Menstrual Migraine-A Mini Review

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Abstract

Menstrual Migraine (MM) without aura is defined as the exclusive occurrence of attacks on day -2 to +3 of menses in at least 2 of 3 consecutive menstrual cycles while menstrual related migraine (MRM) without aura is also characterized by the occurrence of attacks on other days of the cycle. Over 90% of women with migraine attacks during menstruation have MRM. These conditions occur due to fluctuations of estrogen levels.

Acute treatment used includes triptans, nonsteroidal anti-inflammatory agents and ergot derivatives, which are same as for no menstrual migraine. Short term prophylactic therapies are given only at times of need like nonmenstrual migraine, e.g triptans, oestrogen and naproxen while continuous prophylaxis options like oral contraceptives provide ongoing exposure to treatment. Clinical studies of triptans represent the biggest evidence up to date of acute and preventive MM and MRM treatment, supporting almotriptan, sumatriptan, naratriptan and zolmitriptan as acute therapies and frovatriptan, naratriptan and zolmitriptan as preventive therapies. Yet there are adverse effects of triptans and dangers of over use and MM is a little recalcitrant to effects of these drugs.

Novel noninvasive methods like noninvasive vagal stimulation seem to have proven effective as prophylactic therapy.

Keywords: MM; MRM; triptans; sumatriptan; frovatriptan; naproxen; oestrogen; vagal stimulation
Introduction

Menstrual migraine (MM) without aura is defined as the exclusive occurrence of attack on day-2 to+3 of consecutive menstrual cycles according to the International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-III beta) appendix (i.e. requires further validation) and menstrual related migraine (MRM) without aura is also characterized by the occurrence of attacks on other days of the cycle [1]. Greater than 90% of women with migraine attacks during menstruation have MRM [2], the estimated prevalence among migraneurs has varied from 0.85-14.1% for MM and from 3 to 71.4% for MRM [3]. These migraine headaches have a peak incidence of first occurrence at age 15-19, they are most prevalent in women in their late 30’s to early 40’s and are rare after menopause [4, 5]. An observation with menses is observed by 60% of women with migraine headaches. In 7-14% of women with migraine, headache occurs exclusively with menses. Because menstrual migraine improves in pregnancy in two thirds of migraneurs, this type of migraine seems to be due to falling levels of oestrogen and progesterone, which trigger a host of responses such as release of prostaglandins and changes in neurotransmitters [6, 7].

Vascular Headaches

Acute and throbbing headaches are due to abnormal vasodilation. The vasodilation associated with migraine headaches is believed to follow a period of vasoconstriction. Migraine headaches are usually but not always preceded by prodromal symptoms (which may reflect the period of vasoconstriction). Significant vascular headaches can be precipitated by stress, alcohol, or tyramine or tryptophan rich foods (red wine, chocolate, ripe cheese). Vascular headaches can accompany other problems, such as systemic viral infections, fever or hypertension. Common migraine headaches are now known as migraine without aura’’ [4]. Classic migraine is referred to as migraine with aura’’ (visual complaints, nausea or vomiting, paresthesias). Migraine headaches associated with menstruation are typically migraine without aura’’ [5].

Tension Headaches

The common tension headache is due to prolonged excessive muscle contraction. The pain is dull, steady, and bilateral and worsens throughout the day. The headache frequently occurs with worry or emotional stress and commonly last for hours or a couple of days, however every day hassles are a more important factor in the pathogenesis of tension headaches than major stressful events.

Secondary Headaches

Secondary headaches are due to underlying organic disease. Headaches associated with brain tumors are usually accompanied by neurologic abnormalities.
**Evaluation**

The acute onset of severe headache pain deserves attention. The following signs suggest the presence of a serious problem: neck stiffness, altered mental status, focal neurological abnormalities, visual impairment and fever. Any patient with meningeal signs requires hospitalization. Keep carbon monoxide exposure and drug withdrawal in mind as etiologic agents. Chronic headaches should be characterized according to location, quality and course over time. Head trauma in the immediate past is an important piece of information, raising the suspicion of a subdural hematoma, when the headache is cyclic, with periodic complete resolution, one can comfortably ascribe the headaches to a vascular origin. Tension headaches are either variable or relatively constant without relentless progression. Any recurrence or chronic headache that gets worse with time deserves a neurologic evaluation.

