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"MIGRAINE AS A NEUROVASCULAR DISORDER: CURRENT CONCEPTS OF PATHOGENESIS AND CLINICAL MANAGEMENT"

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Annotation: Migraine is a common and disabling neurological condition that is increasingly recognized as a complex neurovascular disorder. Current evidence indicates that migraine pathogenesis involves an interplay between neuronal hyperexcitability, cortical spreading depression, and activation of the trigeminovascular system, leading to the release of vasoactive neuropeptides and subsequent neurogenic inflammation. These mechanisms contribute to both the initiation and maintenance of migraine attacks.

Recent advances have improved the understanding of central and peripheral sensitization processes, as well as the role of calcitonin gene-related peptide (CGRP) in migraine pathophysiology. Such insights have significantly influenced clinical management, resulting in the development of targeted therapies, including CGRP receptor antagonists and monoclonal antibodies. Alongside pharmacological treatment, non-pharmacological approaches—such as lifestyle modification and trigger management—remain essential components of comprehensive care.

This review summarizes current concepts of migraine pathogenesis and discusses contemporary clinical management strategies, emphasizing the importance of an integrated, mechanism-based approach to diagnosis and treatment.

Keywords

Migraine; Neurovascular disorder; Trigeminovascular system; Cortical spreading depression; CGRP; Pathogenesis; Clinical management

Introduction: Migraine is one of the most prevalent neurological disorders and is considered a complex, multifactorial condition involving multiple disciplines. It is characterized by recurrent episodes of headache and may present in either episodic or chronic forms, with or without aura. Historically, migraine was described in the early twentieth century as a "hypoglycemic headache"; however, current understanding recognizes it as a distinct neurological disorder. Patients commonly experience a wide range of transient motor and somatosensory disturbances.

Clinically, migraine is defined by severe, pulsating headaches, often unilateral in nature, and frequently accompanied by nausea, photophobia, phonophobia, and vomiting. The term *migraine* originates from the Greek word *hemicrania*, meaning "half of the head," reflecting the typical unilateral localization of pain. Nevertheless, bilateral headache is also frequently observed, particularly involving the frontal and occipital regions. The pain is usually throbbing and tends to intensify with physical activity or movement. Migraine attacks are generally of moderate to severe intensity.

Pathophysiology Headache has been known for almost 600 years. The modern concept of chronic migraine was known at the beginning of the 17th century. In the early days, the pathophysiology of migraine was principally based on neurological or vascular mechanisms; the metabolic aspects of this disorder were reported only relatively recently [46]. Migraine is divided into four phases including (Premonitory, Aura, Headache and Post dromal) (Fig. 4). These phases can occur sequentially or may show significant overlap. Meningeal vasodilation together with inflammation is caused by activation of vascular networks, resulting in headache [12,13,16]. The

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pathophysiology of migraine involves modulating pain originating in disrupted neural networks in the head [17]. Studies have shown that brain stem and diencephalic nuclei control the trigeminovascular sys tem, which comprises efferent neurons supplying vascular networks and afferent neurons that feed information to the trigeminal nucleus caudalis [17,18]. Head pain is perceived as meningeal inflammation and vaso dilation due to activation of these networks [19,20]. Neurotransmitters, such as serotonin, also play critical roles in the pathophysiology and the treatment of migraine. Serotonin initiates an intracellular network cascade that causes inhibitory or excitatory neurotransmission. Receptors of serotonin are dispersed in the brain, including those used in pain-signaling circuits and cranial blood vessels. Therapies for treating migraine have been tailored to modulate seroto nin receptors. The modulation is directed toward amplifying the sero tonin signal, leading to pain relief via vasoconstriction of blood vessels and inhibition of peptides, for example substance P 21 and calcitonin gene-related peptide (CGRP) [21,22]. The International Classification of Headache Disorders (ICHD) is a standardized tool that helps in the identification of primary and sec ondary headache. The diagnosis of headache disorders is based mainly on the clinical manifestations of the different phases. The aura and headache phases are the main focus, as these mainly require medical attention .

Diagnosis of migraine The guidelines for diagnosing migraine were formulated by the In ternational Headache Society [5] and are summarized in Table 2. There is a difference in the diagnostic criteria for MA and MO. The features of MA involve a minimum of five headaches in 4–72 h. Also, MA demon strates either pulsation, unilateral location, intense pain, or exacerba tion of headache with routine activities. These features are accompanied by vomiting, nausea and phonophobia or photophobia [5]. Notably, the symptoms and headache should not be attributed to other diseases. The diagnostic features for migraine with the typical aura include a minimum of five headaches, among which at least two epi sodes must be accompanied by an aura. The headache should begin or occur within 60 min of the aura. The aura must consist of reversible dysphasic speech or unilateral sensory or homonymous visual symp toms. There must be at least one symptom that gradually increases with time, with each symptom ranging from 5 to 60 min [5]. The features should not be accounted for by a secondary disorder. 4.1. Pattern recognition Initial diagnosis requires an assessment of how the headache origi nated. The patterns involve either pre-existing headache ailments, with an increase in the frequency of attacks, which reach a stage of non- Table 2 The diagnostic criteria for migraine headache as formulated by the International Headache Society [5]. Without aura With aura • Minimum of five headaches within 4–72 h. • Pulsation. • Unilateral location. • Intense pain. • Exacerbation of headache with routine activities. These features are accompanied by vomiting or nausea and phonophobia or photophobia. • Minimum of five headaches, among which at least two episodes must be accompanied by an aura. • The headache should begin with, or be within 60 min of, the aura. The aura must consist of • reversible dysphasic speech. • unilateral sensory. • homonymous visual symptoms. Minimum of one symptom that gradually increases with time and each symptom ranges from 5 to 60 min. recovery or a sudden headache that starts and does not go away. The former is called a transformed migraine, and the latter is known as a new daily persistent headache [72,73]. It is important to recognize these patterns, as they highlight the underlying cause. Establishment of the correct phenotype is vital for an accurate diagnosis as well as for suc cessful treatment. 4.2. Recognition of the migraine phases The most common cause of recurrent headache is migraine, which is experienced by 10% of men and 20% of women. Although there is a genetic basis for migraine, the attacks are usually triggered by external or internal stimuli and sometimes appear for no apparent reason. An aura is experienced by around 20% of

