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The evolving landscape of migraine pathophysiology

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Abstract

Migraine is a complex neurological disorder characterised by recurrent headaches, often accompanied by a range of sensory and autonomic symptoms. While vascular theories once dominated, recent evidence highlights the predominant role of the central nervous system in originating migraine pain. The current consensus emphasises the central roles of trigemino-vascular pathways, brainstem regions, and diencephalic nuclei in migraine pathogenesis. Key neurotransmitters, including monoamines such as serotonin, dopamine, and norepinephrine, as well as neuropeptides such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP), are pivotal in mediating pain transmission within these pathways.

Premonitory phase symptoms like food cravings, yawning, and mood changes are linked to central nervous system alterations and precede the headache phase. The aura phase, characterized by gradual onset symptoms such as scotomas and paraesthesia, is attributed to cortical spreading depression, a wave of self-propagating neuronal depolarisation followed by transient cortical hypoperfusion, underscoring its neuronal basis.

The transition to chronic migraine involves dysfunction in top-down pain modulation and sensitization of the trigeminal system, leading to central sensitization. Peripheral sensitization and molecular mechanisms involving CGRP, Serotonin (5-HT), and PACAP further contribute to migraine chronification. Additionally, oestrogen modulates pain pathways through its effects on the μ-opioid system and neurotransmitters such as serotonin as well as its regulatory action on CGRP. This multifaceted interplay of circuits, neuropeptides, and hormonal influences determines the complex pathophysiology of migraine, providing avenues for targeted therapeutic interventions.

Key words: migraine, pathophysiology, evolution of theories, targeted therapy

Introduction

Migraine is a highly prevalent neurological disorder, affecting approximately 1.1 billion individuals globally, as estimated by the Global Burden of Disease (GBD) 2019 study.[1] It is a leading cause of disability, ranking second among all human diseases in terms of years lived with disability (YLDs).[1] Migraine attacks typically unfold in four distinct phases: the premonitory phase, characterized by early warning signs such as fatigue, irritability, and food cravings; the aura phase, marked by transient neurological disturbances including visual and sensory symptoms; the headache phase, which presents as intense, often unilateral pain accompanied by nausea, sensitivity to light (photophobia), and sound (phonophobia); and the postdrome phase, during which residual symptoms like fatigue and mood fluctuations persist. Recognising these phases is essential for timely intervention and effective management.[2]

Over recent decades, numerous theories have been proposed to elucidate the pathophysiology of migraine. The current consensus highlights the central roles of trigemino-vascular pathways, brainstem regions, and diencephalic nuclei in the generation of migraine.[3] Recent research suggests that the

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headache phase of migraine is primarily driven by neuronal mechanisms, challenging the earlier belief that vascular factors played a dominant role. Migraines occur predominantly in individuals with a genetic predisposition, with strong evidence supporting a polygenic inheritance pattern, except in rare cases of monogenic disorders like familial hemiplegic migraine.[3] While numerous potential triggers such as stress, lack of sleep, and certain foods have been reported, the scientific evidence confirming these associations remains inconclusive.[4] Conversely, there is substantial evidence indicating that female sex hormones significantly impact the onset and progression of migraines through various biological pathways.[5]

A deeper understanding of the underlying pathophysiology of migraine is crucial for the development of more targeted and effective treatment approaches. This review aims to explore the complex mechanisms driving migraine pathology, shedding light on emerging insights that may enhance therapeutic strategies.

The role of the trigemino-vascular system and evolution of theories

The trigemino-vascular system (TVS) is central to understanding migraine headache. It comprises the trigeminal nerve and its axonal projections to the intracranial vasculature.[6] In this system, the first order neuron cell bodies reside in the trigeminal ganglion and innervate the meninges and large intracranial vessels. These nociceptive fibres project to the brainstem, where they activate second-order neurons in the spinal trigeminal nucleus, subsequently sensitising third-order neurons in the thalamus. This pathway culminates in nociceptive transmission to the somatosensory cortex, resulting in migraine pain.[7] Further, projections from the thalamus to the limbic, and prefrontal cortices are thought to play a significant role in migraine, particularly in influencing the emotional and cognitive aspects of the pain.[8] Moreover, TVS has connections to parasympathetic cranial autonomic fibres, which are believed to mediate parasympathetic-mediated symptoms such as lacrimation, nasal congestion, and ptosis, often observed during migraine.[2] The activation of this system has been extensively investigated, and theories have been developed from time to time.

