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MIGRAINE: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY, MANAGEMENT, AND FUTURE DIRECTIONS:

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ABSTRACT

Background: Migraine is a severely disabling neurological disorder driven by deep brain mechanisms. The four-phase attack, marked by unilateral, throbbing pain, is fundamentally linked to the hypothalamus and activation of the trigeminovascular system, where the peptide CGRP acts as the primary pain signal. It's a huge global health burden, yet widely mistreated. **Scope:** This review explores migraine's biological basis and assesses current treatments, from simple analgesics to specialized Triptans. We aim to highlight major gaps in care—such as poor diagnosis, limited provider knowledge, and unequal access to the best medicines—to define a realistic path toward future personalized treatment. **Key Findings:** Migraine is consistently underdiagnosed and undertreated because many healthcare workers aren't fully familiar with diagnostic rules or first-line drugs. This forces patients onto over-the-counter painkillers, increasing the risk of chronic migraine. Effective treatments, especially newer CGRP-targeted drugs, are oftenout of reach due to cost. Research bias toward women also means the significant suffering of men is frequently overlooked. **Conclusion:** Better outcomes depend on adopting a personalized medicine model. This requires substantial healthcare reforms, including mandated medical education and efforts to ensure all patients have equitable access to the full spectrum of modern, evidence-based therapies.

KEYWORDS: Migraine Pathophysiology, Triptans, CGRP Inhibitors, Treatment Gaps, Personalized Medicine**.**

INTRODUCTION

Migraine is a common and frequently disabling neurological disorder, affecting almost ten percent of the population.[1] it's defined as the recurring primary headache disease, with attacks characterized by lasting 4 to 72 hours. The headache typically becomes unilateral, throbbing, and moderate to severe in its severity, and then it is worsened by typical physical activity and associated with nausea, photophobia (abnormal sensitivity to light), and phonophobia (fear of sound).[1-3]

Migraine attacks vary in pain intensity and associated symptoms, such as nausea, photophobia, and audiophobia. This explains the wide variability in clinical presentation.[1] Migraines typically begin during middle age and affect people aged 35 to 45 years.[3] Children usually have shorter migraines and more pronounced abdominal symptoms.[3] Classic fatal attacks involve three phases: the premonitory phase, the headache phase, and the secondary phase.[1]

Fatigue, irritation, yawning, and poor focus are symptoms of the premonitory phase, which can last from hours to days before an attack. The postdrome phase is characterized by tiredness and persistent sensitivity following the headache. Aura is experienced by one-third of patients, along with focal neurological symptoms.[1,2]

It is currently ranked as the sixth most disabling disorder in the world and the most severe of all neurological disorders.[2] Every year, around 14% of the world's population suffers from migraine, making it the second greatest contributor to the global burden of neurological illnesses, and it affects many youngsters.[4] Women are three times more prone than males to suffer migraines, greatly reducing quality of life, specifically during peak productive years.[2]

The majority of the study focuses on female populations. Females are more likely than males to report migraine-related disability. However, the prevalence of migraine in men cannot be ignored. Males are less likely to report severe pain or seek medical attention, which is attributed in part to cultural expectations of traditional sex/gender roles. As a result, migraine in men may go undiagnosed, and there has been few male-specific research, limiting our understanding of the illness in men. These variables may have a negative impact on males'

quality of life and increase the likelihood of various health conditions. Untreated migraines, for example, might result in chronic illnesses and comorbidities.[4] It has been proposed that the pathogenesis of migraine is linked to energy deficit syndrome, highlighting the critical need to find out how mitochondrial dysfunction, impaired glucose metabolism, and oxidative stress contribute to abnormal sensory processing and migraine susceptibility.[5]

The primary goal is to better understand the debilitating effects of migraine on people by investigating its intricate biological mechanisms, including the roles of the hypothalamus, trigeminovascular system, and CGRP. To pinpoint obstacles to effective migraine treatment in the real world, such as underdiagnosis, a lack of provider expertise, and unequal access to therapies, particularly in settings with limited resources.

