RESEARCH PAPER

Menstrual Migraine: Unraveling symptoms, mechanisms, and innovative drug treatments

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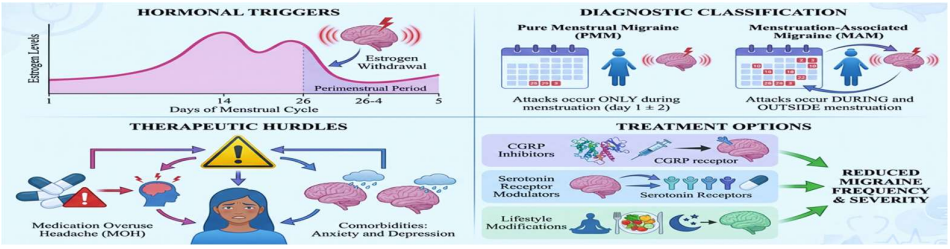
ABSTRACT
Menstrual migraine is the most common type of migraine that is related to a woman's menstrual cycle, Atrial fibrillation is a common medical condition that affects approximately one billion people in the world, especially women. This article gives enough symptoms of menstrual cramp, its most probable underlying causes, problems in its treatment, and possible solutions. Menstrual aches are caused by fluctuations in estrogen levels prior to menstruation. The condition is aggravated by the hormonal variables, chemical imbalances in the brain, and hereditary environmental influences. The present diagnostic classification categorizes migraine into pure menstrual migraine occurring during the menstruation phase and migraine associated with menstruation occurring in different perimenstrual periods of the menstrual cycle. These further puts weight on how important a clinical examination must be before diagnosis is made. Changes in hormones, modifications in lifestyle, and medication which alters CGRP, serotonin receptors and reduce inflammation are some of the treatment options open for multiple myopathies. This study further upholds the difficulties in the treatment of Menstrual Migraine; development of headache following medication for MOH and other comorbidities such as anxiety and depression, which further complicate the treatment options available. Future studies that will focus on how hormones are related to migraine processes are also mentioned. This will allow for better results and customized treatment for every patient.

Graphical Abstract



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INTRODUCTION

Migraine is a common and debilitating neurologic disorder that is inextricably linked with gender inequality. For instance, studies have shown that migraine affects nearly three times as many women as men [1]. There is a group of women among them who have claimed that about 20-25% have an undeniable connection between their menstruation and migraine episode known as menstrual migraine (MM) [2, 3]. A lot of research has been conducted on the relation between migraine and menstrual cycle, indicating that chances for migraine attacks are at peak during perimenstrual period—days just before and after one's monthly bleeding [4]. In this duration significant hormonal fluctuations are observed, particularly in estrogen levels, which is considered as the main cause of the migraine attack [5]. It has been observed that women are more prone to this problem in comparison to the male that worsen during the period of the midlife due to hormonal fluctuations associated with the menopausal phase. It is at its peak in the late thirties and decreases after the menopause, due to the dropping estrogen migraine increases some time. The migraine treatment included the hormonal and non-hormonal treatment according to the behavioural approach. Research by **Stewart *et al*.** [8] has demonstrated that the probability of experiencing migraines without aura found with increased level during first two menstrual days and notable decline in the pain at the time of ovulation time. This rapid decline in the estrogen occurring just before menstruation destabilizes the central nervous system and causes migraine attacks [6]. The duration of migraine problem persists from three to seven days after the onset of menstruation that reflects the profound impact of hormonal fluctuations on the persistence and severity of migraine attacks [3]. Due to the above findings indicating that monthly cramps greatly impair women's life, the International Headache Society created a dedicated menstrual cramp screening program.

The International Headache Association-funded study made a differentiation between the menstruation-related headaches that may occur at various times of the cycle and pure menstrual migraines that occur only during a period [7]. Diagnosis and treatment are effective if based on this. Maintaining detailed headache records for at least three menstrual cycles has often resulted in an accurate diagnosis [8]. It presents a better opportunity to establish the temporal relationship between migraine attacks and menstruation [8]. The timing, duration, and intensity of the migraines, along with associated symptoms and possible precipitating factors, are what should be included in the headache diary record [9]. Close observation of these variables enables physicians to base the treatment for menstrual colic [10].

