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Review Article

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Behind the Headache: A Deep Dive into the Science of Migraines

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Abstract

Migraine is a common, debilitating neurological disorder characterized by recurrent, severe headaches often accompanied by a range of neurological, gastrointestinal, and autonomic symptoms. This review article provides a comprehensive overview of the symptoms, phases, pathophysiology, risk factors, and types of migraine. The article outlines the distinct phases of a migraine attack, including the prodrome, aura, headache, and postdrome, and emphasizes the complex pathophysiological mechanisms underlying migraine, including cortical spreading depression, trigeminovascular activation, and neurotransmitter imbalances. We also discuss the various risk factors, such as genetic predisposition, environmental triggers, hormonal fluctuations, and lifestyle factors that contribute to the onset and frequency of migraine attacks. The review further categorizes the different types of migraine, including episodic, chronic, and various subtypes, such as migraine with aura and without aura. A better understanding of these facets of migraine will facilitate improved management strategies and therapeutic interventions.

Keywords: ***Migraine, symptoms, phases, pathophysiology, risk factors, types, aura, prodrome, chronic migraine, episodic migraine, neurotransmitter imbalances, cortical spreading depression.***

Introduction

Migraine is a common and disabling neurological disorder that affects millions of individuals globally. This condition is characterized by recurrent episodes of severe headache, often accompanied by a range of debilitating symptoms. The purpose of this review is to examine both traditional and adjunctive treatment strategies for managing migraines, offering insight into the clinical presentation, underlying mechanisms, and evolving therapeutic approaches [1].

Discussion

Migraine is a primary headache disorder that typically presents as a unilateral, throbbing headache, though it can affect both sides of the head. In addition to pain, migraines often involve other symptoms such as nausea, vomiting, and heightened sensitivity to light and sound (light and sound sensitivity, or photophobia and phonophobia). The World Health Organization (WHO) recognizes migraines as one of the most disabling conditions globally, impacting individuals' ability to function normally [1].

The prevalence of migraines is widespread, with approximately 12% of the population worldwide affected. Women are disproportionately affected, with studies indicating that they experience migraines three times more frequently than men, particularly during their reproductive years [2].

The prevalence of migraines in India reflects a significant public health concern. Studies indicate that migraine affects approximately 10-15% of the Indian population, with an estimated 100 million individuals experiencing the disorder. Similar to global trends, migraine prevalence is higher in women, especially during their reproductive years, and the female-to-male ratio is around 3:1 in many studies [3].

In India, the age of onset for migraines typically ranges from late adolescence to early adulthood, with peak prevalence occurring between the ages of 18 and 44. This age group often experiences the greatest impact on quality of life and productivity due to the chronic nature of the condition. Furthermore, in urban populations, the prevalence appears to be higher, possibly due to lifestyle factors such as stress, irregular sleep patterns, and environmental triggers like pollution and dietary habits [4].

Recent research suggests that despite the high prevalence, many individuals with migraine in India remain undiagnosed or undertreated. A study published in The Journal of Headache and Pain found that nearly 60-70% of individuals with migraines do not seek medical help, likely due to lack of awareness, stigma surrounding chronic headache disorders, or inadequate healthcare access in rural areas. This underscores the need for greater education and healthcare infrastructure to support diagnosis and effective treatment strategies in India [5].

Moreover, while migraine affects a significant portion of the population, there are also regional variations in prevalence and impact due to factors such as socio-economic conditions, access to healthcare, and cultural differences. There is a growing recognition of migraine as a major contributor to disability in India, and ongoing

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studies aim to improve understanding and management of this condition in diverse Indian populations [6].

Migraines severely impact quality of life by interfering with daily activities, work productivity, and social interactions. Individuals with frequent migraines experience significant disability, as attacks can last from hours to days and often require bed rest. According to the Global Burden of Disease Study, migraine is among the leading causes of disability-adjusted life years (DALYs) due to its chronic nature and high frequency [7].

The economic burden of migraines is substantial, with costs associated with healthcare, lost productivity, and absenteeism. In the United States, the total economic cost of migraines exceeds $36 billion annually, highlighting the widespread impact this condition has on individuals and society at large [8].