In 1993, Moskowitz proposed the neurogenic inflammation theory, identifying vasodilation, protein extravasation, and platelet activation caused by the release of vasoactive peptides such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP) as key contributors to the initial pain sensitisation in migraines. This theory has been further supported by mechanistic evidence, including observations of middle cerebral artery dilation during migraine episodes and the rapid pain relief and arterial constriction achieved with the 5-HT1 receptor agonist sumatriptan.[7,8] However, more recent findings challenge the vascular theory, suggesting that primary neurological mechanisms and a central origin of pain are more likely. These recent insights are supported by neuroimaging studies that challenge the vascular hypothesis.[9] Besides, studies showed that the pulsating quality of migraine pain does not align with arterial pulsation. Additionally, evidence showed that vasoconstriction is not essential for achieving pain relief, further emphasising the shift toward a neuronal basis for migraine pathophysiology.[9,10] Furthermore, medications such as 5-HT agonists, once thought to relieve migraines primarily through vasoconstriction, are now understood to exert additional neuronal effects that may contribute to pain relief.[2,10] However, evidence also indicates that vasodilation and neurogenic inflammation play an essential role in sustaining migraine headaches even though it does not contribute for the origin of pain.[2,9] Recent studies done using advanced functional magnetic resonance imaging (fMRI) support the primary neuronal theory further by identifying central components of the trigeminal complex, primarily located in the brainstem, thalamus, hypothalamus, and their cortical connections, as key regions activated during the headache phase of migraine. Additionally, brainstem structures such as the locus coeruleus, rostral ventromedial medulla, nucleus raphe magnus, and periaqueductal grey (PAG) are highlighted as potential sites of origin in migraine.[11,12]

Neurotransmitters involved in migraine pathophysiology

Monoamines such as serotonin, dopamine, norepinephrine and neuropeptides such as CGRP and PACAP are involved in impulse transmission in the pain pathway associated with migraine.[2,3]

Serotonin (5-HT) plays a crucial role in pain modulation, with multiple 5-HT receptor subtypes identified: some promote pain (nociceptive effects) and others inhibit it (antinociceptive effects).[13,14] Beyond its role in pain pathways, 5-HT possesses vasoconstrictive and anti-inflammatory properties, making it one of the key targets in the treatment of migraine. Its involvement in migraine pathophysiology also explains common comorbidities such as depression, anxiety, and nausea, which are frequently observed in patients with migraine. Interestingly, while 5-HT triggers pain in some regions of the brain, elevated levels of 5-HT have also been found to suppress pain.

This paradoxical effect is believed to be mediated by 5-HT receptor agonists, which, at high concentrations, regulate nociceptive signalling via distinct receptor pathways.[13] Due to this vital role of serotonin, triptans, which counteract migraine by selectively activating specific 5-HT receptor subtypes, are regarded as the first-line acute therapy for patients experiencing migraine attacks with moderate to severe pain intensity.[15] Their mechanism of action involves inducing vasoconstriction, suppressing transmission within the trigeminal pain pathways, and inhibiting the release of CGRP from perivascular sensory nerves.[16] In addition, triptans have also been shown to improve the gastric absorption of other medications used during acute migraine attacks, while also helping to alleviate associated nausea and vomiting.[15]

However, approximately 30-40% of patients do not respond adequately to triptan therapy. In addition, the vasoconstrictive effects of this drug class restrict their use in individuals with conditions such as uncontrolled hypertension, coronary artery disease, or peripheral vascular disease.[15]

Presence of certain purely dopaminergic symptoms associated with migraine such as yawning, nausea and vomiting prove that dopamine has a significant role in generating migraine premonitory symptoms as well as the headache.[17] Further, clinical trials have shown promising evidence for abortion of migraine with treatment of Dopamine antagonists at the premonitory phase of the disease.[18]