Causes and Prevalence of Menstrual Migraine

Menstrual cramps are a complex, multifactorial disorder influenced by a myriad of metabolic, genetic, and environmental factors. The variation in estrogen throughout the post-menopausal period, particularly the abrupt decline following the cessation of the secretory phase, significantly influences menopause [7]. Several physiological pathways in the CNS, including modulation of serotonergic and glutamatergic neurotransmission-important pathways in the perception of pain-and the regulation of the mind and mood, are greatly influenced by estrogen [11]. A sudden decline in premenopausal estrogen may interfere with these pathways through a decrease in serotonin synthesis and facilitation of the release of pro-inflammatory neurotransmitters from trigeminal neurons, such as calcitonin gene-related peptide (CGRP). [12]. Strong vasodilators, these neuropeptides can enlarge brain blood vessels and activate the pain pathways thought to be responsible for migraines [13]. The increased blood-brain barrier during menstruation, which permits pro-inflammatory substances to pass through the meninges and further inflame nerve fibres surrounding the brain within the environment, is another factor complicating the pathophysiological changes associated with menstrual cramps. [14]. These chemicals can induce an inflammatory response in the meninges, thereby releasing and activating trigeminal nerve fibres and releasing additional neuropeptides, which amplify the pain response. These factors can lead to meningeal inflammation, which may activate trigeminal nerve fibres and release additional neuropeptides, which amplify the pain response [15]. Moreover, natural analgesic systems are linked with the menstrual cycle, which can significantly heighten the sensitivity of pain mechanisms to an attack [16].

Genetics also play an important role in the development of menstrual cramps. A comprehensive family history study is necessary to identify individuals with a genetic predisposition to glaucoma, as genetic mutations and hormonal alterations in protein pathway receptors can cause glaucoma susceptibility such as, genes one associated with estrogen receptor 1 (ESR1) and progesterone receptor (PGR) is enriched. is associated with an increased risk of migraine, especially in women with migraine season [17, 18] These genetic variants may affect the body's response to hormonal fluctuations during menstruation, causing attacks of diarrhoea have become more pronounced [18].

In addition to hormonal and genetic factors, environmental triggers such as stress, sleep disorders, dietary factors, and climate change can also contribute to menstrual cramps [19] Stress in particular is a known factor well triggering migraines, mutations occurring with menopause may result in women susceptible to migraine complex [19] which is common during menopause Also may increase the risk of

developing the migraine is worse, because inadequate or poor quality sleep is a known risk factor for migraine [19]. Dietary factors such as consumption of certain foods or beverages known to cause migraine (e.g. caffeine, alcohol, and certain types of cheese) have even the onset of menstrual cramps played a role [19]. Finally, climatic variations (for example, temperature change) or changes in humidity or air pressure can trigger an episode of a migraine, especially in women who are born with a genetic predisposition to develop migraines due to the various types of mutations. Because menstrual migraines are multi-faceted, it will be important to view how these different factors (i.e., hormones, neuroendocrine hormones, genes, and the environment) interact with each other [19].

Pathophysiology

Monthly religious science is characterized by neurotras, genetics, environmental factors, and the complicated origins of the marmonal-cloud, especially in the audience of the monthly religious. iGreen development and central [20]. Estrogen, a potent steroid neurotransmitter, plays an important role in the regulation of vascular excitement, angiogenesis, and muscle tone, all of which are factors that important in the development of glaucoma [21]. Estrogen levels fluctuate dramatically during menstruation, with a sharp decrease during the final storage period before menopause this decrease in estrogen levels can damage excitatory and inhibitory neurons in the brain, especially serotonin and balance of glutamate involved in pain perception. Also participate in the regulation of emotions and feelings [22]. Decreased estrogen levels are associated with decreased serotonin levels, which can lead to decreased inhibition of pain pathways in the brain and increased production of pro-inflammatory neuropeptides such as CGRP and substance P. These neuropeptides are vasodilator ability to dilate cerebral blood vessels, thereby activating and forming trigeminal fibres, which are considered to be the primary mechanisms for the generation of migraine pain

