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Review

Sex-Related Influences in Migraine



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Migraine is a common neurological disorder with significantly higher incidence and prevalence in women than men. The presentation of the disease in women is modulated by changes in sex hormones from adolescence to pregnancy and menopause. Yet, the effect of sex influences has often been neglected in both basic and clinical and in clinical management of the disease. In this review, evidence from epidemiological, clinical, animal, and neuroimaging studies on the significance of the sex-related influences in migraine is presented, and the unmet needs in each area are discussed. © 2016 Wiley Periodicals, Inc.

Key words: hormones; estrogen; menstrual migraine; menopause; cortical spreading depression; trigeminal pathway; neuroimaging

INTRODUCTION

Approximately 18% of women and 6% of men in the United States are affected by migraine, a neurovascular disorder characterized by recurrent headache attacks involving nausea, photophobia, phonophobia, and exacerbation by physical activity (Stewart et al., 1992, 2013; Bigal et al., 2004). Migraine is the fourth leading cause of disability in women worldwide, with women migraineurs experiencing significant burden of disease (Hu et al., 1999; Lipton et al., 2007; Pavlovic et al., 2015) compared with men (Buse et al., 2012). The female preponderance of migraine has been recognized since ancient times (Welch et al., 1984) and has been supported by multiple areas of research. Onset of migraine increases at menarche, with peaks in prevalence in the 30s and 40s, and a significant decline after menopause (Stewart et al., 1992). The changing hormonal milieu is known to affect migraine in women through adolescence, pregnancy, lactation, and menopausal transition. Furthermore, hormonal change is one of the most potent triggers for occurrence of a migraine attack (Sances et al., 2003; MacGregor and Hackshaw, 2004; Sacco et al., 2012; David et al., 2014). Attacks of menstrual migraine are thought to be triggered by the late-luteal-phase decrease in estrogen prior to menstruation, commonly referred to as the "estrogen withdrawal hypothesis" (Somerville, 1972; MacGregor and Hackshaw, 2004). Thus, both timing of migraine development and occurrence of migraine attacks are influenced by ovarian hormones. Here, we review evidence from epidemiological, clinical, and neuroimaging studies in human as well as animal models related to sex-related influences in migraine, and attempt to highlight the significance of such influences in studying migraine disease. Understanding these differences could lead to the identification of sex-specific pathways that may in turn help in the development of new, more effective treatments for migraine in both women and men. Indeed, clinical treatments based on sex-related differences have not been well studied to date, and there is extensive need for further research in this area.

SIGNIFICANCE

Multiple lines of evidence from epidemiological to clinical and animal studies emphasize the significance of sex-related influences in studying and managing migraine disease.

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Epidemiologic Evidence for Sex-Related Differences in Migraine Incidence and Prevalence

While the 1-year migraine prevalence is almost threefold higher in women than men (18% vs. 6%), the cumulative lifetime incidence of migraine in women is more than twofold higher (43% vs. 18%) (Stewart et al., 2008). Similarly, elevated female-to-male ratios in migraine have been reported from studies using various samples and methodologies and from different parts of the world (Russell et al., 1995; Henry et al., 2002; Victor et al., 2010; Buse et al., 2013; Chai et al., 2014). The ratio of migraine prevalence between sexes varies across ages. While boys start developing migraines earlier than girls, by the age of 7 to 9 years, migraine affects the same percentage of boys and girls (2.5% boys, 2.4% girls), with more girls affected than boys in older age groups (age 10–12: 3.9% boys, 5.4% girls; age 13–15: 4.0% boys, 6.4% girls) (Bille, 1962; Macgregor et al., 2011). Migraine prevalence peaks in women during their 30s and 40s and starts to gradually decline across the fifth decade of life, while adult men have a more gradual rise in prevalence, lower peak, and more gradual drop (Stewart et al., 1992; Buse et al., 2013). In a large US population study of over 160,000 individuals, adjusted female-to-male prevalence ratios ranged from 1.48 (among those aged 12–17) to 3.25 (among those aged 18–29) across the lifetime for migraine and from 1.22 to 1.53 for probable migraine (Buse et al., 2013). Similar sex differences were not observed for other types of severe headaches. Furthermore, chronic migraine (i.e., headaches occurring on 15 or more days a month for 3 or more months) is recorded in 1.29% of females and only 0.48% of males (Buse et al., 2012). Sex-specific prevalence for chronic migraine peaks in the 40s at 1.89% for females and 0.79% for males, supporting the clinical notion that women have more frequent migraines (Buse et al., 2012).