CGRP is a neuropeptide with significant roles in both neuromodulation and the promotion of inflammatory responses.[19] It is highly expressed within the TVS and plays a key role in migraine pathophysiology. CGRP is synthesized in the cell bodies of neurons and released in response to various stimuli. Once secreted, it contributes to neurogenic inflammation and the transmission of nociceptive signals, playing a pivotal role in both peripheral and central sensitisation processes that underlie migraine attacks (20-22). Experimental studies, particularly in animal models, have demonstrated that stimulation of the trigeminal ganglion elevates CGRP levels in the superior sagittal sinus, correlating with migraine-like symptoms. Importantly, this CGRP surge can be reversed by serotonin (5-HT) receptor agonists, such as sumatriptan and dihydroergotamine, which are well-established treatments for acute migraine attacks. Role of CGRP modulation in migraine prophylaxis has been explored extensively in the recent past and is recommended as the first line prophylactic therapy available for chronic migraine.[22]

CGRP receptor antagonists, known as gepants (e.g. ubrogepant, rimegepant atogepant) have been developed as novel agents for the migraine prophylaxis by competitively blocking CGRP binding at its receptor. More recently, development of monoclonal antibodies targeting CGRP receptors (e.g. erenumab, fremanezumab) have expanded the treatment options available for prophylaxis.[24] These biologics are particularly attractive due to their long half-life, lack of vasoconstrictive effects, and minimal risk of central nervous system side effects, since they do not cross the blood-brain barrier.[25] Some of their modes of administration are subcutaneous or intravenous injections and could be given as infrequently as once every three months which could improve adherence. Notably, however, patients with familial hemiplegic migraine appear unresponsive to these medications.[24]

PACAP is a neuropeptide involved in migraine development through its roles in neurogenic inflammation and vascular dilation. Beyond its influence on migraines, PACAP also regulates neuronal development, growth and repair, affecting learning, memory, and behaviour. The co-localization of PACAP with CGRP in the trigeminal vascular system suggests that PACAP may play a similar role in migraine pathophysiology. As a result, therapeutic strategies targeting PACAP pathways are under investigation. These include PAC1 receptor antagonists, which block PACAP-induced vascular and inflammatory responses, and monoclonal antibodies targeting PACAP or its receptors, both of which have shown potential in reducing migraine frequency and severity in clinical trials.[26,27] Additionally, the possibility of developing a compound that could potentially act as a multi receptor antagonist blocking both CGRP and PACAP is currently being explored.[28]

Cortical spreading, depression and aura

Migraine with aura is less prevalent than migraine without aura. The gradual onset of aura-related symptoms, such as scotomas and paraesthesia, indicates a primarily neuronal origin for aura. It is thought to arise from cortical spreading depression (CSD), a wave of self-propagating neuronal depolarisation followed by transient cortical hypoperfusion.[29] A proposed hypothesis links CSD to the headache phase in migraine with aura, suggesting that CSD triggers the release of mediators, including nitric oxide, arachidonic acid, and potassium, which induce dural vasodilation and stimulation of first-order neurons of TVS.[30] However, this mechanism is inconsistent with the currently favoured theory that attributes migraine pain to a central neural origin.[2]

Given the distinct underlying mechanism of cortical spreading depression (CSD), the use of triptans is generally not recommended during the aura phase. Nevertheless, current evidence indicates that triptans are not associated with a meaningful increase in cerebrovascular risk and can be safely prescribed for patients who have migraine with aura.[31] An important exception is that women with migraine with aura should avoid combined oral contraceptives, as their use significantly increases the risk of ischemic stroke. Overall, current guidelines recommend similar treatment strategies for both migraine with and without aura, reflecting the fact that most clinical studies do not stratify treatment outcomes based on aura status.[32]