Progesterone, another major menstrual hormone, also plays a role in the pathogenesis of menstrual cramps. Progesterone levels fluctuate during menstruation, peaking during the luteal phase and falling before menstruation [23]. The effect of progesterone on migraine is complex and can vary depending on its concentration and interaction with estrogen. By context, progesterone has been shown to have both pro- and anti-migraine effects. For example, low levels of progesterone with low levels of estrogen can lead to an imbalance between estrogen and progesterone, which is thought to cause menstrual cramps [24] This imbalance can lead to atherosclerosis burns more and reduces pain suppression in the preventive manner, which makes individuals more susceptible to migraines. Imbalances, particularly those involving serotonin, dopamine, and CGRP, are also important in the pathophysiology of menstrual cramps Serotonin, a key neurotransmitter involved in pain control and nerve function, plays a dual role in the pathogenesis of migraine. On the one hand, low serotonin levels are associated with increased pain and decreased pain levels on the other hand, serotonin is also involved in the regulation of blood vessel tone, changes in serotonin levels can has caused changes in the nervous system, and may contribute towards migraine attacks [25]. Dopamine is another important neurotransmitter and is involved in the reward system and changes in dopamine levels are associated with an increased risk of migraine, especially during menstruation, when mutations can affect dopamine signalling mechanisms [26] Mediating vasodilation and primary pain CGRP plays an important role in migraine especially menstrual migraine Chapter. Increased levels of CGRP during migraine attacks are thought to contribute to dilation of blood vessels in the brain and activation of trigeminal nerve fibres, resulting in migraine [27]. In addition to hormonal and neurotransmitter factors, hormonal changes and genetic predisposition also play a role in the menstrual cramps. Clearance of neuroinflammatory peptides Genetic predisposition, which may contribute to the exacerbation of migraine, according to pedigree, mutations in genes related to hormone metabolism, neurotransmitter signalling, and muscle verification of activity also contributes to the risk of menstrual migraine [27]. Environmental factors such as stress, sleep disorders, diet, and climate change further influence migraine incidence as stimulating activity that can exacerbate the underlying pathophysiological processes of menstrual influenza [28]. To create targeted treatments for this complex pathogen, it is vital to understand how these complications can affect a woman's menstrual cycles [29]. The development of this condition is due to many different factors including; hormones, neurotransmitters, neuroanatomy, genetics, and other environmental elements; therefore, managing menstrual cramp pain requires an integrative approach that includes all of these factors.

Management

Successful treatment of dysmenorrhea is best achieved through a multi-faceted approach involving both pharmacological and non-pharmacological treatments tailored to the individual patient’s needs that address not only the physiologic, neurologic and environmental contributors to the condition but also make use of lifestyle modifications. One key aspect of each patient’s lifestyle is their medical and diet, which are critical components of treatment for women suffering from migraine headaches; therefore, when possible, weight management and a proper sleep routine will help to promote healthy day-to-day functioning and minimize the occurrence of menstrual-associated migraines. To be effective, use of medications as a treatment modality for the prevention and/or control of migraine requires close attention to the relationship between menstruation and migraines in patients using oral contraceptives (OC) and for those not in use. Modulation of estrogen levels in a synthetic hormonal manner may help stabilize hormone levels and reduce migraine-inducing changes and help prevent menstrual headaches [30]. If hormone therapy is inappropriate, due to contraindications, patient preference for, or non-compliance with, triptan use is common Triptans used as abortion therapy are serotonin 1B/1D receptor agonists that inhibit the activity of the

trigeminal nerve, inhibit the release of vasoactive peptides and tightens the muscles, reducing migraine symptoms Non-Steroidal anti-inflammatory drugs (NSAIDs) are also effective in treating menstrual migraines, particularly mefenamic acid, which has been extensively studied for its efficacy in managing acute menstrual-related headaches [31, 32]. The cyclooxygenase (COX) enzymes, which generate pro-inflammatory prostaglandins that exacerbate pain and inflammation, are inhibited by NSAIDs. By reducing the levels of these inflammatory mediators, NSAIDs can help alleviate the pain and discomfort associated with menstrual migraines. In emergency settings, intravenous metoclopramide is as effective as triptans for treating migraines, particularly in patients who experience nausea and vomiting during migraine attacks [33]. Even though metoclopramide has the potential risk of causing akathisia (inner unrest), using diphenhydramine to treat this condition can help alleviate symptoms, but it does not decrease the magnitude of the migraine [34,35]. The first row of people will be treated with the highest level of skill and professionalism as possible. As such, pregnant women will be treated with extreme caution while they are receiving the above medications.

