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Genetics of Menstrual Migraine: The Epidemiological Evidence

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Abstract Approximately one of every three to five women with migraine without aura experience migraine attacks in relation to menstruation. The International Classification of Headache Disorders, 2nd Edition provides appendix diagnoses for pure and menstrually related migraine without aura that need further validation. Probands with menstrual migraine might have more affected relatives than probands with nonmenstrual migraine. However, precise epidemiological, family, and twin data still are lacking.

Keywords Menstrual migraine · Epidemiology · Genetics

Introduction

The definition of menstrual migraine varied before the introduction of the International Headache Society's (IHS) Classification and Diagnostic Criteria for Headache Disorders and Facial Pain in 1988 [1]. The IHS classification did not classify menstrual migraine as a specific type of headache, but had a comment in relation to migraine without aura: "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" [1]. The revision of the IHS classification, the International Classification of Headache Disorders, 2nd Edition (ICDH-II) from 2004, does not include menstrual migraine within the main body of the classification [2]. However, it provides diagnostic criteria for pure menstrual migraine without aura and menstrually-related migraine without aura in the appendix. Pure menstrual migraine without aura is defined as migraine without aura that occurs exclusively on day 1 of menstruation ±2 days in at least two out of three menstrual cycles. Menstrually related migraine without aura additionally has attacks of migraine without aura in the nonmenstrual period. Further scientific evidence is needed before these terms can be part of future headache classifications.

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Relation to Female Hormones

Some elegant studies from the early 1970s showed that changes in estrogen levels could precipitate an attack of migraine [3–6]. A population-based survey on migraine with physician-conducted interviews found that menstrual migraine occurred especially in females with similar age at onset of migraine without aura and menarche, while this association was not present in migraine with aura. Attacks in relation to ovulation could not be demonstrated in migraine either with or without aura [7]. This may be because the peak of estrogen at ovulation is of short duration and the fall of serum estrogen must be preceded by several days of exposure to high levels of estrogens to precipitate the attack [5]. Both migraine without aura and migraine with aura improve during pregnancy [7–11]. The results suggest that female hormones are important as a

precipitating factor in migraine without aura, but less so in migraine with aura.

Epidemiology

The prevalence of migraine before puberty is equal in boys and girls [12]. After menarche and during women's reproductive years, the gender ratio shows a two- to threefold preponderance of women, because the prevalence of migraine without aura increases much more in women than men [13, 14]. More than 50% of women with migraine report an association between menstruation and migraine [15, 16]. Table 1 shows the prevalence of pure menstrual migraine without aura and menstrually related migraine without aura. The prevalence varies due to different diagnostic criteria and methodology. The prevalence of pure menstrual migraine without aura varies between 7% and 14% among female migraineurs, while the prevalence of menstrually related migraine without aura varies from 10% to 71% among female migraineurs. Approximately one of every three to five female migraineurs has attacks of migraine without aura in relation to menstruation.

Positive Family History

Transmission of migraine from parents to children was reported as early as the 17th century [17]. Since then, numerous studies have reported a positive family history of migraine [18]. A positive family history is imprecise because it does not specify number of affected family members, family size, or relation to the proband. The lifetime prevalence of migraine is 16%–21% in the general population [10, 13, 14]. This causes a positive family history simply by chance in over 80% of probands with six first-degree relatives (parents, siblings, and children), and one or both parents are affected in over 40% of the families. Thus, a positive family history does not prove the presence of a genetic factor. Furthermore, a positive family history does not include an interview of the relatives by a physician. Migraine assessed by proband report compared to a clinical interview by a physician is not sufficiently precise because the number of affected relatives is highly underestimated and often misclassified [19]. Thus, a clinical interview by a physician is indispensable in family studies of migraine. Only a single study reports a positive family history of menstrual migraine [20]. This study was based on a questionnaire filled in by female students on behalf of themselves and their families. The study showed that students with menstrual migraine significantly more frequently had 2 or more relatives with migraine than other subtypes of migraine. Thus, probands with menstrual migraine may have more affected relatives than those with nonmenstrual migraine, given the abovementioned shortcomings.

