Are Menstrual and Nonmenstrual Migraine Attacks Different?

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Abstract Migraine is the second most common headache condition next to tension-type headache. Up to one fourth of all women have migraine, and 20% of them experience migraine without aura attack in at least two thirds of their menstrual cycles. The current literature is analyzed in response to the question of whether menstrual and non-menstrual migraine attacks are different. The different studies provide conflicting results, so it is not possible to answer the question firmly. Future studies should be based on the general population. Collection of both prospective and retrospective data is warranted, and headache diagnosis base on interviews by physicians with interest in headache are more precise than lay interviews or questionnaires.

Keywords Menstrual migraine · Symptomatology · Disability and treatment · Perimenstrual headache · Nonmenstrual migraine · Attacks · Rizatriptan · Almotriptan

Introduction

The appendix of the second edition of the International Classification of Headache Disorders (ICHD-2) from 2004 describes two types of migraine without aura (MO) related to menstruation: pure menstrual migraine (PMM) and menstrually related migraine (MRM) [1]. Those with PMM have MO attacks exclusively in relation to at least two thirds of their menstrual periods, while those with MRM additionally experience MO attacks outside the menstrual period. Before the ICHD-2 classification, researchers had no specific guidelines for the definition of menstrual migraine. The first classification of the International Headache Society from 1988 did not classify menstrual migraine as a specific type of headache, but had a comment in relation to MO: “Migraine without aura may occur almost exclusively at a particular time of the menstrual cycle—so-called menstrual migraine. Generally accepted criteria for this entity are not available. It seems reasonable to demand that 90% of attacks should occur between 2 days before menses and the last day of menses, but further epidemiological knowledge is needed” [2]. The latter definition encompasses only a few of those with MRM. A recent epidemiological survey suggests that 21% of women with migraine have menstrual migraine, and about two thirds have MRM [3]. These circumstances make the literature on menstrual migraine heterogenous, which one should bear in mind in the current analysis of symptomatology of menstrual and nonmenstrual migraine attacks. To complicate matters, what about migraine with aura (MA)? About one third of all migraineurs have MA [4]. An epidemiological survey implies that headache in attacks of MO may be slightly more severe than headache in attacks of MA [5], but it seems that MA is not associated with menstruation on the same scale as MO. In fact, MA may be unrelated to menstruation [6].

The most precise information on migraine attacks is ascertained from prospective recording (ie, headache diaries with detailed information about pain characteristics, accompanying symptoms, duration, and treatment). Such data may not be generalizable because keeping a headache diary for a longer period is not applicable for a large population.
due to low compliance. In contrast, retrospective data from large population-based studies may be generalizable, but the detailed information about migraine attacks is subject to memory bias. Thus, a combination of prospective and retrospective data is likely to give the most precise description of the migraine attacks.

This review analyzes the literature to enlighten whether menstrual and nonmenstrual migraine attacks are different, given the methodological challenges mentioned above.

Menstrual Versus Nonmenstrual Migraine Attacks

Attack Frequency

A Danish epidemiological survey based on 18– to 65-year-old people from the general population, including a direct clinical interview and a physical and neurological examination by a physician, found that less than 10% of women with MO had more than one MO attack per month [5].

Thus, the vast majority (ie, ≥90%) of all women with migraine have 1 or fewer MO attacks per month. Some of those with PMM will have 1 MO attack per month, while most patients with MRM have more than 1 MO attack per month. Thus, the MO attack frequency is much higher in most women with PMM or MRM than in those with nonmenstrual MO. Although this does not address whether menstrual and nonmenstrual MO attacks are different, it indicates that those with menstrual MO are likely to have a higher disease burden than most women with nonmenstrual MO.

Attack Severity

Pain Characteristics

Table 1 shows attack characteristics of menstrual migraine in relation to nonmenstrual migraine. Two studies from the general population suggest that the pain intensity is higher in menstrual than nonmenstrual MO [7, 8]. Studies on clinic populations provide conflicting results; four studies are in support of the findings in the general population, while four studies suggest similar pain intensity and one study missed information on pain intensity [9–15, 16•, 17•].

Associated Symptoms

The study based on prospective filled-in diaries from the general population suggests no significant difference in associated symptoms in attacks of menstrual and nonmenstrual migraine [7]. This is supported by three studies based on clinic populations [10, 15, 16•]. However, two clinic studies based on prospective filled-in diaries suggest that menstrual migraine attacks are accompanied by more nausea and vomiting than nonmenstrual attacks [11, 14].

Duration

The study based on prospective filled-in diaries from the general population suggests that attacks of menstrual and nonmenstrual migraine have similar duration [7]. In contrast, all the other studies suggest that attacks of menstrual migraine are longer than attacks of nonmenstrual migraine, including data based on prospective filled-in diaries [8, 10, 16•, 17•].

