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Menstrual migraine - pathophysiology, clinical features and treatment options

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ABSTRACT

Introduction and purpose: Migraine is a prevalent neurological disorder, affecting significantly more women, especially during their childbearing years, due to its unique link to the menstrual cycle. Over 50% of women with migraines report a connection between their attacks and menstruation. This review aims to highlight the latest data on the pathophysiology, epidemiology, and treatment of menstrual migraines, emphasizing the need for increased attention to this condition.

Materials and Methods: A literature review was conducted using PubMed and Google Scholar, with search phrases including menstrual migraine, migraine, menstruation, migraine diagnosis, migraine treatment, and non-pharmacological migraine treatments.

Current Knowledge: Misinterpretation of diagnostic criteria results in conflicting information about the incidence, clinical characteristics, and treatment response of menstrual migraines. Furthermore, clinical studies often do not differentiate perimenstrual attacks. The role of ovarian hormones, particularly estrogen, in the pathogenesis of menstrual migraines complicates treatment efforts.

Summary: Due to the common and debilitating nature of the menstrual migraine, more detailed research is essential to expand our understanding of its pathophysiology and to develop more effective treatments. Understanding the mechanisms behind menstrual migraines may lead to new treatment options targeting this specific condition.

Keywords: menstrual migraine; migraine; menstrual cycle; estrogens; migraine diagnosis; migraine treatment

INTRODUCTION AND PURPOSE OF THE WORK

Migraine is a serious neurological disorder affecting about 18% of women and 6% of men. [1] It is an extremely debilitating disease, additionally, due to its prevalence, the World Health Organization ranks it as the second most common (after stroke) neurological cause of disability worldwide. [2,3]

In women, the frequency of migraine attacks varies during the menstrual cycle and pregnancy, and the use of combined hormonal contraception (CHC) or hormone replacement therapy (HRT) can reveal or modify migraine disease. [4] More than 50% of women suffering from migraine report an association between the occurrence of migraine attacks and menstruation. [5] Thus, there is increasing talk of a separate disease entity, menstrual migraine (MM). There is already a large database on the pathophysiological processes underlying MM and its symptoms; however, there is still conflicting information on the epidemiology, characteristics and therapeutic approaches to this disease. The vast majority of the literature focuses on the relationship between MM and hormonal factors, particularly the decline in estrogen levels. Unfortunately, menstrual migraine is still poorly diagnosed and under-treated in clinical practice. [6]

The purpose of this paper is to collect and analyze the current state of knowledge regarding the relationship between migraine and menstruation in women, based on the available scientific literature

CURRENT STATE OF THE KNOWLEDGE

Definition and criteria

The first criteria for menstrual migraine appeared in the International Classification of Headaches II in 2004 (ICHD II) - the first version from 1988 mentioned only its definition. According to ICHD II, MM is defined as migraine without aura occurring during the perimenstrual period, i.e. on days -2 to +3 of menstruation, in at least two of three menstrual cycles. Day +1 is the first day of menstruation, while -1 is the day before - there is no day 0. [7,8].

Further, menstrual migraine is divided into pure menstrual migraine (PMM) and menstruation-related migraine (MRM). [6] Attacks of pure MM occur only during menstruation, and the incidence is about 1%. [9] Menstruation-related migraine is more common, with an incidence of about 6-7%, and occurs both during menstruation and the rest of the cycle. [9]

In the latest 2018 version of ICHD-3, the general definition has not been changed, but criteria have been added to describe PMM and MRM with aura - previous editions only distinguished the above types without aura. Importantly, for the purposes of ICHD-3, menstruation is considered both bleeding resulting from the normal menstrual cycle, as well as withdrawal bleeding occurring during the use of oral contraception or hormone replacement therapy. [10]

Epidemiology

The prevalence of migraine in childhood is similar in boys and girls, but after puberty this relationship changes, becoming two to three times more common in women than in men. [4] The lack of refined and uniform diagnostic criteria, their different interpretations, and the disparity in test results and diagnostic methods have resulted in large discrepancies in the incidence of MM.

Vetvik et al. conducted a population-based study that enrolled 237 women aged 30-34 who had migraine in at least half of their menstrual cycles. The prevalence of MM in this group was 7.6%, of which 6.1% were without aura and 0.6% with aura. [11] Interestingly, in clinical studies, the incidence of MM without aura is higher - up to 45%. [12] This discrepancy is due to the fact that patients treated at a headache clinic typically suffer from chronic migraine, which can cause false positives for MM, since the diagnostic criteria do not take into account the frequency of general migraine. [13] In addition, most clinical trials were completed before the latest versions of the ICHD-3, so their criteria differ - they have a larger peri-menstrual window, which led to a higher likelihood of classifying the symptoms in question as MM. [12]

Pathophysiology

The two main pathophysiological mechanisms best understood to date are as follows
(1) decrease in estrogen levels
(2) prostaglandin release.

