



Sex Differences in Chronic Migraine: Focusing on Clinical Features, Pathophysiology, and Treatments

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Abstract

Purpose of Review This review provides an update on sex differences in chronic migraine (CM), with a focus on clinical characteristics, pathophysiology, and treatments.

Recent Findings Approximately 6.8–7.8% of all migraineurs have CM, with an estimated prevalence of 1.4–2.2% in the general population. The economic burden caused by CM, including medical costs and lost working ability, is threefold higher than that caused by episodic migraine (EM). Notably, the prevalence of migraine is affected by age and sex. Female migraineurs with CM experience higher levels of headache-related disability, including longer headache duration, higher frequency of attacks, and more severely impacted efficiency at work. Sex hormones, including estrogen, testosterone, and progesterone, contribute to the sexually dimorphic characteristics and prevalence of migraine in men and women. Recent neuroimaging studies have indicated that migraine may have a greater impact and cause greater dysfunction in the organization of resting-state functional networks in women. Accumulating evidence suggests that topiramate, Onabotulinumtoxin A and calcitonin gene-related peptide (CGRP) monoclonal antibodies are effective as the preventative treatments for CM.

Summary Recent evidence highlights a divergence in the characteristics of CM between male and female populations. The data comparing the treatment response for CM regarding sex are lacking.

Keywords Chronic migraine · Gender · Sex difference · Pathophysiology · Management

Introduction

Migraine can be subclassified into episodic and chronic migraine (CM), depending on the overall rate of occurrence each month. Episodic migraine (EM) is defined as a headache

occurring < 15 days per month, whereas CM is characterized by a headache occurring \geq 15 days per month for more than 3 months and is underscored by migraine headache \geq 8 days per month [1]. Differentiating EM and CM is essential for determining appropriate treatment because CM is significantly related to higher disability, productivity loss, and more medical resource utilization [2, 3]. This review aims to provide a comprehensive and up-to-date overview of CM, including clinical features, pathophysiology, and treatments, with a focus on sex differences.

Clinical Similarities and Differences in CM Between Male and Female Migraineurs

Prevalence of Migraine

Although the prevalence of migraine is similar between pre-pubertal boys and girls [5], the prevalence is higher in girls than in boys (6.4% and 4.0%, respectively) at approximately 13–15 years [4]. This sex-related difference persists over

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subsequent years. In girls, hormonal changes from puberty may correlate with migraine prevalence as 10–20% of women report their earliest migraine experience at the first menarche [5]. The first peak in sex differences occurs at 35–45 years of age (25–30% of women and 8% of men), the timepoint at which migraine prevalence peaks in both men and women [6•]. The prevalence of migraine decreases after 50 years of age in both sexes, most prominently in women. The new onset of migraine rarely develops after 50 years of age in both sexes, and migraine prevalence further declines after 75 years of age [7] (Table 1).

Subtypes of Migraine

Migraine with aura occurs less frequently than migraine without aura in both sexes. The prevalence of migraine with aura is higher in women than in men (2.6–10.8% and 1.2–3.7%, respectively) [8]. Sex differences in the frequency of aura symptoms have been reported, including visual aura (1.8% in men and 4.2% in women), sensorimotor aura (0.3% in men and 1.7% in women), and a combination of visual and sensorimotor auras (0.4% in men and 1.9% in women) [9].

Approximately 6.8–7.8% of all migraineurs have CM with an estimated prevalence of 1.4–2.2% in the general population [10••, 11]. In both sexes, the highest prevalence of CM occurs in the 40- to 49-year-old age group [12]. The prevalence of CM is 4.7-fold higher in young female adults aged < 30 years than in men [13]. Indeed, the prevalence of CM in women is two to threefold higher than that in men, reflecting the sex differences in the proportion of overall migraine prevalence [12–14]. Nevertheless, the overall proportion of CM in total migraine is higher in male migraineurs than in female migraineurs. After the age of 40 years, this difference becomes particularly prominent, as CM constitutes 9.9–11.7% of all male migraineurs compared to 7.3–8.4% of all female migraineurs [12].