Disability

The study based on prospective filled-in diaries from the general population and one clinic study suggest that attacks of menstrual and nonmenstrual migraine have similar disability [7, 15]. In contrast, all the other studies suggest that attacks of menstrual migraine are more disabling than attacks of nonmenstrual migraine, including data based on prospective filled-in diaries [8, 10, 12, 13, 16•, 17•].

Treatment

Two clinical trials on rizatriptan and almotriptan suggest equal efficacy on pain relief 2 h post-treatment of menstrual and nonmenstrual migraine attacks [9, 15]. Other studies suggest that attacks of menstrual migraine are more treatment resistant than attacks of nonmenstrual migraine [8, 10, 16•] or that menstrual migraine attacks are more likely to relapse [17•].

Conclusions

The question whether menstrual and nonmenstrual migraine attacks are different unfortunately cannot be answered unambiguously because previous studies provide conflicting results. This is mainly due to different patient populations, unequal definitions of menstrual migraine, and different methods employed.

Future studies should focus on the general population to provide generalizable data, in contrast to possibly skewed data from selected clinic populations. Prospective recordings should be employed, combined with retrospective data on the headache history. To provide precise headache diagnoses, interviews by a trained physician or neurologist with special interest in headache is the gold standard. Such a study is likely to more firmly answer whether menstrual and nonmenstrual migraine attacks are different.
Table 1  Attack characteristics of menstrual migraine in relation to nonmenstrual migraine

| Study                  | Population | Country, Year | Design                                                                 | Pain intensity                                                                 | Associated symptoms                                      | Duration | Disability | Treatment                                      |
|------------------------|------------|---------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------|----------|------------|------------------------------------------------|
| Stewart et al. [7]     | General    | USA, 2000     | 81 women filled in diary for 98 days                                  | Slightly higher pain intensity during the first 2 days of menstruation         | No difference                                             | Similar duration | Equally disabling | NR                                             |
| Couturier et al. [8]   | General    | The Netherlands, 2002 | 1,181 women (13-55 y) replied on a questionnaire                     | More painful                                                                    | NR                                                      | Longer duration | More disabling | More treatment resistant |
| Silberstein et al. [9] | Clinic     | USA, 2002     | 95 women                                                             | Similar pain intensity                                                          | NR                                                      | NR       | NR         | Rizatriptan gave equal pain relief (78%) after 2 h |
| Granella et al. [10]   | Clinic     | Italy, 2004   | 64 women filled in diary for 2 months                                | Similar pain intensity                                                          | No difference                                             | Significantly longer duration, more frequent status migrainous | Significant higher work-related disability | More treatment resistant (lower 2-hour pain-free response, lower sustained pain-free response, higher recurrence) |
| MacGregor et al. [11]  | Clinic     | UK, 2004      | 155 women (15–58 y) filled in diary                                  | More painful                                                                    | More nausea and vomiting                                  | NR       | NR         | NR                                             |
| Martin et al. [12]     | Clinic     | USA, 2005     | 21 women filled in diary for 3 menstrual cycles                      | Significant higher headache index during menstruation                           | NR                                                      | NR       | Higher disability index                     | NR                                             |
| Dowson et al. [13]     | Clinic     | UK, 2005      | 30 women from general practices filled in a questionnaire           | NR                                                                              | NR                                                      | NR       | Significant more time with <50% productivity | NR                                             |
| MacGregor et al. [14]  | Clinic     | UK, 2006      | 38 women (29–50 y) filled in a diary                                 | More painful                                                                    | More nausea and vomiting                                  | NR       | NR         | NR                                             |
| Diamond et al. [15]    | Clinic     | USA, 2008     | 190 women in a multicenter, double-blind, parallel-group trial (post hoc analysis) | Similar pretreatment pain intensity                                             | No difference                                             | NR       | Similar pretreatment disability            | Almogran gave similar pain relief after 2 h, pain-free response after 2 h, and sustained pain-free |
| Pinkerman et al. [16]  | Clinic     | USA, 2010     | 107 women not receiving migraine prophylaxis filled in a diary       | More painful                                                                    | No difference                                             | Longer duration higher recurrence within 24 h. Attacks >72 h were twice as frequent | More disabling | Less pain-free response at 2 h; higher recurrence within 24 h; used more doses of triptans per migraine attack and rescue medication required more often |
| MacGregor et al. [17]  | Clinic     | USA, 2010     | 153 women (>18 y) in a 2-month multicenter, open-label study (post hoc analysis) | Similar pain intensity                                                          | NR                                                      | Longer duration | Higher functional impairment | More likely to relapse |

NR not reported
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