CLINICAL BRIEFS

The Etiology Of Menstrual Migraine

A review of the literature with an analysis for managed care decision makers

Migraine annually affects approximately 10 percent of the U.S. adult population, with the prevalence considerably higher in women than in men. ***Menstrual migraine*** may afflict up to 68 percent of female migraineurs, and has its own distinct etiology and disabling effects. Menstrual migraine attacks may be predictable, and thus may be preventable.

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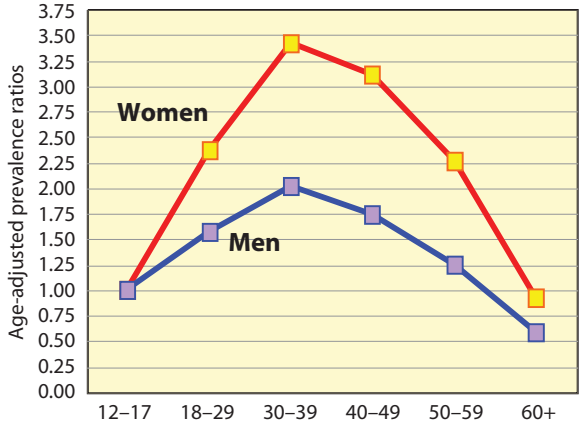
Hormonal Events as Migraine Triggers: The Etiology of Menstrual Migraine

A review of the literature suggests that approximately 13 percent of the U.S. adult population suffers from migraine, with a prevalence that is approximately 3 times greater in women than in men (Lipton 2002). Population-based surveys have found the 1-year occurrence of migraine to be about 6 percent in men versus 18 percent in women (Lipton 2001, Lipton 2002). In women, the prevalence of migraine is highest during the childbearing years, rising through early adulthood and peaking between ages 30 and 50, after which it steeply declines. Relative to girls aged 12 to 17, the adjusted prevalence of migraine is 3.4 times higher in women aged 30 to 39; relative to boys aged 12 to 17, the adjusted prevalence is 2 times higher in men aged 30 to 39 (Figure 1).

Migraine headaches generate substantial disability — the World Health Organization has ranked migraine 19th among disability diseases worldwide (Headache 2004). Migraine also results in substantial health care expenditures. Among working-aged adults, total annual medical costs for patients with migraine have been found to be more than twice as high as total medical costs for control subjects ($7,089 vs. $2,923) (Pesa 2004). Because the overall prevalence of migraine is considerably higher in women than in men, the disease burden is substantially greater among women.

The differences between men and women in migraine epidemiology most likely reflects the influence of hormones, notably estrogen, on the etiology of certain kinds of migraine. Throughout life, women are exposed to various hormonal events that may act as migraine triggers. Chief among them is menstruation. More than 60 percent of female migraineurs may experience *menstrual migraine* — a migraine that occurs within a few days before or after the onset of menstruation. Studies of migraineurs seen at specialty clinics suggest that menstrual migraine is more severe and disabling than nonmenstrual-related migraine (Martin 2006b).

FIGURE 1
Adjusted prevalence ratios for migraine*†



*Adjusted for age, race, household income, population density, and region of the United States.
†$P < .05$ compared with reference category (age 12–17 years) for each gender.
SOURCE: LIPTON 2001

Migraine subtypes

Migraine is divided by the International Headache Society (IHS) into two major subtypes: *Migraine without aura* and *migraine with aura* (Headache 2004). The latter is sometimes called *classic migraine*, and is the less common of the two major subtypes.

The aura is a set of focal, fully reversible, neurologic symptoms that develop gradually, over the course of 5 to 20 minutes, and persist no longer than 60 minutes. In order of frequency, the most common types of aura are visual, sensory, and speech disturbances. These symptoms typically, but not always, follow one another in the order given. Visual symptoms may be positive (flickering lights, spots, lines) or negative (vision loss). Sensory disturbances also may be positive (unilateral sensation of pins and needles, moving slowly away from a point of origin) or negative (numbness). Numbness sometimes follows the positive symptoms, but it may be the only symptom. Speech disturbances usually are dysphasic. The aura usually is followed by a headache with symptoms typical of migraine without aura, the more common migraine subtype (Headache 2004).