The **pathophysiology** of migraines involves both genetic and environmental factors that influence the brain's neural and vascular systems. Cortical spreading depression (CSD) is considered a key event in migraine onset, where a wave of depolarization spreads across the brain's cortex, triggering neuronal and glial responses. This leads to the release of inflammatory molecules such as calcitonin gene-related peptide (CGRP), which sensitizes the trigeminovascular system, ultimately resulting in headache pain [1].

Cortical Spreading Depression (CSD) is a phenomenon in the brain that plays a crucial role in the pathophysiology of migraines. It is a wave of intense neural and glial depolarization followed by a period of neuronal inactivity that spreads across the cortex of the brain. CSD is thought to be the underlying mechanism for the aura phase of migraines and contributes significantly to the pain and other symptoms experienced during a migraine attack [1].

CSD begins when a localized area of the cortex becomes depolarized, meaning that the electrical charge of the neuron shifts from a negative to a positive state. This depolarization triggers a cascade of ion movements and neurotransmitter release, including potassium, calcium, and glutamate. This initial depolarization is followed by a "silent" period, where neuronal activity temporarily ceases, leading to a refractory state. The wave of depolarization then propagates slowly across the cortex at a rate of about 2-5 mm/min. This wave is accompanied by a series of biochemical changes, including the release of inflammatory molecules like calcitonin gene-related peptide (CGRP), which sensitizes the trigeminovascular system and contributes to the headache pain characteristic of migraines [1].

CSD can cause aura symptoms. In individuals who experience migraine with aura, CSD is typically associated with the sensory disturbances that occur before the headache phase. The aura often manifests as visual disturbances, such as flashes of light, zigzag lines, or blind spots, but it can also involve other sensory phenomena like tingling or numbness in the limbs. These disturbances correspond to the spreading wave of CSD through the cortical areas responsible for vision and sensation. The aura typically lasts for 20-30 minutes before resolving, followed by the onset of the headache. The exact mechanism by which CSD triggers the aura is not fully understood, but it is believed to be related to the disruption of normal neural activity in specific regions of the brain [9].

While CSD is primarily associated with the aura phase in migraine, it also plays a role in the subsequent pain phase of the migraine attack. The depolarization wave and the release of inflammatory mediators like CGRP affect the trigeminal nerve system, which is responsible for transmitting pain signals from the head and face to the brain. This leads to sensitization of the pain pathways and can cause the headache phase of the migraine. The increased release of neurotransmitters such as glutamate and CGRP also enhances the excitability of neurons in the pain-processing centers of the brain, contributing to the intense throbbing pain characteristic of migraines [10].

Besides headache and aura, CSD may contribute to other neurological symptoms observed during migraines, such as nausea, vomiting, and photophobia. The complex interaction between the cortex, the trigeminal system, and brainstem structures likely explains the broader spectrum of migraine symptoms, including autonomic disturbances and sensory sensitivities. Researchers have also found that CSD can activate structures in the brainstem, including the area postrema, which is involved in regulating nausea and vomiting [11].

The **trigeminovascular system** is a vital neural pathway in the brain involved in the pain and symptoms of migraine headaches. This system connects the **trigeminal nerve**, which is responsible for sensation in the face and parts of the head, to blood vessels, especially those in the meninges (the protective layers of the brain) and brain. It plays a pivotal role in the **pain perception** and other **neurological symptoms** experienced during a migraine attack.

The trigeminal nerve is crucial in controlling sensations from deeper structures, including the **dura mater** (a membrane surrounding the brain), as well as the large arteries that supply the brain, such as the **middle meningeal artery** [1].

The trigeminal nerve communicates with the blood vessels in the brain, which is particularly significant for the migraine process. When migraine attacks occur, **neurovascular interactions** between the trigeminal nerve and the cranial blood vessels are central to the **pain mechanism** [9].