**Management**

Menstrual related migraine are more refractory to the battery of therapy used by neurologists although oral and s/c sumatriptan has been effective [4, 5, 8]. The nonsteroidal anti-inflammatory agents are also effective, particularly when headaches are associated with dysmenorrhea.

Early studies of menstrual migraine indicated that administration of estradiol (E2) could delay the onset of migraine even if menses were not delayed [9]. Progesterone (Pg.) administration delayed menses but not the onset of headaches. Others have claimed effective treatment of menstrual migraine with maintenance of Og levels, there is reason to believe that a relatively high Og levels is necessary, e.g the use of 100μg transdermal patch [10, 11]. Still others have reported success with tamoxifen or danazol treatment. The field suffers from a lack of well designed, double blind, placebo controlled studies and one must make judgment based on experience.

Headaches have been seen to be alleviated by eliminating the menstrual cycle, or the use of daily oral contraceptives (not the progestin only minipill), the daily administration of a progestational agent, e.g 10mg medroxy progesterone acetate, or the use of depot medroxy progesterone acetate. Some menstrual migraines have extremely gratifying response.

If menstrual headaches are a reaction to cyclic changes in circulating levels of sex steroids, it makes sense to avoid cyclicality and maintain a relatively steady state with daily administration of exogenous hormones. A more expensive approach but one with documented success is the utilization of a long acting GnRH agonist combined with Og-Pg add back therapy [12]. Another option is to use an estrogen transdermal application during the menstrual time period.

The elimination of cyclicity can be applied to post-menopausal women who experience exacerbation or onset of headaches on a sequential hormone regimen. The maintenance of daily, relatively constant hormone levels with the daily continuous program of combined Og-Pg Has been effective.

The run of the mill headache treated with mild analgesic such as aspirin, acetaminophen, and the non-steroidal anti-inflammatory agents. A problem of severe headaches on oral contraceptives requires an immediate response. The conservative reaction is to discontinue oral contraceptives. On the other hand the headache can be due to stress or some
other reversible condition. One would argue that automatic discontinuation of oral contraception is not necessary with the low dose preparation. It would be better to evaluate the patient and find out if the patient can continue her contraceptive protection, by discovering the explanation for the headache. Case control studies with the old high dose O’C’s indicated that migraine headaches were linked to a risk of stroke. Strokes are essentially no longer seen with low dose OC’s. This probably reflects both lower doses as well as the reluctance of clinicians to prescribe oral contraception to women with severe headaches. True severe vascular headaches (migraine with aura) represents a contraindication for the use of combined OC’s and their appearance is an indication to discontinue OC. The symptom complex that’s deserves serious consideration includes headaches that last a long time, dizziness, nausea or vomiting with headache, scotoma or blurred vision; episodes of blindness; unilateral, unremitable and headaches that continue despite medications.

Concerns over headaches with O.C’s should be limited to the use of combined OC’s. The progestin only methods are not associated with problems with headaches. Therefore the sustained release Pg only methods are also free of headache concerns.