The use of calcitonin gene-related peptide (CGRP) inhibitors offers an alternative treatment option for patients who have either not responded or are not candidates for first line treatments of acute migraine [36]. The mechanism of action of CGRP inhibitors is through the inhibition of CGRP, a neuropeptide which is involved in the vasoconstriction of arteries with blood flow. By preventing the action of CGRP on blood vessels, these drugs have the potential to decrease both the frequency and severity of migraines making them a viable option for those patients who experience refractory migraines. A variety of non-drug treatment alternatives such as nerve blocks as well as neuromodulator techniques such as transcutaneous electrical nerve stimulation (TENS) or transcranial magnetic stimulation (TMS) can provide symptom relief for patients who do not respond to conventional methods through the application of electrical or magnetic stimulation to the nervous system [37]. These various techniques produce therapeutic effects on pain pathways within the brain, thereby decreasing their responsiveness to triggers of migraine headache. Surgical interventions at migraine trigger points, such as occipital nerve decompression, are also an option for patients with severe, refractory migraines that do not respond to other treatments. However, these procedures are typically reserved for patients with the most severe cases, as they are associated with a higher risk of complications.

Opioids for menstrual headache are generally contraindicated because of the risk of medication overdose headache (MOH) and chronic changes in the central nervous system (CNS), a Due to increased CGRP in key nociceptive neurons, including potential exacerbation of pain symptoms. Opioids are the greatest risk of dependence and tolerance, and should only be used in cases where other treatments have failed and the benefits outweigh the risks [38]

Complications in Treatment

The management of menstrual cramps is complicated by several factors, including the risk of overdiagnosis, medication overdose headache (MOH), depression, and anxiety, which can block attempts to treat the disease, and menstrual migraine symptoms often interact with other headache problems For example, tension type headaches and cluster headaches can cause similar symptoms, making it difficult to distinguish a between these conditions is menstrual cramps This may lead to inappropriate treatment, which may not address the root cause of the headache and does not result in inadequate symptoms care may paradoxically deteriorate symptomatically [39] . MOH occurs when patients overuse acute migraine medications, such as triptans, NSAIDs, or opioids reversible effects Migraine symptoms may have worsened. This leads to increased drug use and symptom severity, making it difficult to achieve effective control of influenza attacks MOH management requires a comprehensive approach that includes education related to proper medication use, adherence to prophylactic treatment to reduce the frequency of cold attacks in addition [40].

Patients with comorbid conditions such as depression, anxiety, and chronic pain may have altered treatment responses and additional symptom exacerbation, which requires an individualized and comprehensive approach for treatment. For instance, co-occurring anxiety or depression can cause an individual to be more susceptible to stress, which can lead to the onset of a migraine attack in migraine patients. Cognitive-behavioural therapy, stress management strategies, or medications such as antidepressants or anxiolytics may help treat another underlying psychological condition that further increases pain sensitivity among chronic pain patients (including fibromyalgia) and result in increased susceptibility to migraines. Therefore, if all possible treatment avenues for medication are exhausted and the patient is unable to achieve headache relief; all treatments would require additional therapy (in addition to medications) in order to find effective treatments for all conditions [41-43].

Traditional forms of therapy, including NSAIDs, triptans, and high-efficacy preventive therapy, may not be adequate for all patients; thus, they require consideration of alternative therapies or as adjunctive therapies, e.g. Patients who failed to respond to prior treatments may benefit from CGRP inhibitors and/or neuromodulation techniques or even consider surgical treatment. Furthermore, the factors affecting the development of menstrual migraines are multifaceted, such as genetic makeup, hormonal fluctuations, and mutation; therefore, they require tailored approaches based on the individual characteristics of each case, including but not limited to hormonal therapy to balance hormones; antimigraine medication that prevents migraines; and reducing ruck via anti-life triggers [42,43].

