IS IRON DEFICIENCY ANEMIA RELATED TO MENSTRUAL MIGRAINE? – *POST HOC* ANALYSIS OF AN OBSERVATIONAL STUDY EVALUATING CLINICAL CHARACTERISTICS OF PATIENTS WITH MENSTRUAL MIGRAINE

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SUMMARY – The aim of this study was to determine the relative prevalence and clinical characteristics of patients with pure menstrual migraine (PMM) and menstrually related migraine (MRM), and to compare them with the women free of it in an outpatient clinic-based population. Adult menstruating women with ICHD-2 migraine were included. Demographic data were obtained by verbal report. Study women were asked to keep a headache diary for 6 months, in which they recorded information on headache characteristics, medication use and presence of menses. Iron deficiency anemia was considered to be present if the patient had received therapy for iron deficiency anemia or laboratory tests indicated low iron and/or hemoglobin levels (within one year). A total of 289 women were included, 52 (18.0%) with PMM and 116 (40.1%) with MRM, whereas 121 (41.9%) women had not observed any relationship between migraine and their menstrual cycle (non-MM). Duration of migraine attacks was longer in PMM/MRM patients (P<0.0001). No significant difference was observed according to other migraine-associated symptoms. Women with PMM/MRM took significantly more tryptans (P<0.0001) and iron deficiency anemia was significantly more common in women with PMM/MRM (P=0.008). In conclusion, this study supported earlier findings that PMM/MRM has similar clinical characteristics as non-MM, except for longer duration. In addition, iron deficiency anemia is more common in women with PMM/MRM, which may be an underlying mechanism aggravating migraine attacks.

Key words: *Migraine disorders – etiology; Migraine disorders – physiopathology; Anemia, iron – deficiency; Menstrual cycle; Estrogens – metabolism*

Introduction

Relationship between female hormones estrogen and progesterone and migraine is well known[1-3]. According to clinical observations and International Classification of Headache Disorders (ICHD-2) Appendix, migraine attacks that occur in a consistent relationship with menstruation, regularly ± 2 days from the onset of menstruation but do not occur at other times during menstrual cycle can be classified as pure menstrual migraine without aura and as menstrually-related migraine without aura if other attacks occur throughout the month[4]. Approximately 33%-60%

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of women have menstrually related migraine attacks (MRM), while 7%-9% of women have pure menstrual migraine (PMM)[1,5-10].

Clinical observations suggest that MRM attacks are usually more severe, of longer duration and more resistant to treatment[11-14]. Pure menstrual migraine typically improves during pregnancy, mainly during the second and third trimesters, probably due to the constant level of the hormone estrogen[15].

The aim of this study was to determine the relative prevalence and clinical characteristics of patients with PMM and MRM, and to compare them with women without it in a cohort of women presenting to an outpatient headache clinic.

Patients and Methods

This was an outpatient clinic-based population study evaluating the relative prevalence and clinical characteristics of PMM and MRM. Migraine was diagnosed according to the ICHD-2 criteria for migraine with or without aura[4]. Patients were included randomly and all gave their informed consent for participating in the study. The study was approved by the Research Ethics Committee. All patients had episodic migraine. Patients attending the outpatient headache clinic at our University Department of Neurology were asked to keep a headache diary for 6 months (observation period), in which they recorded data on headache characteristics: frequency, duration, migraine associated symptoms, medication usage and presence of menses. All patients were taking acute treatment for migraine, analgesics or tryptans. None of the patients was on prophylactic therapy and there was no analgesic overuse recorded. Patients were screened for comorbidities; iron deficiency anemia (IDA) was considered to be present when confirmed by the patient, receiving treatment for iron deficiency anemia within a year and laboratory tests indicating low iron and/or hemoglobin levels (within one year). The diagnosis of iron deficiency anemia was not based on the best practice guidelines for diagnosing and managing of iron deficiency anemia[16] because it was not the primary point of the present study.

Study patients were categorized as follows: (a) migraine attacks occur only perimenstrually and at no other times during the month; (b) migraine attacks occur always perimenstrually and also at other times during the month; (c) migraine attacks occur occasionally but not always in relation with menstruation; and (d) migraine attacks never occur perimenstrually.

Data were compared between those with PMM (group a), /MRM (groups b and c) and those without (group d).

Statistical analysis

On statistical analysis, χ^2-test and Fisher exact test were used for comparison of proportion, mean and standard deviation for description of continuous variables, and Student's t-test for comparison between different groups. STATISTICA 6.0 (StatSoft Inc., Tulsa, OK, USA) was used for analysis. The level of significance was set at $P<0.05$.