For either subtype, characteristics of the headache are unilateral location, a pulsating quality, pain of moderate or severe intensity, and aggravation either from participation in or avoidance of routine physical activity; 2 of these 4 characteristics are required for a diagnosis. In addition, during the headache, the patient may experience nausea, vomiting, or both, or extreme sensitivity to light (photophobia) and sound (phonophobia). Left untreated or treated inadequately, the symptoms last for 4 to 72 hours (Headache 2004). Because migraine without aura can be confused with an infrequent episodic tension-type headache, the IHS requires at least five attacks with the preceding characteristics to make a diagnosis of migraine without aura. For a diagnosis of migraine with aura, only two attacks are required.

Menstrual migraine

In women, migraine without aura often has a strong association with the menses. The IHS now delineates two types of menstrual migraine: *Pure menstrual migraine*

and *menstrually related migraine* (Headache 2004). Recognizing uncertainty over whether these types of migraine are distinct entities, the Society has placed them in the appendix to the second edition of its *International Classification of Headache Disorders* (ICHD-II) (Headache 2004).

To be diagnosed with pure menstrual migraine without aura per ICHD-II, a menstruating woman must meet the previously described criteria for migraine without aura and her attacks must be perimenstrual, occurring within 2 days before or after the first day of menstruation during 2 of 3 menstrual cycles and at no other time of the cycle. The ICHD-II diagnostic criteria are identical for menstrually related migraine without aura, except that attacks also may occur at other times during the cycle (Headache 2004).

Reviews of various studies, some of which used slightly different definitions and populations, suggest a prevalence of pure menstrual migraine between 3 and 14 percent, while reporting a much higher prevalence of menstrually related migraine, ranging from 34 to 68 percent (Brandes 2006, Dzoljic 2002). With the understanding that their timing often makes menstrual migraine attacks predictable, and that they can be longer in duration and severity than nonmenstrually related migraines attacks (Brandes 2006), prevention may be an important component of care.

Etiology

Numerous physiological mechanisms underlying menstrual migraine have been proposed, including estrogen withdrawal, magnesium deficiency, and alterations in neurotransmitter systems. It also has been postulated that fluctuations in hormone levels modulate various neurotransmitter systems, such as those involving serotonin (5-hydroxytryptamine, or 5-HT), noradrenaline, glutamic acid, GABA, or endogenous opiates (Martin 2006a).

Levels of serum estrogen and progesterone fluctuate widely during the menstrual cycle. Serum estradiol levels peak toward the end of the follicular (proliferative/preovulatory) phase and again in the middle of the luteal (secretory) phase, while serum progesterone peaks in the mid-luteal phase. Just prior to menstruation, serum levels of estrogen and progesterone fall precipitously (Martin 2006b). The cessation of hormone fluctuation during pregnancy may explain why migraine often improves or disappears in pregnant women (Granella 1993). In female migraineurs who do not become pregnant, migraine is more likely to occur during the late luteal and early follicular phase of the cycle when estrogen levels are rising

Managed Care Considerations:
Improving the Treatment of Menstrual Migraine

Migraine headaches and migraine syndromes account for considerable health care resource utilization within commercial health plans. This utilization encompasses ambulatory office visits, urgent care and emergency department services, specialist referrals, diagnostic imaging, and medications (Pesa 2004).

Recent research has elucidated a better understanding of the pathophysiology of migraine headaches and its symptoms. Additionally, studies have determined some of the triggering events that result in migraine.

Menstruation is one of the most significant physiologic factors that may trigger migraine. As many as 60 percent of female migraineurs experience migraine associated with the menstrual cycle. Within the spectrum of menstrual migraine, two variants have been determined — pure menstrual migraine and menstrually related migraine. The distinction between these two entities relates to the timing of the migraine. Pure menstrual migraine occurs 2 days before or after the onset of menses during 2 of 3 menstrual cycles, and at no other time within the cycle. This suggests a predictable nature of menstrual migraine and the potential for managing this phenomenon in a subset of migraine patients.

For medical directors, awareness of the evolving scientific understanding of migraine can help with cost-effective management of migraine headache and its subtypes. Programs that educate physicians, migraineurs, and employers about interventions that may reduce the likelihood of menstrual migraine, and the potential for lost productivity that can result from it, may be worthy of implementation.

Strategies to prevent menstrual migraine will be discussed in subsequent CLINICAL BRIEFS. This information will be of value to medical directors, clinical managers within health plans, pharmacy benefits managers, and provider organizations seeking improved care of members with menstrual migraine, and to employers striving to maintain a productive workforce.