Migraine classification is critical due to clinical unpredictability, symptoms that overlap with other headache categories, and missing clear biomarkers. By classifying migraine into subtypes—such as with or without aura, chronic, retinal, hemiplegic, and pediatric types—clinicians can more accurately diagnose, differentiate, and treat each presentation. This structured approach, guided by International Headache Society criteria, improves diagnostic precision, supports research standardization, and enables targeted treatments based on individual patient profiles.[6] Advances in migraine research, such as the importance of hypothalamic homeostasis, autonomic balance, sleep, and mood, have been found in the hypothesis of a 'high-risk area' of the brain. This has created opportunities for non-pharmacological prevention measures.[1]

PATHOPHYSIOLOGY

Premonitory phase

In this phase, migraine attacks started from two to forty-eight hours ago; it's happening before the aura in migraine with aura and before the pain starts in migraine without aura.[7] This stage may present various symptoms, including oscillation, frequent urination, thirst, nausea/vomiting, mood changes (depression, irritability), tiredness, difficulties concentrating, sleep cycle disruption, dietary changes, dysautonomia symptoms, craving, photo/phono/osmophobia (sensitivity to light, sound, and scents), and neck stiffness.[8] Other symptoms can include dizziness, skin changes, sweating, or blurred vision.[9] These prodromal symptoms were usually mild in intensity, but in about one-third of cases they were moderate or severe.[10] In 1899, Gowers was the first to describe the premonitory phase of migraine, noting that drowsiness is an early sign. Later, in 1980, a researcher named Blau

officially recognized these early symptoms as part of the migraine process and introduced the term "complete migraine" and also suggested that symptoms may be linked to the hypothalamus, a part of the brain that controls many body functions, through understanding the migraine from a vascular problem to a neurological condition.[9] This phase can help researchers understand which parts of the brain are responsible for triggering a migraine. This may lead to new migraine medications that stop experiencing pain before it starts. According to the research, the hypothalamus is responsible for PS: One therapy strategy focuses on neuropeptides such as orexin/hypocretin, which regulate hypothalamic functions such as wakefulness, sleep, hunger, and stress.[9] In pathogenesis, the trigeminocervical complex and trigeminal nucleus caudalis (TNC) are involved in sending pain signals to hypothalamic areas, such as the lateral hypothalamus, dorsomedial hypothalamus, and suprachiasmatic nucleus. Some hypothalamic nuclei return signals to the TCC to regulate pain. The hypothalamus plays a central role in the premonitory phase. The A11, PVN, and lateral hypothalamic nuclei all send projections to the TCC, primarily to the ventrolateral dorsal horn, which receives trigeminal input from the ophthalmic division. These hypothalamic projections regulate migraine-related neuronal activity at the TCC level. Stimulation of the A11 nucleus reduces dural pain processing via dopamine D2 receptors, but injury to the A11 promotes trigeminocervical responses, implying a function in continuous pain management. The PVN also reduces TCC activity and directs projections to the superior salivatory nucleus, which is implicated in cranial autonomic symptoms. Some regulation may also occur indirectly via other brain regions, such as the PAG and dorsal raphe nucleus.[11] Hypothalamic peptides (such as orexins, neuropeptide Y, PACAP, oxytocin, and vasopressin) regulate neuroendocrine, autonomic, and pain pathways involved in migraine pathogenesis.[11] Since the 1970s, early research has indicated that changes in cerebral blood flow, particularly decreased blood flow to the cortex, occur before migraine headaches. More recent imaging studies have found changes in activity and blood flow in deep brain regions, particularly the hypothalamus, thalamus, dorsolateral pons, and other brainstem sites, during the premonitory period.[12] Most neuroimaging studies investigating migraine have treated the hypothalamus as a single, homogeneous structure, neglecting its intrinsic functional subregions. This approach ignores the diverse roles played by different hypothalamic regions in the regulation of important processes such as pain control, circadian rhythms, hormonal control, and autonomic regulation. Understanding the specific contributions of these subregions is essential to elucidate their roles in migraine pathophysiology and identify more precise therapeutic targets.[13]

Dopaminergic hypersensitivity: Impaired dopaminergic neurotransmission leads to enhanced dopamine receptor hypersensitivity, which is a hallmark of chronic migraine. Actually, this hypersensitivity plays a significant role during different migraine phases, particularly the prodromal and headache stages. In the prodromal phase, symptoms like yawning, fatigue, and drowsiness arise due to presynaptic dopamine receptor activation. In contrast, during the headache phase, postsynaptic receptor stimulation leads to nausea and vomiting. These symptoms highlight the central role of dopamine dysregulation in migraine pathophysiology.[14]

