians evaluate the frequency of attacks, duration, triggers, and progression of symptoms. Factors such as stress, disrupted sleep, hormonal changes, and certain foods commonly precipitate attacks. A positive family history further strengthens the suspicion of migraine, given its strong genetic link. Patients are often encouraged to maintain a headache diary to document symptom patterns, which aids in confirming the diagnosis and planning individualized preventive strategies [84].

• Role of Neuroimaging and Other Diagnostic Tools

Although migraine is primarily diagnosed clinically, neuroimaging may be suggested when the presentation is unusual or when neurological deficits are detected. MRI is preferred because it provides more detailed images and helps rule out structural abnormalities such as tumors or vascular malformations. In uncomplicated migraine cases with normal neurological findings, routine imaging is unnecessary. EEG may be used occasionally to differentiate migraine from seizure-related disorders, but it is not a standard diagnostic tool due to limited specificity [85].

• Laboratory Investigations

Blood tests and other laboratory investigations do not diagnose migraine directly but help exclude metabolic, endocrine, or systemic causes of recurrent headaches. Tests such as complete blood count, thyroid function tests, glucose levels, and electrolyte panels may be useful, especially when comorbidities are present. Since no biomarker currently exists that can confirm migraine, these tests serve mainly as supportive tools during diagnostic evaluation [86].

• Identifying Migraine Subtypes

Differentiating between the main forms of migraines is necessary for an accurate diagnosis. Before the headache, migraine with aura often causes transient neurological symptoms, such as vision abnormalities. These warning indicators are absent from migraine without aura, yet the headache symptoms are identical. A headache with migraine symptoms on eight or more days per month for at least three months is referred to as chronic migraine. The subtype must be clearly identified in order to guide proper therapy planning [87].

• Differential Diagnosis and Common Diagnostic Pitfalls

Migraine symptoms may overlap with other headache disorders, making differentiation difficult. Tension-type headaches tend to be bilateral and pressing, without nausea or vomiting. Cluster headaches are intensely painful, unilateral, and accompanied by autonomic symptoms like tearing or nasal congestion. Sinus headaches and medication-overuse headaches can also resemble migraine. The response to migraine-specific therapies, such as triptans, can help

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confirm the diagnosis. Misdiagnosis commonly occurs when psychiatric conditions such as anxiety or depression alter headache patterns, leading to confusion with other disorders [88].

• Recent Advances in Diagnostic Understanding

The brain mechanisms underlying migraine have been better understood thanks to advances in imaging techniques like functional MRI and PET scans. These modalities reveal distinct patterns of brainstem and cortical activation during attacks. Although currently used mostly in research settings, such techniques may eventually support clinical diagnosis in complex cases. A holistic diagnostic approach considering lifestyle, psychological health, and environmental triggers enhances accuracy and improves treatment outcomes [89].

• Significance of Early and Accurate Diagnosis

Identifying migraine early is essential to prevent chronic progression, reduce disability, and apply effective preventive management. Many individuals remain undiagnosed or misdiagnosed due to overlapping symptoms with other headache types. Increased awareness among healthcare providers and proper use of diagnostic criteria can significantly improve recognition and patient care. Accurate diagnosis ensures targeted therapy and reduces longterm burden on patients [90].

Treatment of Migraine

Acute Treatment Options

• NSAIDs

First-line treatments for mild to moderate migraine attacks include nonsteroidal antiinflammatory medicines (NSAIDs) including ibuprofen (Advil®, Motrin®), naproxen sodium (Aleve®, Anaprox®), flurbiprofen, diclofenac potassium (Cataflam®, Voltaren®, Zipsor®), mefenamic acid, and nabumetone. For quick pain relief, these drugs are frequently utilized in emergency and outpatient settings. Ibuprofen is a proven and successful analgesic for treating acute migraine attacks, according to the American Headache Society [91].

• Triptans

A fundamental class of medications designed specifically to treat migraines, triptans work by activating serotonin (5-HT1) receptors. Sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan are among the frequently used triptans. They reduce headache discomfort by constricting dilated cerebral arteries through their impact on 5-HT1B and 5-HT1D receptors. Triptans not only cause vasoconstriction but also lessen neurogenic inflammation by preventing the production of neuropeptides that cause pain, such as calcitonin gene-related peptide (CGRP) [92].

• CGRP Antagonists (Gepants)

CGRP levels are significantly elevated during migraine attacks, contributing to vasodilation, sensitization, and enhanced pain signaling within the trigeminal system. Medications such as rimegepant (Nurtec ODT), ubrogepant (Ubrelvy), atogepant (Qulipta), and zavegepant (Zavzpret) counteract this by blocking CGRP activity. By suppressing CGRP release triggered by trigeminal nerve activation these agents effectively reduce pain and associated migraine symptoms without causing vasoconstriction [93].