The trigeminovascular system is integral to the onset and progression of migraines. **CSD** spreads a wave of electrical depolarization across the cortex, triggering the trigeminal nerve fibers. This results in the release of **inflammatory molecules** such as **calcitonin gene-related peptide (CGRP)**, which sensitizes the trigeminal nerve and causes changes in cranial blood vessel tone. CGRP also contributes to the dilation of blood vessels, which exacerbates migraine pain [10,11].

The trigeminal nerve becomes sensitized during a migraine due to the release of neurotransmitters and inflammatory molecules. Sensitization means that even normal stimuli (like light or sound) can be perceived as painful. The **release of CGRP**, among other molecules, causes **neurogenic inflammation**, further enhancing the sensitivity of pain pathways, leading to the throbbing headache that defines a migraine [12].

Pain Transmission: Once the trigeminal nerve is activated, the pain signals are transmitted to the **brainstem**, particularly the **trigeminal sensory nucleus**, and then relayed to other brain regions, including the **thalamus** and **cerebral cortex**, where they are perceived as intense pain. The pain is also influenced by the **activation of other structures in the brainstem** that process pain and autonomic responses, like nausea and vomiting [13].

Vascular Changes: The trigeminovascular system also mediates changes in the vasculature, including **vasodilation**, which occurs when inflammatory mediators like CGRP are released. The dilation of blood vessels in the meninges results in pain and further triggers the headache. This process is thought to increase the permeability of the blood-brain barrier, allowing more inflammatory molecules to enter the brain and worsen the symptoms [14].

Autonomic Symptoms: The trigeminovascular system is also linked to autonomic symptoms such as **nausea, vomiting**, and **photophobia**. The **brainstem**, which processes both pain and

autonomic responses, becomes involved, leading to these associated symptoms [15].

Understanding the pathophysiology has led to the development of targeted treatments aimed at blocking the molecular pathways involved. For example, CGRP inhibitors and other medications that block specific neurotransmitters involved in CSD are now used as treatments for both acute and preventive migraine management. These treatments aim to disrupt the cascade of events triggered by CSD and provide relief for individuals suffering from migraine attacks. Additionally, **neurostimulation devices** and **monoclonal antibodies** targeting specific elements in the trigeminovascular system are emerging as promising therapeutic options for patients with chronic or frequent migraines [16-18].

Migraine is a complex neurological disorder with a **strong genetic component**, although environmental and lifestyle factors also play a role in its expression. The inheritance pattern of migraine is often polygenic, meaning multiple genes contribute to the susceptibility and severity of the disorder. Genetic research has provided insights into several mechanisms and pathways involved in migraine, including the role of ion channels, neurotransmitter systems, and neurovascular regulation [19].

Studies have shown that migraine tends to run in families, and individuals with a first-degree relative (such as a parent or sibling) with migraines are more likely to develop the condition themselves. Twin studies suggest a heritability estimate of about 50-60%, indicating that genetics significantly influence the risk of developing migraines. While specific genes related to migraine are still being investigated, several genetic variations have been identified in both **episodic migraine** and **chronic migraine cases** [20].

Genetic Variants Associated with Migraine

1. **CACNA1A (Calcium Channel Gene):** The **CACNA1A** gene encodes a voltage-gated calcium channel that plays a role in neuronal excitability. Mutations in this gene are linked to a rare form of migraine with aura called **Familial Hemiplegic Migraine (FHM)**. These mutations lead to alterations in the calcium channel's function, contributing to abnormal neuronal activity and CSD, which is thought to trigger migraine attacks [21].
2. **TRPM8 (Transient Receptor Potential Melastatin 8):** Variants in the **TRPM8** gene, which encodes a receptor involved in the sensation of cold, have been associated with migraine susceptibility. The TRPM8 receptor plays a role in the body's response to temperature changes, and its dysregulation may contribute to the heightened sensitivity to stimuli that occurs during a migraine attack [22].
3. **MT1/2 (Melatonin Receptors):** Studies suggest that mutations in **MT1/2**, the genes for melatonin receptors, might be involved in migraine, especially in individuals who experience attacks triggered by changes in sleep patterns. Melatonin is a hormone involved in regulating circadian rhythms, and its dysfunction can affect migraine onset, especially in those with a genetic predisposition [23].
4. **CGRP (Calcitonin Gene-Related Peptide):** The CGRP gene, along with its receptor components, is another key player in migraine genetics. CGRP is involved in the neurovascular changes that underlie migraine pain. Genetic variations affecting CGRP signaling may increase the susceptibility to migraines by enhancing the release of CGRP in response to various triggers. This discovery has led to the development of CGRP-targeting therapies, such as monoclonal antibodies and CGRP receptor antagonists, as migraine treatments [24].
5. **APOE (Apolipoprotein E):** Some studies have suggested a link between **APOE** gene polymorphisms and migraine susceptibility. While APOE is primarily associated with Alzheimer's disease, certain variants (e.g., APOE ε4) may also influence the vascular tone and inflammatory responses in the brain, increasing the likelihood of migraine development [25].