AURA PHASE

Migraine with aura affects about one-third of individuals with migraine and involves transient, reversible neurological symptoms—most commonly visual, but also somatosensory and speech-related—featuring both positive (added) and negative (lost) sensory changes that occur before or during the headache.[15,18]

Positive symptoms happen when the brain becomes overly active, causing effects like flashing lights, strange sounds, tingling, or unusual sensations. In contrast, negative symptoms occur when brain activity drops, leading to things like blurred or lost vision, numbness, or weakness.[18]

In Pathogenesis, Cortical Spreading Depression (CSD) is a wave of neuronal and glial depolarization in the cortex that triggers migraine aura. It can be initiated or influenced by vascular, metabolic, genetic, and environmental factors, and is also associated with hypoxic-ischemic brain injury mechanisms.[16]

In addition to these neurobiological mechanisms, migraine with aura is associated with significant vascular risks. The risk of ischemic stroke is significantly increased in individuals with migraine with aura. Combined hormonal contraception containing estrogens further elevates this risk in women with migraine with aura.[17]

HEADACHE PHASE

The typical throbbing pain of migraine is thought to happen due to activation of the trigeminovascular system.[8] Migraine pain is increasingly understood to result from sterile, neurogenically driven inflammation of the dura mater. Central to this process is the trigeminovascular system, which connects peripheral nociceptors in the meninges to

terminations within the brainstem. This pathway, involving the first branch of the trigeminal nerve, is a key mediator of migraine attacks in susceptible individuals. Upon activation—by mechanical, electrical, or chemical stimulation—afferent C-fiber meningeal nociceptors release vasoactive and proinflammatory neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P. These peptides cause dilation of meningeal blood vessels, plasma extravasation, and activation of dural mast cells, leading to neurogenic inflammation and pain.

Parasympathetic efferents from the sphenopalatine ganglion and sensory afferents from the trigeminal ganglion also contribute by releasing additional peptides that modulate nociceptive transmission. Notably, CGRP has emerged as a pivotal mediator in migraine pathogenesis and is now a prominent therapeutic target. Decades of research have shown that intravenous infusion of naturally occurring peptides like CGRP can trigger migraine attacks in predisposed individuals, while healthy volunteers typically develop only mild headache. This has led to ongoing investigation into whether such peptides act inside or outside the central nervous system.[1,19]

POSTDROME PHASE

The postdrome is considered the final or latent phase of a migraine, emerging after the resolution of headache pain and typically lasting from several hours to a few days.[20] This pathogenesis is poorly understood.[20] In contrast, during the prodromal phase, there is impaired function in the brainstem and diencephalic regions that regulate pain perception and sensory processing. Changes in the activity of pontine and midbrain areas take place prior to the headache phase, indicating early brain alterations that continue throughout the migraine episode.[21]

Pharmacological Management of Migraine: Acute Therapies

Acute Migraine Management

In India, migraine management based on standard treatment guidelines primarily aims to reduce symptoms and enhance the quality of patient care. NSAID drugs are used as first-line therapy for mild to moderate migraine attacks.[22]

NSAIDs like naproxen suppress central sensitization of trigeminovascular neurons.[25]

PARACETAMOL

It is one of the most common antipyretic and analgesic drugs globally. Still, the exact mechanism is unknown. It involves selective COX-2 inhibition and mainly acts on the central nervous system (brain and spinal cord), where it inhibits prostaglandin synthesis. The combination drug (paracetamol + metoclopramide) and sumatriptan are identically effective for the treatment of headache relief in achieving 2-hour effect, but no data on pain-free status were reported.[23]

NAPROXEN

Naproxen is used to treat acute pain in migraine (moderate to severe). It is *derived from propionic acid and then formed as a* soluble sodium salt. Doses are available as 250 mg and 500 mg tablets. *It causes more serious gastrointestinal adverse effects than ibuprofen.* It is mainly preferred as an *alternative medication to aspirin or ibuprofen, especially in* those who do not tolerate or do not respond to them.