• Ditans (5-HT1F Receptor Agonists)

Unlike triptans, which act on 5-HT1B/1D receptors and may cause vasoconstriction, ditans selectively target the 5-HT1F receptor. This receptor controls neuronal pain pathways without influencing blood vessel tone, making ditans a safer alternative for patients with cardiovascular or cerebrovascular disease. These agents suppress neurogenic inflammation and central pain transmission while avoiding the vascular effects linked to traditional triptans [94].

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Preventive Therapies

Pharmacological Prevention

• Beta-Blockers

The preventive effect of beta-blockers on migraine was first noticed in patients taking these agents for hypertension or cardiac conditions who also experienced fewer headaches. Propranolol and metoprolol remain the most investigated and commonly prescribed betablockers for migraine prevention. Doses of about 160 mg/day for propranolol and 200 mg/day for metoprolol are effective, according to clinical research and meta-analyses. Their efficacy does not appear to depend on whether the drug is selective for β1-receptors, suggesting that blockade of β2-receptors is not essential. Some beta-blockers, including propranolol and pindolol, also interact with serotonin receptors (5-HT1A, 5-HT1B/D, and 5-HT2), which may contribute to their migraine-preventive action [95, 96].

• Antidepressants

Among antidepressant classes, tricyclic antidepressants (TCAs)particularly amitriptyline and clomipramine have shown the strongest evidence for migraine prevention. Although TCAs are still more dependable based on clinical trial results, selective serotonin reuptake inhibitors (SSRIs) as fluoxetine and fluvoxamine have also been investigated [97].

• Non-Pharmacological Management

Non-drug approaches are considered essential components of migraine care since they help lower attack frequency, reduce the need for medications, and improve overall well-being [98]. These strategies are especially crucial for patients who cannot tolerate pharmacologic therapy or who do not respond adequately to medications [99]. A combination of lifestyle adjustments, behavioral therapies, dietary control, and physical activity forms the foundation of holistic migraine management [100].

• Lifestyle Modifications

Maintaining stable lifestyle habits plays a major role in migraine prevention. Patients are encouraged to adopt regular sleep schedules, take meals at consistent times, and stay wellhydrated, as fluctuations in these factors often trigger attacks [101]. Stress-relief methods such as meditation, yoga, and mindfulness can help reduce the severity and number of headaches [102]. Aerobic exercise performed several times per week increases endorphin levels and has been shown to decrease migraine frequency [103]. Avoiding excessive use of caffeine, nicotine, and alcohol is also advised because these substances can provoke or worsen migraine symptoms [104].

• Emerging and Advanced Migraine Therapies

Recent progress in migraine research has led to therapies that target specific molecular mechanisms rather than relying solely on vasoconstrictive processes. Patients who do not respond to traditional treatments now have hope thanks to newly developed choices such as CGRP inhibitors, 5-HT1F agonists, monoclonal antibodies, neuromodulation devices, and genetic therapy [105].

• CGRP Monoclonal Antibodies

One of the most important advancements in migraine care has been the introduction of monoclonal antibodies that inhibit CGRP signaling. CGRP promotes inflammation, vasodilation, and pain sensitization during migraine attacks. Agents that significantly reduce monthly headache days and improve quality of life include erenumab, fremanezumab, galcanezumab, and eptinezumab. While the others directly target the CGRP ligand, erenumab specifically disables the CGRP receptor [106, 107]. These injectable drugs provide long-lasting action, administered monthly or quarterly, and have shown good tolerability in long-term studies, with only mild side effects reported [108].

II. CONCLUSION

Migraine is a long-term neurological condition that continues to affect a large portion of the global population and often disrupts normal daily activitiesIn addition to nausea, vomiting, and increased sensitivity to light and sound, it is characterized by recurrent episodes of excruciating headache. The disorder develops through the combined influence of genetic makeup, neural mechanisms, and environmental triggers. Although its complete origin has not yet been fully established, current evidence suggests that abnormal brain signaling, vascular changes, and fluctuations in key

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neurotransmitters play major roles. Continuous advancements in scientific understanding have helped researchers uncover new insights into migraine biology and have supported the development of more focused therapeutic options. Acute treatments, which take effect during an attack, and preventative therapies, which lessen the frequency and intensity of subsequent episodes, are the two main categories of management techniques. NSAIDs, triptans, and CGRP-targeting medicines are examples of acute treatments that have demonstrated significant efficacy in symptom alleviation. For long-term control, preventive techniques such beta-blockers, anticonvulsants, lifestyle modifications, and trigger identification are still crucial. Nondrug measures like stress reduction, proper sleep hygiene, hydration, and regular exercise further strengthen treatment outcomes. Modern research is increasingly moving toward personalized care, where treatment is aligned with an individual's unique biological and genetic characteristics. Overall, migraine continues to be a major health concern requiring a balanced approach that integrates medical therapy, lifestyle management, and patient awareness. To enhance treatment outcomes and the quality of life for those who suffer with this crippling illness, ongoing research initiatives and better information are essential.

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