Family and Twins Studies of Migraine without Aura

An increased familial risk can be caused by genetic as well as environmental factors. The risk among spouses can be used to evaluate this relation because probands and spouses in part share a common environment but differ in genetic constitution [21]. Thus, an increased risk among first-degree relatives and no increased risk among spouses favor importance of genetic factors, while no increased risk among first-degree relatives and spouses favors importance of environmental factors. The relative risk of migraine without aura is increased by a factor of 1.86 in first degree relatives of probands with migraine without aura [22]. Studies of twin pairs are the classical method to investigate the relative importance of genetic and environmental factors. Most twin studies have been case reports or small series; larger samples are limited. Unfortunately, most studies have not discriminated between migraine without aura and migraine with aura. A Danish study included 1013 monozygotic and 1667 dizygotic twin pairs of the same gender from a population-based twin register [23]. The pairwise concordance rate was significantly higher among monozygotic than dizygotic twin pairs ($P < 0.05$). However, environmental factors also seem to play an important role because the pairwise concordance rate in monozygotic twin pairs never reached 100%. Thus, family and twin studies suggest that migraine without aura is caused by a combination of genetic and environmental factors. A complex segregation analysis suggested that migraine without aura has multifactorial inheritance [24]. Unfortunately, family and twin studies on menstrual migraine are lacking.

Conclusions

Migraine without aura is a syndrome. Pure menstrual migraine without aura and menstrually related migraine without aura most likely are subtypes or subsyndromes of migraine without aura. At least a recent study suggests that menstrual versus nonmenstrual attacks of migraine are more intense and of longer duration in people with menstrual migraine [25•]. Future epidemiological surveys on menstrual migraine in the general population should focus on and work out a more precise definition for menstrual migraine. The current ICHD-II provides excellent provisory criteria, but it is important to record other features that can add to an even more precise diagnosis. Similarly, precise family and twin studies of menstrual migraine based on physician interview in a blinded fashion would be important in the future to elucidate whether pure

Table 1 Prevalence of pure menstrual migraine without aura and menstrually related migraine without aura

Study	Country	Year	Study population	Participants, *n*	Design	Definition	Prevalence among migraineurs	
							PMM	MRM
Vetvik et al. [26•]	Norway	2009	General population: 30–44y	10,176	Questionnaire	ICHD-II	7.7%	13.2%
Tepper et al. [27]	United States	2008	OB /GYN clinic: mean age, 32y	610	Physician interview and prospective diary	ICHD-II	12.1%	10.0%
Bekkelund et al. [28]	Norway	2008	Advertisement: 16–46y	62	Telephone interview and prospective diary (12months)	ICHD-II	46.7%[b]	
Couturier et al. [29]	The Netherlands	2003	General population: 13–55y	1181	Questionnaire	PMM: migraine attack exclusively during menstruation (±2days of onset); MRM: attacks during menstruation (±2days of onset) and at other times	0.85%[a]	3.0%[a]
Mattson [30]	Sweden	2003	General population: 40–74y	728	Questionnaire and physician interview	> 75% of attack of MO within day 1 of menstruation ±2d	21.0%[b]	
Dzoljic et al. [31]	Serbia	2002	Female students: 18–28y	1943	Questionnaire	PMM: migraine attack exclusively on day 1 of menstruation ±2d; MRM: aggravated during menstruation	12%	68%
Russell et al. [7]	Denmark	1996	General population: 40y	1000	Questionnaire and physician interview	Attacks occurring ±48h from the start of menstruation in > 90% of the cycles	24.8%[b]	
Cupini et al. [32]	Italy	1995	Headache clinic; women with MO	154	Prospective diary (3months)	PMM: Migraine attack exclusively from 2days before to 3days after menstruation; MRM: not defined	13.6%	56.4%
Granella et al. [33]	Italy	1993	Headache clinic: 18–70y	1300	Physician interview	PMM: migraine attacks from 3days before to 3days after onset of menstruation (> 90% attacks in perimenstrual period); MRM: attacks occurred predominantly in this period	9.1%	50.8%
Beckham et al. [34]	United States	1992	Headache clinic: 26–46y	14	Physician interview and prospective diary	PMM: migraine attack from 3days before to 3days after onset of menstruation; MRM: the mean of the total headache activity was greater during the premenstrual and menstrual phases compared to other phases	7.1%	71.4%
MacGregor et al. [35]	United Kingdom	1990	Headache clinic: 17–50y	55	Physician interview and prospective diary (3 cycles)	PMM: migraine attack exclusively on day 1 of menstruation ±2d; MRM: increased number of attacks within this period	7.2%	34.5%

ICHD-II—International Classification of Headache Disorders, 2nd Edition; MO—migraine without aura; MRM—menstrually related migraine (without aura); PMM—pure menstrual migraine (without aura)

[a] Data given for unspecified menstrual migraine

menstrual migraine without aura and menstrually related migraine without aura are specific subforms of migraine without aura or simply variations within the migraine without aura syndrome spectrum.

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