More recent studies have focused on the prevalence of migraine during the menopausal transition (MacGregor, 2009; Ripa et al., 2015). Though no longitudinal studies have been performed to date, the available data suggest that migraine prevalence is thought to gradually decrease in the population across menopausal transition (Wang et al., 2003). In addition, a subset of migraineurs appear to be at risk of increased frequency of headache, with a 1.7-fold increase in episodic migraine among women in late perimenopause compared with premenopausal women with migraine (Martin et al., 2016). There is a lack of understanding of the underlying pathophysiology of why the majority of women do better with the approach of menopause, while a subset of women migraineurs appear to worsen.

Clinical Aspects of Sex-Related Differences in Migraine Presentation

Migraine sufferers often identify specific triggers for headache and related symptoms. These include food, lack of sleep, stress, and exercise, among other causes (Pavlovic et al., 2014). In women, hormonal fluctuation has been established as a trigger so much so that there are special criteria within the International Criteria of Headache Diagnosis for the diagnosis of menstrual migraine (Olesen 2014). Menstrual migraine is defined as the headache that occurs within 2 days prior to the onset of menstrual bleeding and up to 3 days of bleeding with at least two out of three menstrual cycles. To accurately establish the diagnosis, a woman must track her menstrual cycle and her migraines. As noted above, this headache is commonly attributed to the sudden drop in estrogen prior to menses. A very recent study showed that women with a history of migraine have faster decline of estradiol prior to menses (late luteal phase) than controls irrespective of whether they have experienced a headache in that cycle (Pavlovic et al., 2016). Authors concluded that this faster rate of estrogen withdrawal is an endogenous trait of women with migraine and proposed that migraineurs may be at increased risk for perimenstrual attacks due to neuroendocrine vulnerability conferred by faster estrogen decline (Pavlovic et al., 2016). A similar decrease in circulating estrogen occurs at ovulation and has been related to increased frequency of migraine in some women (Sulak et al., 2007), but not consistently as to be described in larger population studies (Chai et al., 2014). Comparison of rates of estrogen decline in the periovulatory period did not reveal any significant differences between women with a history of migraine and controls (Pavlovic et al., 2016) providing a mechanistic explanation for the lack of consistent recognition of periovulatory migraine.

Research demonstrates that for women with menstrual and hormonal migraine, it may be possible to decrease the frequency of events by eliminating cycling. Monophasic estrogen/progesterone oral contraceptive pills (OCPs) can be used continuously with rare off-cycling to prevent spotting, and for many women who have a monthly menstrual migraine, this can effectively eliminate the events (Calhoun and Hutchinson, 2009). However, migraine with aura (MwA) carries an increased risk of stroke compared with migraine without aura (de Falco and de Falco, 2015). Older studies with significantly higher doses of estrogen in OCP formulations have correlated MwA and stroke, thus making OCPs an unsafe choice in these patients; however, newer clinical practice is emerging that the current low-estrogen formulations are prescribed to women with MwA under the assumption that they are nonsmokers and do not have other cardiovascular risk factors (Sacco et al., 2012). Inducing chemical menopause has not been shown to substantially decrease menstrual migraines, and there are no data to support elective hysterectomy or combined hysterectomy and oophorectomy in the treatment of ongoing hormonal migraine (Martin et al., 2003). There are few data around the use of hormonal replacement therapy or selective estrogen receptor modulators for menopausal women who continue to have migraine expression (MacGregor, 1999; Hodson et al., 2000; Misakian et al., 2003; Nappi et al., 2011).