Results

Data on 289 patients were analyzed. The mean age of patients was 39.9±12.3 years, all Caucasians. Data analysis showed the following: migraine attacks occurred only perimenstrually and at no other times during the month in 52 (18.0%) women (group a); migraine attacks occurred always perimenstrually and also at other times during the month in 21 (7.3%) women (group b); migraine attacks occurred occasionally but not always in relation with menstruation in 95 (32.9%) women (group c); and migraine attacks never occurred perimenstrually in 121 (41.9%) women (group d).

According to the proposed criteria, in our group of patients pure menstrual migraine was present in 52 (18.0%) women. The women reporting that they had not observed a clear pattern of migraine attacks always perimenstrually but only occasionally were categorized in group c, meaning that they experienced an attack in at least 2 of 3 menstrual cycles and additionally at other times of the cycle. Therefore, in our study population, MRM was present in 116 (40.1%) women.

The women with PMM or MRM differed significantly from those whose attacks were not related to menstruation (non-menstrual migraine, non-MM) in the following: 1) the group of PMM women was older than non-MM group: mean age 43.1±11.2 *vs.* 39.3±12.3 ($P=0.043$); 2) duration of migraine attacks

was longer in the PMM group: 1-3 days in 67.3% (PMM) *vs*. 37.1% (non-MM) and more than 3 days in 17.3% (PMM) *vs*. 6.9% (non-MM) ($P<0.0001$); 3) nausea with or without vomiting was significantly more common in non-MM group: 57.5 *vs*. 36.5% (PMM) ($P=0.0014$); 4) women with PMM were taking significantly more triptans: 61.5 *vs*. 30.2% (non-MM) ($P=0.0001$); 5) women with non-MM were taking more simple analgesics or NSAIDs: 66.6% *vs*. 36.5% (PMM) ($P=0.0001$); and 6) IDA was significantly more common in women with PMM: 38.5% *vs*. 22.9% (non-MM) ($P=0.008$).

There was no significant difference between patients with PMM/MRM and non-MM according to localization, intensity and quality of pain, laterality of headache pain, presence of photophobia, phonophobia and osmophobia. Clinical characteristics of patients with PMM/MRM and non-MRM are shown in Table 1.

Discussion

A normal hormonal cycle in women's life has several important points that may influence the occurrence or change in the character of migraine: menarche, pregnancy, use of contraception, menopause and use of hormone replacement therapy[1]. Before puberty, the prevalence of migraine does not significantly differ between girls and boys, however, in adolescence, the incidence and prevalence of migraine increases more rapidly in girls. Migraine usually begins to occur in the second decade and its prevalence decreases after the fourth decade; it is believed to be influenced largely by female hormones[15,17,18].

It is believed that the primary trigger for menstrual migraine is the decrease in estrogen level[15]. Estrogens and progestins have a significant influence on central serotoninergic and opioid neurons, modulating neuronal activity and receptor thickness. Based on experimental studies, the decrease in estrogen levels just before the onset of menstruation leads to disorder of homeostatic gene regulation and hyperexcitability of cell membranes, which sensitizes the neurons to triggers, thus leading to the activation of migraine attack. In the interictal phase when the level of estrogen is highest, the increased neuronal excitability is balanced by homeostatic gene regulation in cerebral cortex and nociceptive systems[19]. Due to stable (i.e. increased) estrogen levels in pregnancy, the frequency of migraine decreases. The frequency of migraine increases postpartum and in some women during the pause of taking oral contraceptives; these are periods when the level of estrogen in the woman's body decreases[20].

The results of our study showed that PMM occurred in 18% of patients with migraine and MRM was present in 40.1% of women. Our results are comparable to similar studies in which the prevalence of PMM was also investigated in patients attending headache clinics and is reported to be 26%-60%[21]. Approximately 60% of women have migraine attacks more frequently during menstruation, while 7%-9% of women have migraine attacks only during menstruation[5,6]. A study in The Netherlands established a prevalence of 3% for MRM and 0.85% for PMM in the population[11].

Clinical characteristic		PMM/MRM n=168	non-MRM n=121	P value
Age (yrs)		43.1±11.2	39.3±12.3	0.043
Duration	4-12 hours	3.9%	10.5%	
	13-24 hours	9.6%	44.4%	
	1-3 days	67.3%	37.9%	0.0001
	>3 days	17.3%	6.9%	
Nausea/vomiting	always	36.5%	57.5%	
	frequently	36.5%	22.2%	0.0014
	rarely	25.0%	11.6%	
Triptans		61.5%	30.2%	0.0001
NSAIDs, simple analgesics		36.5%	66.6%	0.0001
Iron deficiency anemia		38.5%	22.9%	0.008

Table 1. Clinical characteristics of patients with pure menstrual migraine (PMM) and menstrually related migraine (MRM) vs. non-MRM patients