Table 1 Clinical features of male and female patients with chronic migraine

	Male	Female
Prevalence in all migraine population	5.9–6.5	6.9–9.6
Education		
At least graduate degree (%)	0.4	1.2
Less than 12 years (%)	1.2	4.6
Median headache frequency (days/month)	20.0–21.7	20.0
Median MIDAS scores	32–33	38–45
Rates of moderate/severe disability (%)	66.9–71	78.9–82.6
Lost 20 working days within 3 months due to migraine (%)	9.9	15.8

MIDAS Migraine Disability Assessment questionnaire

Family History

Previous surveys have revealed a higher risk of migraine in first-degree relatives of both MA and MO emphasizing its causal genetic architecture [15–17]. Hsu et al. reported that the proportion of male participants with a positive family history was higher in the EM group than in the CM group (49.5% vs. 26%; $P < 0.001$), especially in male migraineurs without aura (50.3% vs. 21.9%; $P = 0.003$). In contrast, the proportion of female migraineurs with aura with a positive family history was higher in the CM group than in the EM group (73.7% vs. 58.7%; $P = 0.048$) [18]. Chambers et al. reported that daughters' subjective reports of pain were directly affected by maternal behavior [19] that might partially explain the different pattern of correlation between family history and CM in men and women.

Race

The prevalence and sex ratio of CM varies among races. Stark et al. reported the CM prevalence in Asia–Pacific region ranged from 0.6 to 1.7%. However, overall gender ratio in CM population was lacking in this review [20]. Scher et al. reported that the prevalence of frequent headache with migraine-like features was lower in African American women (1.3%) and men (0.3%) than in Caucasian women (1.8%) and men (0.8%) [21]. The AMPP study reported that the prevalence of CM differed among races based on unadjusted assessments [12], whereby the prevalence of CM was lower in Caucasians (1.21% of women and 0.46% of men) than in African Americans (1.76% of women and 0.72% of men). Nevertheless, the effects of race and ethnicity were not statistically significant after adjusting for socioeconomic factors, implying that the variation in CM prevalence is more strongly associated with socioeconomic variables rather than race or ethnicity [12].

CM-Related Disability and Socioeconomic Impact

Messali et al. reported that CM caused over three times the economic burden of episodic migraine in the USA, including medical costs and lost working ability [22]. Notably, the proportion of individuals with CM in full-time employment is significantly lower than migraineurs with ≤ 3 headache-days per month [23]. Further, the AMPP study revealed sex differences in the negative correlation between annual family income and the prevalence of CM. Only 0.52% of women with a total annual income > \$90,000 experienced CM, whereas 2.71% of women with a total annual income < \$22,500 experienced CM. In the male population, the prevalence of CM in the highest and lowest income groups was 0.23% and 1.32%, respectively.

Female migraineurs with CM experience higher levels of headache-related disability compared to those with EM, including longer duration and higher frequency of attacks, and significantly lower efficiency at work [12]. Hu et al. reported that female migraineurs contribute to approximately 80% of the direct and indirect migraine-related expenses in the US population [24]. Fuh et al. reported migraine is associated with a median of 2 work absence days and causes noteworthy economic harm to the society in Taiwan. About 80% of this total expense is contributed by female migraineurs, and employed female migraineurs aged 35–54 years makes up for nearly 56% of the cost [25]. The Eurolight project, constituting approximately 3000 migraineurs from nine European countries, reported that a higher proportion of female migraineurs had lost more than 20 days in total due to migraine compared to men during the preceding 3 months (15.8% and 9.9%, respectively) [26]. The Global Burden of Disease (GBD) study reported that migraine is a leading cause of years lived with disability (YLDs) and sex differences exist in this relationship. In this regard, migraine is the second and third cause of YLDs among 15- to 49-year-old women and men, respectively. Within each age group, migraine-related YLDs are consistently higher in women than in men. Further, the prevalence of CM is associated with educational level and socioeconomic status. Scher et al. reported that 1.2% of women and 0.4% of men that had obtained at least graduate degrees had CM, compared to 4.6% of women and 1.2% of men that had not completed high school [21].

Comorbidities

Epidemiological surveys have indicated that CM is associated with higher risk of comorbidity profiles than EM. The AMPP study reported there were about twofold risk of depression, anxiety, and chronic pain in CM compared with EM suffers [27]. Moreover, cardiovascular risk components including diabetes, high blood pressure, elevated cholesterol and obesity, and respiratory illnesses including asthma, chronic bronchitis, and emphysema or chronic obstructive pulmonary disease, were also significantly more common in those with CM than EM [27]. Using a national database in Taiwan, Chen et al. reported there was a higher relative risk of depression (RR = 1.88; $P < 0.0001$), bipolar disorder (RR = 1.81; $P = 0.022$), asthma (RR = 1.77; $P = 0.007$), anxiety disorder (RR = 1.48; $P = < 0.0001$), and hyperlipidemia (RR = 1.32; $P = 0.041$) in CM than those with other migraines [28]. Nevertheless, there is a paucity of CM studies on the association between sex differences and comorbid diseases.

