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Menstrual migraine

Abstract An association between migraine and menstruation can be ascertained by use of a diary for a minimum of three cycles. The pathophysiological and clinical peculiarities of menstrual migraine indicate that its management should differ from that of non-menstrual migraine. NSAIDs or migraine-specific medications (e.g. triptans) are often effective for the acute management of menstrual migraine. Preventive treatment is indicated when the attacks are long-lasting, severe and disabling and do not respond to acute treatments. Short-term prophylaxis (at the time of headache vulnerability) employs standard drugs such as magnesium, ergotamine or

NSAIDs; triptans are currently being evaluated for short-term prophylaxis. If severe menstrual migraine attacks cannot be controlled by these, hormone therapy (percutaneous or transdermal estrogen) may be indicated. Antiestrogen agents (danazol, tamoxifen) are indicated only in rare resistant cases.

Key words Menstruation • Migraine • Therapy • Sex hormones

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Introduction

Migraine is more common in women than in men and there is much evidence indicating a link between migraine and female sex hormones [1]. Thus, migraine affects children in a sex ratio of 1:1 which rises to 3–4:1 in favour of women after puberty. Migraine begins at menarche in 33% of affected women and improves during pregnancy, while hormone replacement can exacerbate the condition [2].

The 1988 International Headache Society (IHS) classification did not recognise menstrual migraine as a distinct category. Various definitions of menstrual migraine are used in the literature and this probably explains the enormous varia-

tion in its reported prevalence (4%–73%) [3]. Recently Mac Gregor [3, 4] proposed that true menstrual migraine (TMM) should be defined as “migraine attacks that regularly occur on or between day 1 ± 2 days of the menstrual cycle and at no other time.” By contrast menstrually related migraine (MM) should be defined as “migraine attacks which occur throughout the cycle but which regularly increase in frequency on or between day 1 ± 2 days of the menstrual cycle.” In Mac Gregor et al.'s study [5], which employed prospective diary cards, 7.2% of female migraineurs had TMM, while 34.6% had MM; in some women the attacks occurred at each menstruation, whereas in others they occurred only in some cycles. Apparently all women who suffer from TMM and MM have migraine without aura [6, 7].

Pathophysiology of menstrual migraine

The menstrual cycle is the result of a complex interplay of positive and negative feedback systems involving the hypothalamus, pituitary gland, ovary and uterus [1]. The hypothalamus and pituitary are the main sites responsible for regulation of the cycle, while sex hormones act directly on the anterior pituitary and the hypothalamus [8]. An alteration in the hypothalamic-pituitary-ovarian axis is suspected to be involved in the pathophysiology of menstrual migraine. The condition may be related to the estrogen withdrawal that occurs immediately before menstruation and following several days of high estrogen levels [9]. Serotonin receptors are modulated by estrogen and progesterone, but why the abrupt decrease should trigger migraine attacks remains obscure. Prostaglandins have also been implicated in the pathophysiology of menstrual migraine: estrogen withdrawal increases the secretion of prostaglandins in the uterine endometrium from the follicular to the luteal phase with maximal release during the first 1–2 days of menstruation [10].

Acute treatment of menstrual migraine

The types of drugs used for the acute treatment of menstrual migraine are the same as those used for non-menstrual migraine: analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), ergot derivatives and triptans. These can control the pain and the associated symptoms, however clinical experience suggests that menstrual attacks are more resistant to therapy, last longer and are more severe than other migraine attacks (although no studies are available to support this). Perhaps the reason for is the longer duration of the “menstrual” trigger [4].

No studies have specifically investigated the efficacy of analgesics and NSAIDs in menstrual migraine [11]. However parenteral administration of the non-selective 5-HT₁ agonist dihydroergotamine (DHE) was significantly more effective than placebo for this condition [11]. Sumatriptan [12], zolmitriptan [13], rizatriptan [14] and naratriptan [15] have also been shown effective for aborting attacks of menstrual migraine, and also for relieving the associated nausea and vomiting.

Preventive treatment

Preventive treatment is indicated when the attacks are long-lasting, severe and disabling and do not respond to acute treatments. However, before using these more powerful medications, the association between migraine and menstru-

ation should be confirmed with a headache diary kept for at least three months. Women who have migraine exclusively with menstruation can be treated by the perimenstrual use of prophylactics [4]; those already using prophylactic medication for non-menstrual migraine can increase the dose prior to menstruation [16]. Several standard drugs given perimenstrually have been assessed for short-term prophylaxis including magnesium (360 mg magnesium pyrrolidone carboxylic acid) [17], sumatriptan (25 mg tid) [18], and naratriptan [19]. However these drugs require further assessment in comparative trials involving larger series of patients. The utility of naratriptan in the prophylaxis of menstrual migraine is being assessed in an ongoing Italian multicentric open study on patients with TMM of a least one year's duration and confirmed with a headache diary kept for three months pretreatment. Treatment consists of naratriptan taken perimenstrually for the three successive cycles.

Ergotamine tartrate, ergonovine maleate and DHE (the latter as spray nasal) can be used prophylactically at the time of menses without significant risk of developing ergot dependence [16]. NSAIDs (mefenamic acid, naproxen sodium or fenoprofen) can be used, in adequate doses as prostaglandin inhibitors, 1–2 days before the expected onset of headache and continued for the duration of vulnerability, particularly in the presence of dysmenorrhoea or menorrhagia [4]. If the first used NSAID fails, a different NSAID is worth trying.

If severe MM cannot be controlled with these measures, hormone therapy may be indicated. Progesterone had been found ineffective [16]. Because estrogen withdrawal seems to be the trigger of menstrual migraine, peri-menstrual (days -4 to +4) estrogen replacement is a logical approach. The best results have been obtained by de Lignieres et al. [20] with percutaneous estradiol gel (1.5 mg estradiol in 2.5 g gel) in women with regular menstrual cycles. The most practical way of administering estrogen is by means of transdermal patches. In the transdermal therapeutic system (TTS), three dosages of estradiol are available: TTS 25 (25 µg/24 h), TTS 50 (50 µg/24 h) and TTS 100 (100 µg/24 h). Serum estrogen levels have been found proportional to the dose. TTS 100 was superior to TTS 25 in one open trial [21] while the TTS 50 dose was not superior to placebo in two double-blind trials [22].

Other hormonal therapies have been tried with improvement of MM [4, 16]. These include: danazol, a synthetic androgen (200–600 mg/day from the third to the 28th day of the cycle); tamoxifen, an anti-estrogen (10–20 mg/day before menstruation and 5–10 mg/day for the three days starting from menstruation); bromocriptine, a dopamine agonist (2.5–7.5 mg/day during the luteal phase of the menstrual cycle); and gonadotropin-releasing hormone which causes medical ovariectomy so that treatment must be limited to six months. All these therapies can be associated with serious side effects as they profoundly alter the physiology of the menstrual cycle; they should therefore be reserved for

resistant cases. The benefits versus risks of these hormonal treatments have not been established.

Conclusions

Acute therapy is the mainstay of treatment for most women with MM. Prophylaxis is required rarely. A rational sequential therapeutic approach should be adopted.

We suggest the following: (i) acute treatment (triptans, other selective 5-HT₁ agonists, or NSAIDs); (ii) if severe MM is not controlled by these medications, intermittent prophylaxis with ergot derivatives, NSAIDs or magnesium should be tried especially when the attacks are associated with irregular menses or menorrhagia/dysmenorrhoea; (iii) estrogen supplements for severe MM with regular menses; and (iv) anti-estrogen agents only for severe resistant cases.

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