Reference

Pesa J, Lage MJ. The medical costs of migraine and comorbid anxiety and depression. *Headache*. 2004;44:562–570.

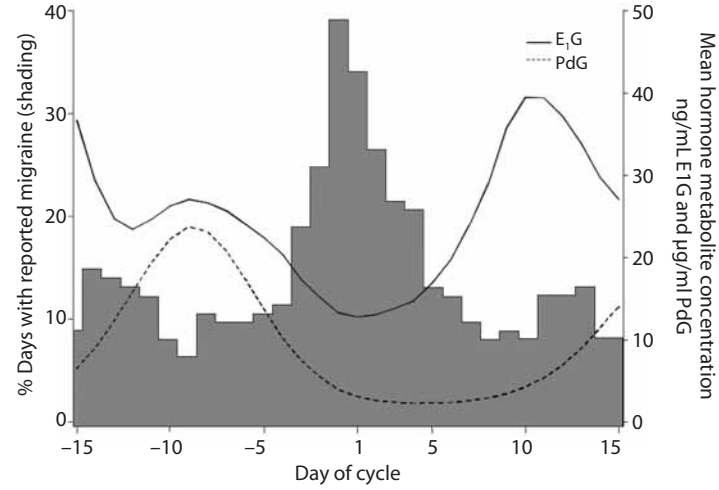
(Figure 2), rather than when estrogen levels are falling (MacGregor 2006).

The chief effects of estrogen appear to be inhibition of the sympathetic nervous system and facilitation of glutamergic and serotonergic systems, while progesterone seems to activate GABAergic systems and modulate the central nervous system effects of estrogen (Martin 2006a). It has been suggested that menstrual migraine may be triggered if estradiol serum levels fall below 45 to 50 pg/mL during the perimenstrual period (Martin 2006b). Clinical evidence supporting this theory comes from a study showing that a 100-mcg estradiol patch applied perimenstrually was effective in preventing menstrual migraine, but a 50-mcg patch was not, presumably because only the former maintained serum estradiol in the range of 45 to 75 pg/mL (Martin 2006b).

Given the demonstrated efficacy of 5-$HT_{1B/1D}$ agonists (triptans) in the abortive treatment of menstrual migraine, the complex relationship between serotonin and estrogen is of particular interest. Serotonin is widely distributed throughout the body, acting not only as a neurotransmitter but also as a hormone. Its effects, including vasoconstriction, are mediated through at least 14 different 5-HT receptor subtypes. Increases in estrogen levels heighten serotonin levels in two ways: By increasing production of an enzyme responsible for synthesizing 5-hydroxytryptophan from tryptophan, and by suppressing activity of the serotonin reuptake transporter (SERT) through suppression of the SERT gene and antagonizing the SERT itself (Rybaczyk 2005). In addition, a rise in estrogen levels upregulates the estrogen-ß receptor (ERß), which in turn upregulates the 5-HT_{2A} receptors. At the same time, increased estrogen downregulates the estrogen-α receptor (ERα), leading to a decrease in 5-HT_{1A} receptors. Increased serotonin concentrations resulting from estrogen exposure also enhance activation of the $5HT_{1B}$ receptors. Found in abundance on vascular endothelium and vascular smooth muscle, the 5-HT_{1B} receptor mediates contraction of vascular smooth muscle (Tepper 2002). The 5-HT_{1D} receptors are found in trigeminal nerves that project to the dural vasculature, where they inhibit release of vasoactive neuropeptides, and in trigeminal nuclei in the brainstem, where they disrupt vascular pain signals.

FIGURE 2

Menstrual migraine in relation to urinary metabolites of estrogen and progesterone



The incidence of migraine plotted against levels of urinary metabolites of estradiol (estrone-3-glucuronide, E1G) and progesterone (pregnanediol-3-glucuronide, PdG) on each day of the menstrual cycle in 120 cycles from 38 women with menstrual migraine.

SOURCE: MACGREGOR 2006. USED WITH PERMISSION.

Conclusion

Menstrual migraine has been demonstrated to be a unique clinical entity. Its etiology suggests predictability that may lend itself to a distinct approach for its management.

This publication has been independently peer reviewed by a member of the editorial board of MANAGED CARE.

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