The role of ovarian hormones in the pathogenesis of menstrual migraine

The hormones secreted by the ovaries - progesterone and estrogen - fluctuate throughout the menstrual cycle. Progesterone levels are highest during the luteal phase, the phase between ovulation and menstruation, then reach their lowest concentration immediately before menstruation. Estrogen levels, on the other hand, show two peaks - during ovulation and in the premenstrual phase. [14]

Reproductive hormones have a key influence on women's susceptibility to migraine. A decrease in plasma estrogen levels can trigger migraine attacks, while higher estrogen levels can have a protective effect. [15] During the menstrual cycle, a decline in estrogen levels occurs after ovulation and immediately before menstruation, however only the premenstrual decline is associated with migraine. This is most likely related to high estrogen exposure during the luteal phase, or progesterone levels may also play a role here. [16] In addition, the presence of ovulation and bleeding is not necessary for a migraine attack, as women using hormonal contraception and postmenopausal women taking estrogen also suffer from MM. [17,18] The hypothesis that a drop in estrogen levels after long-term estrogen exposure in susceptible women can trigger migraine is supported by numerous studies. [19-22]

The first evidence of a link between estrogen and migraine dates back to 1972, when Somerville [19] showed that an intramuscular injection of estradiol valerate (ester 17 of β-estradiol [E2]), shortly before menstruation delayed the onset of menstrual migraine in women with migraine, while bleeding occurred at the expected time (after a natural decline in progesterone). [19]

A similar study was conducted with intramuscular administration of progesterone before the expected date of menstruation, resulting in delayed menstruation, while migraine occurred when estrogen levels dropped while still in the premenstrual phase. [20]

The influence of estrogen on the development of MM, namely its deficiency, can also be confirmed by the fact that patients reported the highest severity of headaches in the early stages of pregnancy and after delivery, while about 50% of women reported improvement by the 12th week of pregnancy, and about 80% noticed improvement by the second trimester. During the second half of pregnancy, an increase in estrogen levels is observed. [21,22]

It now seems likely that physiological fluctuations in estrogen levels also play a role in the pathogenesis of migraine. [4] Biological predisposition may also be important, as not all women develop migraine attacks during menstruation. Studies have shown that in women with a history of migraine, the rate of estrogen decline differs significantly from that seen in healthy patients. In contrast, peak and average estrogen levels are at similar levels in both groups. [6]

A study of postmenopausal women found that despite similar serum estradiol levels, only women with a history of MM before menopause developed migraine when estrogen levels dropped after a single injection of estradiol depot. In contrast, women without premenopausal migraine did not develop a migraine attack under the same conditions. [16]

This relationship indicates that women with migraine have a neuroendocrine vulnerability that may influence the initiation of a migraine attack.

Biological effects of estrogens

The effect of the presence of estrogen on the occurrence of headaches in women is explained by the fact that this condition may cause greater sensitivity to prostaglandins, whose levels increase during menstruation. Prostaglandins, in turn, affect the release of pro-inflammatory factors, i.e. substance P, neurokinin and calcitonin gene-related peptide (CGRP). [6] It has also been observed that women suffering from migraine have elevated levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8) both during a migraine attack and during the migraine-free period. [23]

Calcitonin gene-related peptide (CGRP) is a sensory neuropeptide that plays a role in peripheral and central pain mechanisms, including those leading to migraine. [24] It has strong vasodilatory properties and is involved in trigeminal pain transmission. [6]

A number of studies have shown that plasma CGRP levels are higher in women than in men, in addition, increased levels are observed during an acute migraine attack and during the migraine headache-free period in migraineurs. [25] In addition, a clinical study involving healthy women found that the highest release of CGRP into the circulation was detected during the peri-menstrual period, when estrogen levels were low. [26]

Receptors for estrogen (ER) are expressed in the same brain areas as CGRP receptors, indicating that estrogen may affect CGRP release. [15]

Substance P (SP) is another vasoactive neuropeptide released from trigeminal nerve fibers on the cranial meninges, thus contributing to the neurogenic inflammatory process that contributes to migraine pain. [27] In summary, CGRP and SP are neurogenic inflammatory factors involved in the pathophysiology of migraine. Estrogen modulates the release of CGRP and SP, reducing their concentrations - thus playing a protective role against inflammation. [27]