In recent years, advances in genomic research have led to the development of **polygenic risk scores (PRS)**, which are calculated by combining the effects of multiple small genetic variants associated with migraine. PRS could help identify individuals at higher risk for developing migraine, particularly in populations with a family history of the disorder. However, migraine genetics is still a rapidly evolving field, and further research is needed to understand the full scope of genetic factors involved [26].

Genetic and Environmental Interaction

While genetic factors contribute significantly to migraine, environmental factors such as stress, sleep patterns, diet, and hormonal changes can modulate the expression of genetic predispositions [27].

Environmental Factors in Migraine Pathogenesis

Migraine is a multifactorial disorder influenced by both genetic predisposition and environmental factors. While genetics plays a substantial role in migraine susceptibility, environmental triggers can significantly affect the frequency, intensity, and duration of migraine attacks. Understanding these factors is crucial for managing and preventing migraines, as lifestyle modifications can help mitigate some of the environmental triggers [28].

Common Environmental Triggers of Migraine

1. **Stress:** Stress is one of the most commonly reported migraine triggers. Both acute and chronic stress can lead to the release of certain hormones, such as cortisol and adrenaline, which can alter brain function and vascular tone, potentially triggering a migraine attack. Psychological stress can also affect sleep and dietary habits, which are known to influence migraine frequency and severity. Stress management techniques, including relaxation exercises, yoga, and mindfulness, have been shown to help reduce migraine attacks [28,29].
2. **Sleep Disturbances:** Both insufficient sleep and excessive sleep can trigger migraines in susceptible individuals. Irregular sleep patterns, such as disrupted circadian rhythms, can exacerbate migraine attacks. Migraine patients often experience poor sleep quality, and improving sleep hygiene-maintaining regular sleep-wake cycles and creating a restful sleep environment-can be an effective strategy in migraine management. Moreover, sleep deprivation is a well-known trigger for many migraineurs [30].
3. **Dietary Factors:** Certain foods and beverages are known to trigger migraines in some individuals. Common food triggers include aged cheeses, chocolate, caffeine, alcohol (especially red wine), processed meats, and foods

containing high levels of monosodium glutamate (MSG). These foods can lead to the release of inflammatory molecules or cause changes in neurotransmitter function. Additionally, fasting or skipping meals can also be a trigger, as it leads to drops in blood sugar, which may increase the risk of a migraine attack. Keeping a migraine diary to track food intake and potential triggers can help individuals identify their specific dietary triggers [31].