Pathophysiology of premonitory phase of migraine

Prodromal symptoms reported in migraine, including food cravings, yawning, and mood changes, are believed to stem from alterations in central nervous system function. Emerging evidence suggests that disruptions in hypothalamic activity, which regulate sleep-wake cycles and appetite, are primarily responsible for food cravings and changes in sleep patterns observed in migraine patients during this phase.[33] Additionally, mood disturbances are thought to result from dysfunction within the limbic system and its associated neural pathways. Sensory disturbances, commonly reported during the prodromal phase, are attributed to abnormalities in thalamocortical connectivity.[2,34]

During this phase, patients are advised to avoid known triggers, such as specific foods or environmental stimuli like bright light, loud noise, or strong odours. Adequate hydration and maintaining regular meals are important, as dehydration and skipped meals can precipitate migraine attacks. Resting in a quiet, dark environment may also help alleviate early symptoms and prevent progression.[3] In some cases, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) during this stage has been reported to reduce the propagation of headache and improve overall outcome.[12]

Transition to chronic migraine

Chronic migraine is defined as a headache occurring on 15 or more days per month for more than 3 months, of which at least 8 days per month have features of migraine headache.[2] The progression to chronic migraine (CM) is mainly driven by impaired top-down pain modulation and heightened trigeminal system sensitivity, leading to central sensitization. Additional contributing factors include peripheral sensitization and molecular mechanisms involving CGRP, 5-HT, and PACAP.[36]

The top-down pain modulation pathways through which the brain regulates and influences the perception of pain include higher brain centers (such as the cerebral cortex, limbic system, and brainstem), and their connections to the neurones in the spinal cord and peripheral nervous system. Patients with CM exhibit disruption of this pathway resulting in cortical hyperexcitability and brainstem dysfunction.[36] Studies have revealed increased responsivity of somatosensory and visual cortices in patients with CM.[37] Regarding brainstem dysfunction, the periaqueductal gray matter (PAG) which is a critical center for descending pain modulation is believed to play a vital role in CM patho-physiology. The PAG receives inputs from the frontal cortex, hypothalamus, and other supraspinal structures and projects to the medulla and, subsequently, to the spinal dorsal horn.[38] Dysfunction within the PAG leads to impaired pain inhibition and hyperexcitability in nociceptive pathways, facilitating the transformation of episodic migraine (EM) into CM.[32,33] Structural changes in the PAG further support its role in CM. MRI studies have shown iron accumulation in the PAG, resulting in increased density and volume, potentially mediated by oxidative stress seen in CM.[41]

Central sensitization, defined by the enhanced amplification of neural signalling within the central nervous system (CNS) leading to pain hypersensitivity, is a well-recognized mechanism underlying CM. This phenomenon primarily involves the second- and third-order neurones within the trigeminal pathway.[42] The development of central sensitization in CM is attributed to several mechanisms, including synaptic plasticity, imbalances between excitatory and inhibitory neurotransmitters such as glutamate and glutamate and gamma-aminobutyric acid (GABA), and dysregulation of monoamine neurotransmitters.[43]

The role of hormonal fluctuations in migraine pathophysiology among females

Numerous studies demonstrate significant sex and age-related differences in migraine prevalence. There is a clear female preponderance in migraine. These differences become particularly evident after puberty and decline following menopause, indicating a role for sex hormones in migraine pathophysiology, with oestrogen showing more influence than other hormones. Oestrogen modulates pain pathways by influencing the μ-opioid system and certain neurotransmitters, including serotonin, GABA, and Noradrenaline.[5] Furthermore, oestrogen influences CGRP, which, as described above,

plays a central role in migraine pathophysiology.[44] Menstrual migraines are categorised into two types: pure menstrual migraine (PMM) and menstrual-related migraine (MRM). PMM is characterised by migraine attacks that occur exclusively around menstruation, typically from two days before the onset of menstruation to three days after, with no attacks at other times of the cycle.[45] In contrast, MRM involves migraines that worsen during menstruation but can also occur at other times. The underlying pathophysiology is closely associated with hormonal fluctuations, particularly the decline in oestrogen levels during the late luteal phase, which can trigger migraines by altering neuronal excitability and vascular reactivity. Additionally, increased prostaglandin secretion during menstruation may exacerbate migraine symptoms through inflammatory and vasodilatory mechanisms.[5] Oestrogen fluctuations outside of the menstrual cycle also influence migraine patterns; for example, during the perimenopausal period, when oestrogen levels are highly variable, there is often an increase in the frequency and severity of migraine attacks.[46] Conversely, during pregnancy, especially in the second and third trimesters when oestrogen levels are more stable and consistently elevated, many individuals experience an improvement in migraine symptoms, highlighting the role of hormonal stability in migraine modulation.[47]