In addition, female sex hormones are involved in the modulation of several neurotransmitter systems involved in migraine pathophysiology and pain transmission. Estrogens modulate the activity of the μ-opioid system, which is important for several types of headaches. During the late luteal phase, low levels of estrogen (and low levels of progesterone) were associated with reduced activation of the opioid system, resulting in increased susceptibility to pain. [28] Another system modulated by estrogen levels is the serotonergic system, which is involved in the pathophysiology of migraine. [13] Moreover, estrogen increases excitatory glutamate neurotransmission, thus explaining the increased risk of migraine auras in states of high estrogen levels, such as during pregnancy or hormone intake.[4]

Estrogens achieve their physiological effects by activating various estrogen receptors (ERs), including three known forms: estrogen receptor-α (ERα), estrogen receptor-β (ERβ) and G-protein-coupled estrogen receptor-1 (GPER/GPR30). [29] During animal studies, all three receptor subtypes were identified in the hypothalamus, a region critical for migraine initiation. [30] Both ERα and ERβ are expressed in the cerebral cortex, suggesting that estrogen may modulate pain perception at the highest cognitive level. In addition, both the trigeminal ganglia (TG) and the cluster of sensory neurons that innervate the dura mater and cranial vasculature show expression of all three ERs. [15]

In addition, estrogen can affect areas of the brain potentially involved in some migraine-related behaviors, i.e. allodynia, mood or appetite changes. [6]

In conclusion, estrogens alone are not able to exert a direct antimigraine effect, but act indirectly by stimulating antimigraine factors and inhibiting promigraine factors, thus increasing the pain threshold and suppressing headache initiation, especially in the trigeminal vascular system, which plays an important role in the pathogenesis of migraine[15].

The role of prostaglandins in the pathogenesis of MM

Much less is known about the role of prostaglandins in the pathophysiology of menstrual migraine. During the first 48h of menstruation, prostaglandins are released from the endometrium into the blood, which may indicate their association with migraine attacks during this time. [4] There was also a study in which prostaglandins E2 and I2 were injected, which triggered migraine-like attacks in migraine patients. [31] In addition, women with painful menstrual periods (dysmenorrhea) are more prone to menstrual migraines, and it is prostaglandins that are involved in the pathogenesis of this disorder. [32]

Genetic aspects of MM

Polyformisms of genes involved in estrogen metabolism, i.e. COMT, CYP1A1, and CYP19A1, have not been shown to be associated with a higher incidence of MM. [33] However, there is the neuropilin 1 (NRP1) gene, which encodes a protein involved in the menstrual and neurovascular tissue pathways - it is thought to be associated with neuronal and vascular aspects of migraine pathology. The SYNE1 and TNF genes have also been linked to MM. However, further, more detailed studies involving a larger group of patients are needed. [34,35]

Clinical manifestations

Migraine is defined as a severe, throbbing and unilateral headache often combined with nausea, photophobia, hypersensitivity to sounds and vomiting. The nature of the pain is throbbing, which intensifies with exertion or movement. Migraine attacks are usually moderate to severe. We can divide it into two main forms - migraine without aura and migraine with aura. [36] Aura is a fully reversible focal neurological phenomenon involving visual, sensory, speech and/or motor symptoms that develops gradually and usually precedes the headache phase. [37]

MM usually occurs without aura, and attacks are more painful and have been shown to be more prone to recurrence and resistant to treatment. [9] It has also been shown that for MM without aura, attacks were longer and accompanied more often by intractable nausea, compared to non-menstrual migraine. [38] They are also accompanied more often by allodynia, which is pain caused by a stimulus that does not cause pain in healthy individuals. [39,40]

Menstruation is an important risk factor for migraine without aura during childbearing age, but the relationship is not continuous throughout this period. The relationship between menstruation and migraine can change over a woman's lifetime. Migraine usually subsides during pregnancy due to stable hormone levels and higher estrogen levels during this period. In contrast, a worsening of symptoms is often observed during the peri-menopausal period due to large hormonal fluctuations. After menopause, when plasma hormone levels stabilize, there is a sustained improvement and the frequency of attacks decreases. [22]

Diagnostics

The correct diagnosis of MM poses problems in clinical practice for two main reasons.