4. **Hormonal Changes:** Hormonal fluctuations, particularly in women, are a significant environmental factor in migraine pathogenesis. Menstrual cycles, pregnancy, and menopause can all influence migraine frequency and severity. Estrogen, in particular, plays a key role in this process. Many women experience menstrual migraines, which occur just before or during menstruation when estrogen levels drop sharply. Hormonal therapies such as oral contraceptives can have both positive and negative effects on migraine frequency, depending on the individual. Pregnancy may reduce migraine frequency for some women, while others experience exacerbations, especially in the first trimester [32].
5. **Weather Changes:** Changes in weather, such as shifts in temperature, humidity, or barometric pressure, can trigger migraines. These environmental factors may lead to vasodilation or constriction in the brain's blood vessels, initiating migraine pain. Many migraine patients report increased attacks during hot weather, thunderstorms, or changes in altitude. While these triggers are often difficult to control, maintaining a comfortable environment and staying hydrated can help reduce their impact [33].
6. **Environmental Toxins and Pollution:** Exposure to environmental toxins, including cigarette smoke, strong odors (like perfumes or cleaning products), and air pollution, has been reported as a trigger for migraines. These triggers can cause neuroinflammation or lead to hypersensitivity of the trigeminovascular system, a key player in migraine pathophysiology. Individuals with sensitivities to these environmental factors may benefit from avoiding areas with high pollution levels or using air purifiers indoors [34].
7. **Bright Lights and Loud Noises:** Sensory sensitivities, including photophobia (sensitivity to light) and phonophobia (sensitivity to sound), are common in people with migraines. Exposure to bright lights, flickering lights (such as those from fluorescent bulbs), and loud noises can trigger or worsen migraine attacks. This is thought to be related to increased cortical excitability, a hallmark of migraineurs. Wearing sunglasses or avoiding noisy, bright environments can help mitigate these triggers [35].
8. **Dehydration:** Dehydration is another important environmental factor that can trigger migraines. Insufficient fluid intake can lead to changes in electrolyte balance, which may increase the risk of migraine attacks. Ensuring adequate hydration, particularly during hot weather or after physical exertion, is a simple yet effective preventative measure for many migraine sufferers [36].

Gene-Environment Interactions

While environmental factors can trigger migraines in individuals who are genetically predisposed to the condition, the interaction between genes and environment is complex. Research suggests that certain genetic factors may make individuals more sensitive to environmental triggers. For instance, individuals with specific genetic variants in **CGRP** or ion channels may be more susceptible to the effects of stress, sleep disturbances, or dietary triggers. Understanding these gene-environment interactions can help refine migraine management strategies and lead to more personalized treatments [37].

Migraine sufferers can manage their condition by identifying and minimizing exposure to known environmental triggers. Keeping a **migraine diary** that tracks potential triggers (such as stress levels, diet, sleep, weather conditions, etc) can help individuals pinpoint their specific environmental triggers. In addition, lifestyle modifications, such as establishing regular sleep patterns, maintaining hydration, reducing stress, and avoiding known food triggers, can significantly reduce the frequency and severity of migraine attacks [37].

Common Types of Migraines

Migraines are a group of neurological disorders characterized by recurring headaches that can vary significantly in their presentation. There are several types of migraines, each with distinct characteristics. Understanding these different types is essential for proper diagnosis and treatment [38].

1. Migraine with Aura (Classical Migraine)

Migraine with aura is characterized by neurological disturbances (aura) that precede the headache phase. Auras typically last for 5 to 60 minutes and are followed by the headache phase. Common symptoms include visual disturbances (e.g., zigzag lines or blind spots) and sensory symptoms (e.g., tingling or numbness). This type of migraine is thought to be related to CSD [38].

2. Migraine without Aura (Common Migraine)

Migraine without aura is the most common form, accounting for about 70-80% of migraine cases. It is not preceded by aura and typically presents with throbbing, unilateral pain, often accompanied by nausea, vomiting, and photophobia (sensitivity to light). The headache usually lasts from 4 to 72 hours [39].

3. Episodic Migraine

Episodic migraine occurs less than 15 days per month. It is often triggered by external factors such as stress, sleep disturbances, or certain foods. Episodic migraines can be treated with acute medications like triptans and NSAIDs. Treatment focuses on minimizing the frequency and intensity of attacks [40].

4. Chronic Migraine

Chronic migraine is defined as experiencing headache on 15 or more days per month for at least 3 months, with at least 8 migraine days. It can develop from episodic migraines, often with medication overuse, which can lead to rebound headaches. Chronic migraine is usually treated with a combination of preventive treatments such as Botox injections and CGRP inhibitors [41].

5. Complicated Migraines

Complicated migraines include subtypes that present additional neurological features that can mimic other disorders. These include:

- **Hemiplegic Migraine:** Characterized by temporary paralysis or weakness on one side of the body. It can be familial or sporadic [42].
- **Retinal Migraine:** Involves temporary vision loss or disturbances in one eye. The vision changes typically last for less than 30 minutes [43].