Sex-Related Differences in Migraine Found in Animal Models

While there are numerous animal models of pain, most experimental pain models have been performed in

male rodents in order to achieve stable results. In a similar manner, migraine models in female animals have been lacking (Bolay et al., 2011).

Brain serotonergic and dopaminergic functions are intricately related to ovarian hormones. In comparison with males, females have a higher brain serotonin synthesis and more active dopamine transporter system that is critical for dopamine function (Fillingim et al., 2009). In available animal studies, female rodents have been shown to have lower pain thresholds to thermal, chemical, and mechanical painful stimuli (Cairns, 2007; Hurley and Adams, 2008).

Estrogen also enhances susceptibility to cortical spreading depression (CSD), which is a pathophysiological correlate of migraine aura (Bolay and Moskowitz, 2005; Eikermann-Haerter et al., 2009b; Bolay et al., 2011). In a study by Brennan et al., the CSD threshold was found to be 50% lower in female mice than in male mice, unrelated to the phase of estrous cycle (Brennan et al., 2007). In the animal model of familial hemiplegic migraine, female FHM1 mutant mice were more susceptible to CSD compared with males (Moskowitz et al., 2004; Eikermann-Haerter et al., 2009b; Bolay et al., 2011). Furthermore, *Cacna1a* transgenic mice have been shown to display photophobia and head pain induced by stress similar to human migraine (Chanda et al., 2013).

The critical role of estrogen is revealed by reversal of increased susceptibility by oophorectomy and maintenance of CSD vulnerability by estrogen replacement. On the other hand, testosterone has been reported to suppress CSD via androgen receptor–dependent mechanisms in experimental studies (Eikermann-Haerter et al., 2009a), which implicates its protective potential.

Estrogen receptors are widely expressed in the trigeminal sensory system. Trigeminal nociceptive pathways are sensitized in female rats (Schenck-Gustafsson et al., 2012), and the trigeminal ganglion (TG) and second-order trigeminal sensory neurons are vulnerable to estrogenic modulation (Cairns, 2007). In addition, effects of estrogenic fluctuations on glucose intolerance and hypoglycemia are likely confounding factors triggering migraine attack. Prostaglandins released from endometrium during menstruation can contribute to development of menstrual-related migraine (Schenck-Gustafsson et al., 2012).

Estradiol affects neuropeptide release and receptor coupling. Upregulation of extracellular signal-regulated kinase by estradiol increases nociception. Estrogen receptors ER_α and ER_β and new estrogen receptor GPR30 are expressed in trigeminal nucleus caudalis; moreover, GPR30 is expressed also in trigeminal nociceptors and is upregulated by inflammation (Liverman et al., 2009). Estrogen stimulates intracranial dural mast cells, initiating mast cell degranulation (Boes and Levy, 2012). Furthermore, high estradiol levels decrease Mg^{++} and open NMDA channels (Muneyvirci-Delale et al., 1998; Bolay et al., 2011). On the contrary, progesterone attenuates trigeminovascular nociception by reduced dural plasma extravasation (Multon et al., 2005; Bolay et al., 2011).

Finally, calcitonin gene-related peptide (CGRP) is a major contributor to migraine headache, as a peptide player in vasodilation, and neurogenic inflammation (Karsan and Goadsby, 2015). CGRP receptors are detected in trigeminal ganglia (Capuano et al., 2009). Decrease of CGRP release in high-estrogen states has been reported, which may explain the association of migraine attacks with estrogen withdrawal states (Cairns, 2007). Also, in a peripheral inflammatory model by complete Freund's adjuvant administration on TG function, increased expression of proinflammatory cytokines and brain-derived neurotrophic factor was significantly increased in male trigeminal ganglia compared with female TG. In contrast, expression of CGRP in TG was significantly higher in female compared with male mice (Kuzawinska et al., 2014).