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migraine patients. The aura consists of visuals, as negative phenomena (blind spots caused by loss of vision) or positive phenomena (flashes of light, floaters, expanding or moving zig-zag patterns). Tingling or numbness is also experienced as a sensory aura by many individuals which occurs on the arms, lips, tongue, face, and hands. Premonitory symptoms are observed by 10–20% of individuals for nearly 48 h before an episode [48,74]. These symptoms include an abnormal burst of energy, yawning, neck stiffness, fatigue, and frequent urination. The active areas of the brain during the premonitory phase have been identified [75]. A postdrome is also experienced by most cases, including a bruised feeling in the head, grumbling headache, nausea, fatigue and sensitivity to smell, noise, light and movement.

Diagnosis Chronic headache lacks a clear phenotype. An a priori assumption is useful in this case, depending on which cases presented to doctors are primary headache diseases and not a secondary headache. It is less common for individuals to seek medical consultations for mild head ache, such as those related to stress and tension. An individual's head ache episodic pattern is revealed during evaluation of a history that progressed into a chronic form of migraine. Sometimes these headaches were driven by caffeine or painkiller overuse [95], or psychological abnormalities such as depression or anxiety, or physical situations such as significant life events or sleep apnea. A definite diagnosis may not be possible in some cases. Nonetheless, if signs of severe and chronic headache are interfering with normal daily activities, then treatment should be provided based on migraine being the most likely cause. It is vital to make a diagnosis and to explain it to the patient. The discussion should include reassurance that nothing serious has happened. This is the first step in treatment; the next step is to prescribe medication, and in rare instances an intervention may be required. 5. Treatment strategies The main goal of treatment for migraine is to reduce the severity and duration of the migraine attack [96]. Other objectives include restoring functioning ability, reducing the use of rescue medications and pro moting overall management with no or minimal side effects [97]. The current therapies for migraine include acetaminophen [98,99], triptans (sumatriptan, eletriptan, rizatriptan, almotriptan, frovatriptan, nara triptan and zolmitriptan) [100,101], Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (naproxen sodium, acetylsalicylic acid (ASA), ibuprofen, and diclofenac potassium [102–105], dihydroergotamine [106], non-opioid analgesics (ASA, acetaminophen, and caffeine) [107], NSAID-triptan combinations [108], and anti-emetics (chlorpromazine, metoclopramide and prochlorperazine) [109–111]. Drugs such as acet aminophen, butorphanol and tramadol show some efficacy; however, the disadvantages of NSAIDs surpass their benefits and hence they are less recommended for use [96,112]. Opioids should be avoided due to their addiction risk [97]. Opioids can reduce the efficacy of triptans and promote sensitization to medications. Chronic migraine pa tients always require prophylactic treatment, while migraine patients with low frequency of symptoms can be managed with effective acute therapy. OnabotulinumtoxinA has been approved for treating chronic migraine in European Union, since it was in use countries like Italy . CGRP receptor antagonists was reported for decreasing migraine frequency . The most important risk due to the overuse of symp tomatic medication should be considered during migraine progression. A key component of migraine therapy involves over-the-counter medications, which are considered the first-line therapy by most peo ple suffering from migraine. Medications such as naproxen, ibuprofen, acetaminophen and aspirin form the first line of treatment for a migraine attack . These medications have fewer side effects and a favorable administration route, in addition to low cost and high efficacy.

Conclusion

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Migraine is a complex neurovascular disorder characterized by recurrent, often debilitating headache attacks and a wide spectrum of neurological symptoms. Advances in understanding its multifactorial pathogenesis—particularly the roles of neuronal hyperexcitability, cortical spreading depression, and trigeminovascular system activation—have significantly reshaped current concepts of the disease. These mechanisms highlight migraine as more than a primary headache disorder, emphasizing its systemic and neurological complexity.

Contemporary clinical management has increasingly shifted toward mechanism-based and individualized treatment strategies. The introduction of targeted therapies, especially those acting on the CGRP pathway, has marked a substantial improvement in preventive and acute migraine care. Nevertheless, optimal management requires a comprehensive approach that integrates pharmacological treatment with lifestyle modification, trigger avoidance, and patient education.

Further research into the molecular, genetic, and neurophysiological aspects of migraine is essential to improve diagnostic accuracy and to develop more effective and personalized therapeutic interventions. A deeper understanding of migraine pathophysiology will ultimately enhance patient outcomes and reduce the global burden of this highly prevalent neurological disorder.

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