- **Ophthalmoplegic Migraine:** A rare form that causes ocular palsies, such as diplopia (double vision) and ptosis (drooping eyelid), and is often seen in children [44].
- **Basilar Migraine:** Also known as migraine with brainstem aura, it includes symptoms originating from the brainstem, such as vertigo, ataxia, and tinnitus [45].
- **Abdominal Migraine:** Affects children and presents with severe abdominal pain and nausea without the typical headache [46].
- **Menstrual Migraine:** Occurs in association with menstruation, triggered by hormonal fluctuations, particularly the drop in estrogen levels [47].
- **Vestibular Migraine:** Involves episodes of vertigo and dizziness, along with other migraine-related symptoms such as nausea and photophobia [48].
- **Silent Migraine:** Also called acephalgic migraine, this type involves all the typical migraine symptoms (e.g., aura) but without the headache phase [49].
- **Hormonal Migraine:** Occurs due to hormonal fluctuations, especially in women during menstruation, pregnancy, or menopause, often linked to estrogen levels [50].

Stages of Migraine

Migraines generally follow a four-stage pattern:

1. **Prodrome:** This phase can occur 1-2 days before the headache and includes symptoms like fatigue, mood changes, food cravings, and neck stiffness.
2. **Aura:** This phase occurs before the headache and lasts for 5-60 minutes, featuring symptoms such as visual disturbances, tingling, and speech changes.
3. **Headache:** The headache phase typically lasts 4-72 hours and involves unilateral, throbbing pain, often with nausea and photophobia.
4. **Postdrome:** This phase occurs after the headache subsides and involves symptoms like fatigue, mood changes, and mild headache [51].

MRI Findings in Migraine

Magnetic resonance imaging (MRI) is typically normal in individuals with migraines, but studies show that chronic migraine sufferers may have subclinical white matter lesions. These lesions are generally non-specific and not considered diagnostic for migraine. MRI may also be used to rule out other conditions like stroke or brain tumors [51].

CT Head in Migraine

A CT scan is not routinely used for diagnosing migraines. However, it may be performed if there is suspicion of another intracranial pathology such as hemorrhage, tumor, or stroke. The CT findings are generally normal for migraines, and the use of CT is often limited to the acute phase of headache to exclude other serious conditions [52].

EEG in Migraine

Electroencephalogram (EEG) is generally not indicated for diagnosing migraine. However, it may be helpful when there is concern about seizure activity or unusual neurological symptoms. In some cases, particularly in those with migraine with aura, EEG may show focal slowing or abnormal waves, but these findings are typically transient and non-specific [53].

CSF in Migraine

Cerebrospinal fluid (CSF) analysis is not required for typical migraine diagnosis. However, in cases where other conditions such as meningitis or intracranial infections are suspected, CSF analysis may be conducted. In migraine patients, the CSF is typically normal, with no evidence of infection or inflammation [54].

Conclusion

In conclusion, migraines are complex neurological disorders with multifaceted symptoms, distinct phases, and varying underlying pathophysiological mechanisms. A comprehensive understanding of the migraine attack phases-prodrome, aura, headache, and postdrome-along with the intricate processes such as cortical spreading depression and trigeminovascular activation, is essential for advancing both diagnosis and treatment. The risk factors, which range from genetic predisposition to environmental triggers and hormonal influences, underscore the personalized nature of migraine management. With various types of migraine, including episodic, chronic, and those with or without aura, recognizing these variations is crucial for effective treatment strategies. Traditional treatments generally focus on pharmacological interventions aimed at aborting or preventing migraine attacks. These include medications such as triptans for acute attacks and beta-blockers or antiepileptic drugs for preventive therapy. However, there has been growing interest in adjunctive treatments, which are non-pharmacological or newer therapeutic approaches. Examples of adjunctive treatments include neurostimulation devices, CBT, acupuncture, and the use of monoclonal antibodies targeting CGRP pathways [20].

Declarations

Ethics approval and consent to participate

Not applicable

Data

Bibliography attached

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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