Conclusion

Migraine remains a significant global health burden, affecting over a billion individuals and ranking high among the leading causes of disability. Understanding its pathophysiology has evolved considerably, shifting from a vascular-centric view to a more comprehensive neuronal framework involving the trigeminovascular system, brainstem, and diencephalic structures. Despite advancements in identifying potential triggers and mechanisms, many aspects of migraine pathogenesis remain incompletely understood. Improving the understanding of the complex interplay between neural, vascular, and genetic factors would pave the way for more precise and personalised treatment approaches, ultimately improving the quality of life for those affected by this debilitating disorder.

Author declaration

Conflict of interests

None.

Criteria for authorship

Conception and drafting the manuscript: UKE, MSM; Editing and revision: UKE, MSM, and SPM; All authors approved the final version of the manuscript.

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References

1. Steiner TJ, Stovner LJ, Jensen R, Uluduz D, Katsarava Z, Lifting the burden: the Global Campaign against Headache. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. *J Headache Pain.* 2020; 21(1): 137. doi: 10.1186/s10194-020-01208-0
2. Karsan N. Pathophysiology of Migraine. *Contin Lifelong Learn Neurol.* 2024; **30**(2): 325. doi: 10.1212/CON.0000000000001412
3. Ashina M. Migraine. *N Engl J Med.* 2020; **383**(19): 1866-76. doi: 10.1056/NEJMra1915327.
4. Hougaard A, Amin FM, Hauge AW, Ashina M, Olesen J. Provocation of migraine with aura using natural trigger factors. *Neurology.* 2013; **80**(5): 428-31. doi: 10.1212/WNL.0b013e31827f0f10.
5. Vetvik KG, MacGregor EA. Menstrual migraine: a distinct disorder needing greater recognition. *Lancet Neurol.* 2021; **20**(4): 304-15. doi:10.1016/S1474-4422(20)30482-8.
6. Moskowitz MA, Reinhard JF, Romero J, Melamed E, Pettibone DJ. Neurotransmitters and the fifth cranial nerve: is there a relation to the headache phase of migraine? *Lancet Lond Engl.* 1979; **2**(8148): 883-5. doi:10.1016/s0140-6736(79)92692-8.
7. Cen J, Wang Q, Cheng L, Gao Q, Wang H, Sun F. Global, regional, and national burden and trends of migraine among women of childbearing age from 1990 to 2021: insights from the Global Burden of Disease Study 2021. *J Headache Pain.* 2024; **25**(1): 96. doi: 10.1186/s10194-024-01798-z.
8. Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. *Nat Rev Neurosci.* 2011; **12**(10): 570-84. doi: 10.1038/nrn3057.
9. Noseda R, Jakubowski M, Kainz V, Borsook D, Burstein R. Cortical projections of functionally identified thalamic trigeminovascular neurons: implications for migraine headache and its associated symptoms. *Journal of Neuroscience*. 2011; **31**(40): 14204-17. doi: 10.1523/JNEUROSCI.3285-11.2011.
10. Moskowitz MA. Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. *Trends Pharmacol Sci.* 1992; **13**(8): 307-11. doi: 10.1016/0165-6147(92)90097-p.
11. Schramm S, Börner C, Reichert M, et al. Functional magnetic resonance imaging in migraine: A systematic review. *Cephalalgia Int J Headache.* 2023; **43**(2): 3331024221128278. doi: 10.1177/03331024221128278.

12. Karsan N, Goadsby PJ. Neuroimaging in the pre-ictal or premonitory phase of migraine: a narrative review. *J Headache Pain.* 2023; **24**(1): 106. doi: 10.1186/s10194-023-01617-x.