Pathophysiological Similarities and Differences in CM Between Male and Female Migraineurs

Impact of Sex Hormones

Accumulating evidence suggests that sex hormones, including estrogen, testosterone, and progesterone, contribute to the sexual dimorphism in the characteristics and prevalence of migraine.

Estrogen

The estrogen withdrawal hypothesis proposes that attacks of menstrual migraine are elicited by a reduction in estrogen levels prior to menstruation [29]. The decline in estrogen may upregulate the sensitivity to prostaglandins and increase the release of neurogenic inflammation-related peptides, such as substance P, calcitonin gene-related peptide (CGRP), and neuropeptides [30]. Recent studies have demonstrated that a rate of estrogen decline of $> 10 \mu\text{g}$ can trigger migraines [31] and that female migraineurs have a faster drop in estrogen levels compared to non-migraineurs [32].

Progesterone

Progesterone exerts modulatory effects on estrogen in migraineurs. Escalating levels of progesterone may attenuate the impact of periovulatory estrogen drop [32]. Taha et al. reported that female migraineurs without aura had significantly higher levels of progesterone in the follicular and luteal phases of the menstrual cycle [33]. A translational study exploring the connection between the progesterone receptor gene and migraine discovered that a PGR polymorphism indicated a later onset of migraine theoretically via diminished neuronal excitability in the brain [34].

Testosterone

One study analyzed total serum testosterone levels in men with CM and age-matched non-migraine controls. Total testosterone levels were lower in the male CM group, suggesting dysfunction in the hypothalamus-pituitary-gonadal (HPG) axis [35]. Li et al. examined HPG axis-related hormones in migraine patients and observed significantly higher levels of gonadotropin-releasing hormone in male migraineurs [36]. These reports highlight the involvement of testosterone in migraine.

Neural Substrates of Sex Differences in Migraine

Several neuroimaging studies have investigated sex differences in migraine. Gray matter thickness of the posterior insula and precuneus was found significantly greater in

women with migraine than in men with migraine and healthy women [37••]. In addition, the volume of the parahippocampal gyrus, an anxiety- and stress-related region surrounding the hippocampus, was smaller in male migraineurs. These findings may explain the differences in response to intermittent stress (migraine attacks) and influence of hormones (estradiol or progesterone versus testosterone) on hippocampal function, as well as the differential effects of treatment responses to triptans between female and male migraineurs. Furthermore, female migraineurs exhibited higher activation of brain areas involved in emotional processing (such as the amygdala) in response to thermal pain. A follow-up study investigated age-related alterations in cortical thickness using high-field MRI [38] reported abnormalities in the insula, with an atypical pattern of a lack of bilateral insular thinning in adult female migraineurs between the ages of 20 and 65 years.

A recent meta-analysis of nine voxel-based morphometry (VBM) neuroimaging studies of migraine revealed that a higher percentage of female migraineurs exhibited reduced gray matter in the right dorsolateral prefrontal cortex. To date, quantitative whole-brain VBM meta-analysis of migraine has provided strong evidence of gray matter anomalies within pain-processing neural networks in female migraineurs [39].

Studies have provided evidence for sex differences in increased deep white matter hyperintensity volume and incidence of progression in female migraineurs compared to age-matched healthy female controls, with no such differences observed in men [40].

Several neuroimaging studies have explored sex-related differences in migraine patients using functional MRI (fMRI). A study revealed that more regions in female migraineurs exhibited decreased nodal centrality and poorer network resilience based on graph theory analysis than in male migraineurs, which may reflect more dysfunctional communication within and between brain areas in female migraineurs [41].

A more recent neuroimaging study used graph theory analysis [42] to evaluate the topological organization of functional networks according to reported extensive alterations in functional connectivity in female migraineurs. The topological metrics of functional networks in female migraineurs without aura comprised changes in the nodal centrality of brain areas and interrupted connections between areas principally involved in pain modulation or processing, sensory discrimination of painful stimuli, and sensory integration processing.

A recent study on CM [43] compared resting-state connectivity reported significantly decreased functional connectivity of three major intrinsic brain networks in women with CM. These networks comprised the default mode network (DMN), central executive network, and salience network.