Naproxen works by inhibiting COX-1 and COX-2 enzymes, which reduces prostaglandin production, the substances responsible for pain and inflammation. *Nausea, abdominal discomfort, dry mouth, dyspepsia, somnolence, paraesthesia, and dizziness* are the *most commonly reported specific adverse events*.[24]

IBUPROFEN

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that works by inhibiting prostaglandin biosynthesis. Research has shown that ibuprofen is more effective than paracetamol in treating acute migraine, primarily by reducing headache severity, duration, and associated symptoms such as nausea and vomiting.[26] It is used for mild to moderate migraine attacks.[27]

Aspirin

Aspirin is used for acute migraine headaches and also used as prophylactic treatment of migraine, generally administered in low doses of 81–325 mg. In addition, a high dose (900–1300 mg) taken at the onset of symptoms is effective and safe.[27,28] Although aspirin may lead to adverse effects, including gastrointestinal and renal dysfunction, it is generally regarded as safe and more affordable compared to medications such as beta-blockers and anticonvulsants.[28]

Combination of acetaminophen, aspirin, and caffeine

This premium combination of acetaminophen, aspirin, and caffeine delivers fast, reliable relief for migraine sufferers. Exceptionally safe and well-tolerated, offering uncompromised over-the-counter relief. It effectively targets not only migraine pain, but also relieves nausea, light and sound sensitivity, and helps restore daily function.[29]

MELATONIN

Melatonin isn't fully trusted for migraine prevention because there aren't enough strong studies proving it works well. While melatonin is usually safe, some forms can cause serious side effects like liver problems. Because of these reasons, doctors want more research before they can fully recommend melatonin for migraines.[30]

TRIPTANS

Triptans reduce migraine pain by blocking the transmission of pain signals to the trigeminal nucleus caudalis and by decreasing the release of inflammatory substances from trigeminal nerves, which in turn lowers calcitonin gene-related peptide (CGRP)-mediated blood vessel dilation. Naproxen works by suppressing the sensitization of central trigeminovascular neurons involved in migraine progression. The combination of sumatriptan and naproxen targets both the early and late stages of migraine, making it an effective treatment option.[25] The triptans include sumatriptan, zolmitriptan, rizatriptan, naratriptan, almotriptan, eletriptan, and frovatriptan. Among these, the slow-acting drugs are naratriptan and frovatriptan.[37]

SUMATRIPTAN

The bioavailability of oral sumatriptan is 14 percent, tmax for plasma concentration is 1.5h and elimination half-life is 2h. The sumatriptan tablet is greater effective than naratriptan.[31] Sumatriptan is the most likely adverse effects drug; common symptoms include dyspnoea, chest discomfort, chest pain, and paraesthesia.[32]

NARATRIPTAN

The low dose of oral naratriptan 2.5 mg noticed a slow onset of action and low efficacy in migraine treatment. The pharmacokinetic parameters are bioavailability available at 74 percent, tmax at 2 h, and elimination half-life in plasma at 5-8 h. But subcutaneous naratriptan 10 mg has a greater effect than other triptans.[31] Compared to other triptans, naratriptan is noted as a less likely adverse effects drug.[32]

Zolmitriptan

Zolmitriptan acts as a 5-hydroxytryptamine (serotonin) receptor agonist and therapeutically induces vasoconstriction of dilated meningeal blood vessels.[33] It provides rapid relief of headache and associated symptoms like nausea, photophobia, and phonophobia. The optimal dose balancing efficacy and tolerability is 2.5 mg.[34]

RIZATRIPTAN

Rizatriptan is a selective 5-HT_1B/1D receptor agonist that exerts its therapeutic effects by causing cranial vasoconstriction, inhibiting the release of vasoactive neuropeptides, and blocking pain signal transmission in the trigeminovascular system, making it effective in the acute treatment of migraine attacks.[35]

ELETRIPTAN

It acts by binding to 5-HT1B, 5-HT1D, and 5-HT1F receptors in cerebral blood vessels and perivascular nerve terminals, leading to vasoconstriction, reduced neuropeptide release, and inhibition of pain signal transmission in the trigeminal pathway.[36]

FROVATRIPTAN

Frovatriptan demonstrates notable efficacy in averting the return of headaches.[38] Frovatriptan 2.5 mg was selected as the starting dose because it provides effective migraine relief with a lower incidence of side effects. It works like other triptans in conventional therapy.[44]

Challenges in Evidence-Based Migraine Management

Effective migraine management is contingent upon timely diagnosis and the implementation of evidence-based interventions, as delineated in the International Classification of Headache Disorders, 3rd edition (ICHD-3), and the authoritative guidelines of the Indian Academy of Neurology. Studies frequently ascribe this disparity to insufficient clinical knowledge among healthcare professionals, underestimation of migraine's debilitating nature, and a disproportionate dependence on analgesic therapies.