First, the criteria published in the ICHD are underdeveloped and variously interpreted. They do not take into account the total frequency of migraine in female patients. For example, a woman with chronic migraine (i.e., >15 days per month) is highly likely to have migraine attacks during the perimenopausal period - such a patient would meet the diagnostic criteria for MM, but may be a false positive. [6,41] Moreover, the criteria do not distinguish between bleeding associated with a normal cycle and that from withdrawal. [10] Because bleeding associated with exogenous hormones disrupts the hypothalamic-pituitary-ovarian system, the pathophysiology of MM in women taking exogenous hormones may differ from the pathophysiology of menstrual migraine associated with physiological hormonal cycles. [6]

In addition, studies show that women tend to over-report the association of migraine with menstruation, so it is recommended that such patients keep a diary for diagnosis. [42] Headache diaries and calendars are extremely useful at several stages of migraine diagnosis and treatment. They are even more useful in the diagnosis of MM, where the prospective use of such a pain diary helps verify the three main features of MM - (1) the type of migraine (without aura or with aura), (2) the correlation of migraine attacks with menstruation, and (3) the frequency of attacks in relation to menstruation (at least two out of three consecutive menstrual periods according to ICHD-3 criteria). [43]

Treatment

Despite the distinct pathophysiology and more severe course of the disease, there are no separate guidelines or recommendations for the treatment of menstrual migraine. [6]

Treatment of acute attacks

Drugs used for the acute treatment of non-menstrual migraine are also effective for MM attacks. Studies show that frovatriptan, a serotonin 5-HT1B and 5-HT1D receptor agonist that has a long half-life (26 h), is suitable for the acute treatment of MM attacks, which relatively last longer than non-menstrual migraine attacks. [44]

In addition, the combination of nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen with triptans, yields a good response in acute treatment, especially for women also suffering from painful menstruation (dysmenorrhoea).[45]

Prevention

Standard migraine prevention, according to international guidelines, targets women with frequent attacks of both non-menstrual and menstrual migraine.

If treatment with triptans and/or NSAIDs is ineffective, the next step is often short-term prophylaxis (also called miniprophylaxis). There are no guidelines for this type of prophylaxis, so any medication is implemented off-label.

The use of triptans, particularly the long-acting naratriptan and frovatriptan, bring good efficacy in preventing menstrual migraine. Zolmitriptan, a shorter-acting triptan, has also proven effective in clinical trials. [46]

Some studies have shown that topiramate at a dose of 50-200 mg per day reduces the incidence of attacks, but does not affect their severity or duration. [47]

In addition, anti-CGRP antibodies or CGRP receptor antagonists have shown good efficacy and safety in the treatment of MM. However, more prospective and multicenter studies are needed to further investigate their role and therapeutic index in the treatment of MM. [48]

Hormone treatment

The demonstration that declining estrogen levels are correlated with migraine activity has led to two hormone treatment strategies. [22]

The first is combined hormonal contraception with different ethinylestradiol (EE) regimens depending on the duration of the hormone-free interval (HFI). [49] The most common regimen for COCs is the 21/7 schedule (i.e., 7 days of HFI). However, the use of regimens with a shorter (6, 4 or 2 days) or no hormone-free interval has a positive effect on migraine attacks, reducing their frequency, intensity and duration. [50] Another strategy for improving MM during COC use includes estrogen supplementation during HFI to prevent an estrogen drop situation. [4,50] Transdermal (patch or gel) application of E2 (biologically active estrogen) offers the possibility of more stable circulating hormone levels due to its special pharmacological properties. Consequently, transdermal estrogens can be used in women who suffer from headaches caused by hormonal fluctuations occurring before menstruation and in peri-menopausal women.[51]

For migraine with aura, the use of combined contraceptives is contraindicated due to the increased risk of ischemic stroke in both conditions. Progesterone-based contraceptives are recommended for women with migraine with aura. Interestingly, when tested on a small sample of women with MM, achieving amenorrhea was associated with a significant reduction in headaches. [52]

SUMMARY

Menstrual migraine is a common condition associated with significant disability. The pathophysiological mechanisms of this condition are not yet fully understood, so effective preventive and therapeutic options are still lacking. It should be considered a separate disorder requiring more attention and further research. In women diagnosed with MM, perimenopausal attacks differ in duration, severity and response to symptomatic treatment compared to non-menopausal attacks. The main pathophysiological mechanisms best understood to date are a drop in estrogen levels before the onset of menstruation, hormonal fluctuations and the release of prostaglandins. Since the cause is hormonal, effective treatment should be based on maintaining a stable hormonal environment.

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