Notably, weaker executive and salience network connectivity was associated with higher headache frequency in these patients. The results of these fMRI studies indicate that episodic and/or CM may additionally impact females and cause more dysfunctional organization in their resting-state functional networks [44]. Collectively, recent neuroimaging studies have confirmed sexual dimorphism in the structural and functional connectivity of the brain in migraineurs.

Several issues remain to be resolved in neuroimaging studies of sex differences in migraine. First, current neuroimaging studies on sex differences in migraine (episodic or chronic) have predominantly focused on the interictal phase and demonstrated brain abnormalities outside of an attack. Second, given the sex differences in migraine, studies on female and male migraineurs should investigate the underlying pathophysiology more comprehensively. To date, most neuroimaging studies in patients with migraine have focused on female patients. Accordingly, more studies on male migraineurs are warranted given that basic research typically employs male animals [45].

Neuroendocrinology

Migraine is a neurovascular disorder that involves trigemino-vascular system activation [46] resulting from the release of CGRP from sensory fibers, leading to vasodilation of the cranial vasculature [47]. Variations in female sex hormones may influence CGRP release and sensitivity. CGRP levels are higher in women than in men and are even higher in women taking contraceptive pills [48]. In addition, CGRP concentrations increase during pregnancy and peak near term, followed by a sharp decline at term and normalization after delivery [49].

A case–control study using a laser Doppler imager explored the impact of the menstrual cycle on trigeminal nerve-induced vasodilation in healthy women and patients with menstrual migraine. Healthy women exhibited increased dermal blood flow (DBF) responses to capsaicin during menstruation. In contrast, patients with menstrual migraine did not exhibit changes in DBF during their menstrual cycle, and their estradiol levels during the luteal phase were lower than those in healthy women, indicating a reduced menstrual cyclicality of estradiol levels and the trigeminovascular vasodilator system in menstrual migraine [50••].

A recent study demonstrated that capsaicin-induced, CGRP-mediated DBF responses on the forearm did not change over time and were equivalent to those in male migraineurs without evidence of major desensitization. Unlike men, healthy women exhibited fluctuations in DBF responses, which increased during menstruation [51]. Despite the evident sex differences in the trigeminovascular system, it is crucial to clarify whether hormonal

fluctuations directly influence the vasculature, CGRP release, or central activation of the trigeminal system. Monoclonal antibodies against CGRP and its receptors have emerged as therapies for CM prophylaxis. To date, no sex differences have been observed in the tolerability and efficacy of these antibodies, although the long-term effects of blocking CGRP have not been fully elucidated [52, 53].

In summary, the literature indicates that CGRP expression and secretion are modulated by hormonal changes during the menstrual cycle, although the precise mechanisms have not been clarified. Further studies are warranted to deepen our understanding of this field, which may facilitate the development of novel sex-specific pharmacotherapies for migraine.

Treatments

Acute and preventive treatment approaches for migraine are similar between men and women, although specific preventive strategies for menstrual migraine or hormone therapy are adopted in women. Moreover, data comparing specific treatment response regarding gender is lacking. Women are more likely to use prescription drugs for migraine attacks, including triptans, and preventive drugs [54, 55]. A possible reason is that men are less likely to seek professional medical opinions for their migraine [54, 55]. In addition, for women planning to become pregnant, the potential benefits of any drug must exceed the potential risk to the fetus. If women of childbearing age require contraindicated drugs such as topiramate or valproate, they should be informed of the need for contraception.

Acute therapies, including non-steroidal anti-inflammatory drugs, triptans, and opioids, are administered to shorten or terminate migraine attacks in patients with CM [56–58]. Adequate pain control in episodic migraineurs is also beneficial for reducing the risk of EM progression to CM [59•, 60]. However, the use of opioids and triptans for CM warrants caution due to their strong correlation with medication overuse headache (MOH) [57, 61]. For example, triptan, a migraine-specific medication that impedes CGRP release by stimulation of presynaptic 5HT₁ receptors, should not be used for more than 2–3 days a week in order to prevent MOH [57, 62]. The optimal treatment strategy is to prevent migraine attacks in CM, rather than harnessing medications to stop migraine attacks [60].

Preventive Medications for CM

Prophylactic treatment for CM should be offered to ensure successful prevention of migraine attacks [63, 64••]. Most of the commonly used migraine preventive agents may be

working for both EM and CM, the evidence for CM is only for some of them.