Though conventionally female preponderance is mainly associated with sex hormones, nonhormonal sex differences need to be considered as well. There is increasing evidence for sex-specific genomic imprinting that plays a role in the development of the cerebral cortex functions in the mammalian brain (Gregg et al., 2010). Rodent strain-dependent sex-related differences, independent of ovarian hormone effects, have also been reported (Mogil et al., 2000). As sex differences in nociceptive processing are still poorly understood, more experimental data are needed to elucidate these important sex-specific mechanisms.

Neuroimaging Findings on Sex-Related Differences in the Brain of Migraineurs

Neuroimaging studies have revealed multiple structural and functional abnormalities in multiple cortical and subcortical brain regions in association with migraine (Mailis-Gagnon et al., 2003; Moulton et al., 2008; Schmidt-Wilcke et al., 2008; Burstein et al., 2010; Russo et al., 2010; Tessitore et al., 2011; Maleki et al., 2012a,b). However, the sex specificity of such abnormalities and their links to the sex-related epidemiological and clinical patterns have been less studied. In contrast to the basic science studies in animals, the majority of neuroimaging studies in migraineurs have been dominated by female subjects, while the male migraineurs are understudied.

There are disease-related changes in the structure of insula and precuneus that seem to be specific to women suffering from migraine (Maleki et al., 2012b), whereas disease-related structural changes in parahippocampal gyrus seem to be specific to male migraine patients. There is also an abnormal pattern of lack of thinning of gray matter in the insula of adult female migraineurs (Maleki et al., 2015), which is of interest because studies in healthy subjects show that the relative gray matter loss rate of the insular cortex is approximately twice higher than that seen in other cortical areas during aging (Grieve et al., 2005). It is not clear whether this pattern of aging is specific to female migraineurs or whether it happens in male patients as well. The insular abnormalities are particularly notable as insula is involved in multiple functional

processes such as pain, interoception (Craig, 2009), autonomic function (Critchley et al., 2011; Beissner et al., 2013), sensation (Henderson et al., 2007; Nieuwenhuys 2012), and affective processing that may be impaired or abnormal during a migraine attack (Goadsby et al., 2009; Ferrari, 2013; Noseda and Burstein, 2013). Furthermore, insular involvement in migraine has been reported in a number of functional imaging studies (Bahra et al., 2001; Schmidt-Wilcke et al., 2008; Kim et al., 2010; Xue et al., 2012; Yang et al., 2012). Given the increase in the incidence of migraine during puberty, it is very likely that such plasticity may start appearing during puberty. In fact, physiologically, insula is the most divergently modulated brain region by puberty in females vs. males (Herting et al., 2012).

Sexual dimorphism in the resting state networks (RSNs) of functional connectivity has also been reported in migraine, with female migraineurs shown to have more dysfunctional organization of their RSNs (Liu et al., 2011a). One of the main RSNs is the default mode network (DMN) or the task-negative network (Raichle and Snyder, 2007) that is active during the resting state or no-task. This network includes precuneus, posterior cingulate, medial prefrontal, medial temporal lobe, and angular gyrus (Buckner et al., 2008). The intrinsic connectivity between the DMN and the executive control network in healthy women has been shown to be modulated by the phase of the menstrual cycle (i.e., follicular vs. luteal) and also by the use of OCPs, especially in the anterior cingulate cortex (Petersen et al., 2014). The contribution of hormonal fluctuations on the dysfunctional organization of RSNs in women also needs to be examined. Precuneus, a core region of the DMN, is a highly metabolically active region in both sexes but is more active in women (Liu et al., 2011b). There is also a sex-specific increase in the cortical thickness of this region in female migraineurs (Maleki et al., 2012b). While the exact role of precuneus in migraine is not clear, given the "state-dependent changes of the functional connectivity" in this region, it is likely that the plastic changes in the brain of female migraineurs may serve a functional link to the migraine pathophysiology that is sex-specific. For instance, episodic migraine patients without aura show greater connectivity between both the DMN and central executive network and the insula (Xue et al., 2012), and there may be sex-specific differences in the strength of such connectivity.