Prophylaxis

These conditions are believed to be a result of fluctuating oestrogen levels; steady state or elevating levels are associated with a protective effect whereas abrupt oestrogen withdrawal are associated with precipitation of migraine attacks [2,13]. In the late luteal phase of the menstrual cycle, decreased oestrogen levels have been observed to lead to serotonin decline and are likely responsible for the triggering of MM/MRM attacks just prior to menses [2,13]. No acute or prophylactic therapies are currently approved specifically for the treatment of MM/MRM in the European Union or the United States [14, 15]. Acute treatment used for these conditions are the same as those used for non-menstrual migraine and include triptans, nonsteroidal inflammatory drugs (NSAIDS) and ergot derivatives [2, 15]. Prophylaxis comprises short term and continuous treatment [2]. Short term prophylactic therapies are administered only during the time of need (e.g perimenstrually) which includes triptans, oestrogenand naproxen while continuous prophylactic options like hormonal contraception provide ongoing exposure to the treatment [2]. In a systematic review of MM/MRM clinical trials it was shown that there was weak evidence supporting most categories of prophylactic MM/MRM treatments [15]. The strongest evidenceuptodate for acute and preventive MM/MRM treatment comes from clinical studies of triptans, which supports almotriptan, naratriptan, sumatriptan and zolmitriptan as acute therapies and fuvatriptan, naratriptan and zolmitriptanas preventive therapies [15]. Although triptans are generally safe and tolerable, with appropriate patient selection [2, 16, 17] the MM/MRM population may have unique challenges related to the adverse events associated with these treatments. As compared with nonmenstrual migraine attacks, MM/MRM attacks are generally longer lasting, more debilitating and more prone to recurrence and less responsive to therapies such as triptans [18, 19]. Results from a large study demonstrated that 44 % and 48 % of migraines were dissatisfied with triptan associated tolerability and general work related functional ability respectively [16] and these concerns maybe even more prominent in the relatively treatment refractory MM/MRM population [19]. Menses is generally considered to be period of inherent discomfort [20] and the repeated treatment required to mitigate the effect of MM/MRM could further exacerbate the levels of discomfort while providing early minimal response [19, 21]. Evidence based guidelines for migraine suggest limiting the use of
triptans to 2 headache days per week to decrease the risk of rebound or medication overuse headache [17] and frequent use of these agents may lead to misuse/overuse and has been significantly associated with the development of chronic migraine [22,23]. Thus the prophylactic administration of triptans over the course by several days during menstruation coupled with the potential need for acute triptan therapy in women with MM/MRM could complicate the condition [21, 22]. Patients may be unwilling to accept the side effects burden and/or potential complication of sticking to the monthly prophylactic MM/MRM therapies [24], defining a need for alternative options among this population.

Noninvasive vagus nerve (nVNS) (gamma core; electrocere, LLC, Basking Ridge; NI, USA) provides neuromodulator that transfers electrical impulses transcutaneous to the cervical branch of the vagus nerve. In 4 open label 12 week studies, nVNS demonstrated efficacy, safety and tolerability as an acute prophylactic therapy for migraine and cluster headaches [25-28]. Thus Grazzi et al based on treatment benefits observed in previous studies and the potential for reducing medication overdose and medication associated AE’s [25]. Evaluated nVNS used as mini prophylaxis for MM/MRM in a 24wk study in 56subjects.56enrolling subjects (MM 9 %, MRM 91 %, 33(59 %) of who were receiving other prophylactic therapies entered a 12wk baseline period.51subjects subsequently entered a 12 wk treatment period to receive open label prophylactic noninvasive vagus nerve stimulation adjunctively (3/51;61 %) or as monotherapy20/51, 39 % on day 3after the end of menses. The number of MM/MRM days/mth was significantly reduced for baseline (mean+_standarderror,7.2+-0.7days) to the end of treatment (mean+standard error 4.7+-0.5 days p<0.001) (primary end point) of all subjects, 39 % (95 % confidence interval: 26 % 54 % (20/51) had a >=50 % reduction (secondary end point). For the other 2 end points clinically meaningful reductions in analgesic use (mean change+-standard error-3.1+0.7 p<0.001) and migraine disability assessment score (mean change +std error11.0+-3.4; p<0.001were observed along with a modest reduction in pain intensity mean change+-stderrror-5+-0.2. There was no safety, tolerability concerns. Thus they concluded that noninvasive vagus nerve stimulation is an effective treatment that decreases the number of MM/MRM days and analgesic use without safety /tolerability concerns in subjects with MM/MRM.RCT are warranted. [29grazzi2016].
References