Topiramate

Topiramate is proved for the prophylaxis of CM in adults. Silberstein et al. reported topiramate approximately 100 mg daily significantly decreased monthly migraine attack days than placebo (−6.4 vs −4.7, $P=0.01$) in a randomized and double-blind trial [65]. Diener et al. reported similar findings that topiramate (50–200 mg/day) significantly reduced headache intensity and diminished the average number of monthly migraine days [66]. Female migraineurs should be aware that topiramate doses exceeding 100 mg may affect estrogen metabolism and influence the efficacy of oral contraception. Moreover, pregnant women using topiramate during the first trimester have higher risks of teratogenicity, such as oral clefts and hypospadias [67, 68].

Flunarizine

Flunarizine is a nonspecific calcium channel blocker, and its reported efficacy is based on several controlled studies. The recommended dose of flunarizine is 5–10 mg daily [64••, 69]. A randomized trial reported flunarizine 10 mg/day is more effective than topiramate 50 mg/d for CM prevention evidenced by significantly decline in the numbers of days using acute abortive drugs (−2.3 vs −0.2, $P=0.005$) and a higher 50% responder rate regarding total migraine days (75.9% vs 29.6%, $P=0.001$) [70]. Currently, flunarizine is unavailable in the USA.

OBT-A

Onabotulinumtoxin A (OBT-A) (155–195 units to 31–39 sites every 12 weeks) has been reported to be an effective therapy for CM in randomized controlled trials [71] and several real-world studies [72]. One meta-analysis revealed that OBT-A treatment decreased the number of monthly migraine days by 2 days compared to a placebo [73]. OBT-A is only indicated for patients with CM with an inadequate response or intolerance to oral migraine drugs [63, 64••, 72].

Anti-CGRP Monoclonal Antibodies

Monoclonal antibodies targeting the CGRP ligand (galcanezumab, fremanezumab, and eptinezumab) and CGRP receptor (erenumab) have been approved for preventive treatment of migraine based on high-quality evidence [74]. The long half-life of these medications enables subcutaneous once-monthly administration of erenumab and galcanezumab, subcutaneous once-quarterly administration of fremanezumab, and intravenous quarterly administration of eptinezumab [64••]. Treatment with CGRP inhibitors

significantly reduces the number of migraine days per month and number of days using migraine-specific drugs for CM and significantly increases the success rate of > 50% reduction in migraine days per month [74]. Erenumab, galcanezumab, and fremanezumab have been demonstrated to be effective for migraineurs with a failure to respond to more than two other preventive drugs [64••]. Moreover, there is no significant gender difference in efficacy and safety with erenumab [75]

Neurostimulation Therapy

Transcranial Magnetic Stimulation

Several observational studies have recommended the use of single-pulse transcranial magnetic stimulation (sTMS) for migraine prevention. One systematic review of 213 patients from eight studies concluded that high-frequency TMS on motor cortex areas was effective for migraine therapy, with minimal adverse effects [76].

Transcutaneous Supraorbital Nerve Stimulation

The efficacy of transcutaneous supraorbital nerve stimulation as a therapy for migraine prevention was first reported in a randomized controlled trial of 67 participants. Supraorbital transcutaneous stimulation significantly decreased headache days (6.94 vs 4.88; $P=0.023$) and resulted in a higher 50% responder rate in the treated group than in the sham group (38.1% vs. 12.1%, respectively) [77]. Evidence from two small open-label surveys also supports the use of this approach for prevention of CM [78, 79].

nVNS

A pilot study of 59 patients with CM reported a trend for a reduction in headache days in the noninvasive vagus nerve stimulation (nVNS)-treated group, but this did not reach statistical significance [80]. More studies are warranted to examine the efficacy of nVNS for migraine prevention.

Conclusions

This review provided a comprehensive overview of sex differences in CM, with a focus on clinical characteristics, pathophysiology, and treatments. The economic burden of CM is more than three times that of EM. Female migraineurs with CM report higher levels of headache-related disability, including longer duration and higher frequency of attacks, and lower efficiency at work. Sex hormones, including estrogen, testosterone, and progesterone, contribute to the differences in characteristics and prevalence of migraine in

men and women. Recent neuroimaging studies suggest that migraine may additionally impact females and cause greater dysfunction in the organization of resting-state functional networks in women. The effectiveness of acute and preventive treatment of migraine in women of reproductive age is an essential factor in clinical management. Accumulating evidence indicates that topiramate, OBT-A and anti-CGRP monoclonal antibodies are effective preventive treatments for CM. However, the data comparing specific treatment response regarding sex is lacking. Further surveys are needed for the development of sex-specific pharmacotherapies for CM.

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Declarations

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- Of major importance

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