Brain white matter abnormalities commonly manifest as hyperintensities on magnetic resonance images. These abnormalities are more prevalent in migraine patients than in the general population (Kruit et al., 2010), although the pathophysiological basis of these abnormalities is not well understood. There are sex-related differences in the incidence of these abnormalities in migraine patients: while there are no known differences in white matter hyperintensities between men with migraine and their matched controls, among women, deep white matter hyperintensity volume as well as the incidence of progression is higher in the migraineurs than in their matched healthy controls (Kruit et al., 2010). This may be an indicator of potential differences in the inflammatory marker in female vs. male migraineurs or, alternatively, sex differences in the sensitivity or the brain region–specific expression of the inflammatory marker receptors in the brain of female migraineurs, or the modulatory effect of hormones on the inflammatory markers.

CONCLUSION

In has become increasingly recognized that sex has a significant role in migraine pathophysiology, and sex influences cannot and should not be ignored in both the study and treatment of migraine. However, there is a paucity of studies in this area, and there are unmet needs in many domains:

In epidemiological studies, there is a need for longitudinal studies as well as a need to focus on transitional periods such as puberty and menopause. Consistent diagnostic criteria should be used to make accurate conclusions from studies with comparable findings.

In clinical studies, there is a need for establishing sex-related treatment efficacy guidelines which requires extensive research into the pharmacokinetics of abortive and prophylactic treatments currently used in managing migraine. There is also a need for research on using hormones to treat migraine, particularly in mini-prophylaxis of migraine that is felt to be menstrual or cyclic.

In animal studies, there is a need for standardization of sex-related changes in animal models. Estrous cycle hormone levels are not within the physiological limits in gonadectomized and hormone-replaced rodents (Bolay et al., 2011). Clinically relevant migraine models (Akcali et al., 2010; Tepe et al., 2015) should be recapitulated with female animals to evaluate the sex differences and female vulnerability in order to extract conclusions potentially relevant to women migraineurs. Although there are excellent single-gene animal models that have been effectively used to study underlying pathophysiology, these may have limited generalizability as the majority of migraine cases are likely polygenic. Furthermore, more information is needed to understand the mechanisms and the role of sex hormone regulation in migraine.

In neuroimaging studies, there is a need to take into account the significant influence of circulating sex hormones (such as estrogen, progesterone, and testosterone) on the functional brain measures, which could potentially be significant confounders, as these hormones influence functional processing in the brain (Goldstein et al., 2005, 2010; Choi et al., 2006; Pletzer et al., 2010). Menstrual cycle phase needs to be assessed and controlled in imaging studies, or even better, the levels of sex hormones should be measured and used as another variable in analyses. However,

accounting for modulatory effects of sex hormones on neurotransmitter functioning of the brain may be more complicated and less trivial to account for by only the measurement of hormonal levels. These influences could manifest in the form of facilitation or inhibition of cortico–cortical or cortico–subcortical functional connectivity patterns (Peper et al., 2011). Understanding the dynamics of interactions between the hormonal changes and the brain's activity and connectivity patterns in migraine will provide more insights into the pathophysiology of this disease.

CONFLICT OF INTEREST STATEMENT

Jelena Pavlovic, MD, PhD, receives consulting honoraria from Allergan Inc and is a principal investigator of a clinical trial sponsored by Alder Pharmaceuticals for which she does not receive compensation.

The other authors have no conflicts of interest to disclose.

ROLE OF AUTHORS

All authors listed on the paper have conceptualized and contributed equally to the preparation of this manuscript.

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