Gaps in Healthcare Professional Knowledge, Attitude, and Practice

Migraine remains underdiagnosed and undertreated, particularly in low-resource settings. Healthcare professionals play a pivotal role in its management; however, gaps in knowledge, attitudes, and practices may significantly impede the delivery of optimal care.

KNOWLEDGE

Only 65% of healthcare professionals (HCPs) accurately recognized the diagnostic criteria delineated in the International Classification of Headache Disorders, 3rd Edition (ICHD-3), while a mere 40% were aware of triptans as a first-line therapeutic option. These findings resonate with evidence from low- and middle-income countries (LMICs), where non-specialist providers frequently exhibit limited familiarity with established, evidence-based migraine management guidelines. A study in Nigeria revealed only 32% of GPs could correctly define migraine. This gap affects migraine therapy.

ATTITUDE

Despite 72% of healthcare professionals acknowledging migraine's profound effect on quality of life.

Positive Attitudes, Persistent Treatment Challenges

Only 58% consistently adhered to guideline-recommended practices. In rural India, it was reported that 60% of healthcare professionals continued to rely on NSAIDs despite recognizing their limitations, predominantly due to financial constraints and limited access to alternative therapies.

Barriers to Migraine Management [1-5 Mean score]

1. Lack of time for counselling :4.2
2. Limited access to prophylactics :3.9
3. Patient preference for analgesics :3.7

These findings highlight systemic challenges in migraine care, underscoring the need for enhanced resources and patient education to foster adherence to evidence-based practices.[39]

Unmet Needs and Emerging Solutions in Migraine Treatment

Addressing unmet needs is crucial for preventing chronic migraine and medication overuse. Several studies support the development of future personalized treatment approaches, given that a subset of patients does not respond to current preventive therapies.[40] Inadequate GP expertise and patient education result in delayed diagnoses and inappropriate management, increasing chronic migraine and medication overuse risks; optimizing education, referrals, and access to novel preventive therapies is essential.Nowadays, doctors commonly prefer new drugs such as anti-CGRP medications and anti-CGRP–botulinum toxin combinations due to their proven effectiveness and favourable safety profiles. However, these treatments

are not effective for all patients, and their high cost limits accessibility, especially in low- and middle-income countries. This highlights the need for a personalized medicine approach, which aims to tailor treatments to individual patient profiles, reduce medication overuse, and prevent the progression to chronic migraine. To fully realize this potential, broader health system reforms are necessary—integrating cost-effective headache services, widespread continuous medical education for healthcare providers, and clear treatment guidelines. Only through this combined effort can we close the gap between scientific advances and real-world patient outcomes, ensuring that unmet needs in migraine care are adequately addressed.[40,41] Recent unmet needs findings reveal significant gaps in data, treatment guidelines, and patient care, emphasizing the need for better migraine management.[42]

Despite advances in migraine treatment, significant drug-based unmet needs remain. Traditional acute therapies like triptans and NSAIDs are often ineffective or poorly tolerated, especially in patients with cardiovascular risks. Opioids are still overprescribed despite their harmful effects, including increased risk of chronic migraine. Newer options like gepants and ditans show promise but lack long-term data and broad accessibility. Preventive treatments, including CGRP monoclonal antibodies, are effective but underused due to cost, limited availability, and inadequate physician education.[43]

CONCLUSION

Migraine, a severely disabling neurological disorder, is driven by a complex pathophysiology involving the hypothalamus, Cortical Spreading Depression (CSD), and the trigeminovascular system, with CGRP as a key mediator of pain. Despite clinical guidelines, management is undermined by significant barriers. Widespread underdiagnosis and undertreatment stem from a lack of knowledge among healthcare providers, leading to reliance on basic analgesics and escalating the risk of chronic migraine. This challenge is amplified by limited access to first-line therapies like triptans and newer drugs. The focus on women in research also neglects the significant, often undiagnosed, burden on men. The future of migraine care is shifting towards targeted therapies, particularly CGRP antagonists and monoclonal antibodies, which offer better efficacy. However, cost and accessibility remain hurdles. The ultimate goal is a personalized medicine approach, supported by systemic healthcare reforms and enhanced provider education, to ensure every patient receives optimal, evidence-based care.

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