13. Paredes S, Cantillo S, Candido KD, Knezevic NN. An association of serotonin with pain disorders and its modulation by estrogens. *Int J Mol Sci.* 2019; **20**(22): 5729. doi: 10.3390/ijms20225729.

14. Yan XJ, Feng CC, Liu Q, et al. Vagal afferents mediate antinociception of estrogen in a rat model of visceral pain: the involvement of intestinal mucosal mast cells and 5-hydroxytryptamine 3 signaling. *J Pain.* 2014; **15**(2): 204-17. doi: 10.1016/j.jpain.2013.10.012.

15. Diener HC, Limmroth V. Advances in pharmacological treatment of migraine. *Expert Opin Investig Drugs.* 2001; **10**(10): 1831-45. doi: 10.1517/13543784.10.10.1831.

16. Loder E. Triptan therapy in migraine. *N Engl J Med.* 2010; **363**(1): 63-70. doi: 10.1056/NEJMct0910887.

17. Barbanti P, Fofi L, Aurilia C, Egeo G. Dopaminergic symptoms in migraine. *Neurol Sci.* 2013; **34** Suppl 1: S67-70. doi: 10.1007/s10072-013-1415-8.

18. Waelkens J. Domperidone in the prevention of complete classical migraine. *Br Med J Clin Res Ed.* 1982; **284**(6320): 944. doi: 10.1136/bmj.284.6320.944.

19. Glintborg D, Hass Rubin K, Nybo M, Abrahamsen B, Andersen M. Morbidity and medicine prescriptions in a nationwide Danish population of patients diagnosed with polycystic ovary syndrome. *Eur J Endocrinol.* 2015; **172**(5): 627-38. doi: 10.1530/EJE-14-1108.

20. Eftekhari S, Warfvinge K, Blixt FW, Edvinsson L. Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. *J Pain.* 2013; **14**(11): 1289-303. doi: 10.1016/j.jpain.2013.03.010.

21. Gulbenkian S, Merighi A, Wharton J, Varndell IM, Polak JM. Ultrastructural evidence for the coexistence of calcitonin gene-related peptide and substance P in secretory vesicles of peripheral nerves in the guinea pig. *J Neurocytol.* 1986; **15**(4): 535-42. doi: 10.1007/BF01611735.

22. Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A. American Headache Society. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. *Headache.* 2024; **64**(4): 333-41. doi: 10.1111/head.14692.

23. Zagami AS, Goadsby PJ, Edvinsson L. Stimulation of the superior sagittal sinus in the cat causes release of vasoactive peptides. *Neuropeptides.* 1990; **16**(2): 69-75. doi: 10.1016/0143-4179(90)90114-e.

24. Lambru G, Andreou AP, Guglielmetti M, Martelletti P. Emerging drugs for migraine treatment: an update. *Expert Opin Emerg Drugs.* 2018; **23**(4): 301-18. doi: 10.1080/14728214.2018.1552939.

25. Zeller J, Poulsen KT, Sutton JE, et al. CGRP function-blocking antibodies inhibit neurogenic vasodilatation without affecting heart rate or arterial blood pressure in the rat. *Br J Pharmacol.* 2008; **155**(7): 1093-103. doi:10.1038/bjp.2008.334.

26. Schytz HW, Birk S, Wienecke T, Kruuse C, Olesen J, Ashina M. PACAP38 induces migraine-like attacks in patients with migraine without aura. *Brain J Neurol.* 2009; **132**(Pt 1): 16-25. doi: 10.1093/brain/awn307.

27. Akerman S, Goadsby PJ. Neuronal PAC1 receptors mediate delayed activation and sensitization of trigeminocervical neurons: Relevance to migraine. *Sci Transl Med.* 2015; **7**(308) :308ra157. doi: 10.1126/scitranslmed.aaa7557.