Future Therapeutic Approaches

Future therapies for treating menstrual craniofacial hypertension focus on the complex interplay of neurotransmitters, gonadal hormones, and genetic components. Advances in genetics have identified some key

genes that are closely associated with migrainous pathophysiology, *i.e.* the progesterone receptor (PGR) and the estrogen receptor 1 (ESR1). [44].

Genetic differences linked to migraines The discovery of pertinent genetic factors will probably lead to particular diagnostic and treatment approaches as this field of study develops. For example, women who have certain gene defects are more susceptible to migraine attacks due to their heightened sensitivity to hormonal fluctuations during menstruation. In order to provide individualized care that takes into account a patient's genetic profile, hormonal status, and environmental background, it will be crucial to clarify these genetic factors.

Studies reveal that aberrant oestrogen metabolism in migraine is caused by altered gene expression and its vascular effects. Unlike menstrual cycles, high levels of estrogen balance the production of estrogen with vascular excitement, which can result in neurologic fever and hyperexcitability. [45]. This body of evidence indicates the need for more investigation into the neurological and genetic causes of menstrual craniosynosis as well as the possibility of developing novel, individualized therapies. Correcting gene mutations is another aspect of gene therapy [46-48].

Future research may look into the connection between arthritis and menstrual migraines. To understand how rheumatoid arthritis contributes to menstrual cramps, it would be necessary to take into account the proliferation of immune cells in the brain and the release of pro-inflammatory cytokines, which may result in the generation of new antibodies targeted against this pathway. The modulation of specific brain regions that can affect headaches is a very interesting line of research. The use of TENS and TMS, which stimulate the cranial and peripheral regions of the body, can reduce the activity of certain pain pathways in the brain to decrease the frequency and severity of headaches [49,50]. Future studies could compare these treatments with existing pharmacological agents to determine their effectiveness for managing headaches. In addition to exploring potential medical treatments, modifications to lifestyle may also help counteract environmental triggers of headaches. Some of the types of modifications to the way we live and behave include changes to our sleep patterns, relaxation techniques such as yoga and meditation, and the use of biofeedback. Many treatments explore multiple aspects of treatment using a holistic approach [51, 52].

Conclusion

Menstrual Headaches are complex, heterogeneous, cyclic headaches with multiple genetic connections and hormonal dysregulation that make it difficult to treat them as a team of headache attacks related to menstruation, indicating when and how long they will last. Although there are alternative options for the treatment of these symptoms, the care of menstrual cramps is far from optimal due to the consideration of analgesic rebound headaches, associated diseases, and inconsistencies in the response to various pharmacological therapies. Future research in the ethology of the neurological and genetic cause of menstrual cramps will very likely bring about more selective therapeutic measures for treatment. It is important to realize that understanding the neurological aspect of menstrual cramps will help in the formulation of patient-centred strategies for its treatment. A holistic approach for the treatment of the syndrome of menstrual cramps is required to improve its efficacy for sufferers of this debilitating syndrome.

Declaration

Ethics approval and consent to participate: Not applicable

Human and Animal Rights: "All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines)."

Consent for publication: Not applicable

Availability of data and material:

All data generated or analysed during this study are included in this manuscript.

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SRS, BVC, KSR and SV designed and conceptualized the overall study structure. SRS planned, collected the resources and wrote the original manuscript. SV wrote, revised and edited the final manuscript. All authors provided expert opinion, reviewed and revised the manuscript.

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Abbreviations:

CGRP- Calcitonin gene-related peptide; MOH- Medication overuse headache; MM -menstrual migraine; CNS- Central nervous system; PGR- Progesterone receptor; OCP- oral contraceptives; NSAID's- non-steroidal anti-inflammatory drugs; COX- Cyclooxygenase; TENS-Transcutaneous electrical nerve stimulation; TMS-Transcranial magnetic stimulation; ESR1- estrogen receptor 1

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