28. Tasma Z, Siow A, Harris PWR, Brimble MA, Hay DL, Walker CS. Development and pharmacological characterization of novel multi- calcitonin gene-related peptide and pituitary adenylate cyclase-activating peptide receptor antagonists. *Headache.* 2025; **65**(7): 1064-79. doi:10.1111/head.14916

29. Dalkara T, Nozari A, Moskowitz MA. Migraine aura pathophysiology: the role of blood vessels and microembolisation. *Lancet Neurol.* 2010; **9**(3): 309-17. doi: 10.1016/S1474-4422(09)70358-8.

30. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat Med.* 2002; **8**(2): 136-42. doi: 10.1038/nm0202-136

31. Fraser CL, Hepschke JL, Jenkins B, Prasad S. Migraine Aura: Pathophysiology, Mimics, and Treatment Options. *Semin Neurol.* 2019; **39**: 739-48. doi: 10.1055/s-0039-1700525.

32. Hansen JM, Charles A. Differences in treatment response between migraine with aura and migraine without aura: lessons from clinical practice and RCTs. *J Headache Pain.* 2019; **20**(1): 96. doi: 10.1186/s10194-019-1046-4

33. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain J Neurol.* 2014; **137**(Pt 1): 232-41. doi:10.1093/brain/awt320.

34. Karsan N, Bose RP, O'Daly O, Zelaya F, Goadsby PJ. Regional cerebral perfusion during the premonitory phase of triggered migraine: A double-blind randomized placebo-controlled functional imaging study using pseudo-continuous arterial spin labelling. *Headache.* 2023; **63**(6): 771-87. doi: 10.1111/head.14538

35. Haghdoost F, Togha M. Migraine management: Non-pharmacological points for patients and health care professionals. *Open Med.* 2022; **17**(1): 1869-82. doi: 10.1515/med-2022-0598.

36. Su M, Yu S. Chronic migraine: A process of dysmodulation and sensitization. *Mol Pain.* 2018; **14**: 1744806918767697.

37. Coppola G, Schoenen J. Cortical excitability in chronic migraine. *Curr Pain Headache Rep.* 2012; **16**(1): 93-100. doi: 10.1007/s11916-011-0231-1

38. Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: specificity, recruitment and plasticity. *Brain Res Rev.* 2009; **60**(1): 214-25. doi: 10.1016/j.brainresrev.2008.12.009.

39. Mainero C, Boshyan J, Hadjikhani N. Altered functional MRI resting-state connectivity in periaqueductal gray networks in migraine. *Ann Neurol.* 2011; **70**(5): 838-45. doi: 10.1002/ana.22537

40. Chen Z, Chen X, Liu M, Liu S, Ma L, Yu S. Disrupted functional connectivity of periaqueductal gray subregions in episodic migraine. *J Headache Pain*. 2017; **18**(1): 36. doi: 10.1186/s10194-017-0747-9.

41. Chen Z, Chen X, Liu M, Liu S, Ma L, Yu S. Volume expansion of periaqueductal gray in episodic migraine: a pilot MRI structural imaging study. *J Headache Pain.* 2017; **18**(1): 83. doi: 10.1186/s10194-017-0797-z.

42. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain.* 2011; **152**(3 Suppl): S2-15. doi: 10.1016/j.pain.2010.09.030

43. Aguggia M, Saracco MG, Cavallini M, Bussone G, Cortelli P. Sensitization and pain. *Neurol Sci.* 2013; 34 Suppl 1: S37-40. doi: 10.1007/s10072-013-1382-0.

44. Labastida-Ramírez A, Rubio-Beltrán E, Villalón CM, MaassenVanDenBrink A. Gender aspects of CGRP in migraine. *Cephalalgia*. 2019; **39**(3): 435-44. doi: 10.1177/0333102417739584.

45. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia.* 2013; **33**(9): 629-808. doi: 10.1177/0333102413485658. PMID: 23771276.

46. Bernstein C, O'Neal MA. Migraine and menopause – a narrative review. *Menopause*. 2020; **28**(1): 96-101. doi: 10.1097/GME.0000000000001635.

47. Sances G, Granella F, Nappi RE, et al. Course of migraine during pregnancy and postpartum: a prospective study. *Cephalalgia Int J Headache*. 2003; **23**(3): 197-205. doi: 10.1046/j.1468-2982.2003.00480.x.