Typical clinical characteristics of migraine are more pronounced in the 30-49 age group, while less typical ones are present in younger and older age groups that can also be in part influenced by the change in hormone status[22]. PMM has a number of clinical characteristics in common with other types of migraine and is typically not related to aura[1,23]. Although the majority of studies found the attacks in menstrual migraine to be more severe, of longer duration, more resistant to therapy and associated with more functional disability[1,11,24,25], some studies showed small differences between the attacks of menstrual migraine and attacks in other periods of the menstrual cycle[9]. In our study, the duration of migraine attacks in patients with menstrual migraine was longer, lasting one to three days or more; however, nausea with or without vomiting was frequently or rarely present as compared with patients with non-MM who reported a significantly higher rate of nausea and vomiting. In our study, significantly more women with PMM were taking triptans for the treatment of migraine attacks, possibly reflecting the fact that their headaches were more disabling.

Anemia is considered to aggravate and be a cause of headache; our study showed that iron deficiency anemia was significantly more common in women with PMM. Low iron levels may be due to mechanical hemolysis, intestinal bleeding, hematuria, sweating, low iron intake or poor intestinal absorption[26]; patients included in our study did not suffer from any of chronic diseases that would cause iron deficiency anemia. Women of childbearing age are at an especially high risk of iron deficiency due to ongoing menstrual blood losses. Findings from our study suggest that iron deficiency anemia, found to be more common in patients with menstrual migraine, may contribute to the severity and duration of headache in these patients. It is easily evaluated and treated, but often remains undiagnosed. The optimal diagnostic approach is to measure serum ferritin as an index of iron stores and serum transferrin receptor as an index of tissue iron deficiency[16,26].

Although anemia is considered to aggravate headaches, we found no clinical studies in the literature that prove the relationship between migraine, particularly menstrual migraine, and iron deficiency anemia. In this study, we only screened for comorbidities and did not perform additional diagnostic tests if iron deficiency was noted. Since our study was not designed to prove such a relationship, we did not perform additional clinical tests. *Post-hoc* analysis revealed the possible relationship between iron deficiency anemia and PMM/MRM.

Anemia may be treated by preventing decreased iron stores through a balanced food intake or iron supplements. The treatment of iron deficiency should always be initiated with oral iron. When this fails because of large blood losses, iron malabsorption, or intolerance to oral iron, parenteral iron can be given using iron dextran, iron gluconate or iron sucrose[26].

Menstrual migraine is often related to dysmenorrhea, and can be related to other somatic changes that precede menstruation like nausea, low back pain, breast sensitivity, and cramps, which is the consequence of decrease in the level of hormones[1]; however, we found no literature report on the relationship between iron deficiency anemia and PMM/MRM. This might be explained by the relationship between dysmenorrhea, menstrual migraine and iron deficiency anemia, although the present study was not intended to prove such a relationship.

PMM is in some cases unrecognized. Keeping a diary for at least 3 months is an efficient way to diagnose PMM[27]. Patient diaries that record headache onset and relationship to the menstrual cycle will allow for accurate prediction of the onset of PMM; this information is also needed to decide on timing of intermittent preventive therapy. In women with regular menstrual cycle, a short prophylaxis 3-4 days before the anticipated onset of menstruation can be recommended, usually with non-steroid antirheumatic drugs, tryptans, or ergotamine derivatives, and in some cases percutaneous estrogen patch gel[28-31].

This study suffered from some limitations, as it was not designed as a cross sectional population-based study and the diagnosis of iron deficiency anemia was not based on the best practice guidelines for diagnosing and managing iron deficiency anemia. It was *post hoc* analysis that revealed a possible relationship between iron deficiency anemia and PMM/MRM. Therefore, we did not perform additional laboratory tests to compare the PMM/MRM group with non-MM group in order to elucidate the pathophysiology of iron deficiency anemia in PMM patients. These issues need further evaluation in another study.

Conclusions

Results of this study showed that migraine related to menstrual cycle to be present in a relatively large number of fertile women. In this cohort of patients referred to a specialist headache clinic, pure menstrual migraine was present in 18% of patients, while additional 40% had menstrually-related migraine. Results of our study are in line with clinical observations that menstrual migraines are of longer duration but we could not confirm them to differ in other clinical characteristics from non-menstrual migraines. Interestingly, our results showed iron deficiency anemia to be significantly more common in women with menstrual migraine; this observation needs to be further validated. In guidelines for the treatment of primary headaches, iron deficiency anemia is not mentioned as an important factor that physicians should check for. Therefore, we suggest that iron deficiency anemia be looked for in patients with menstrually related migraines and appropriately treated. We hope that the results of our study will open new research perspectives in the field.

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Sažetak

JE LI ANEMIJA ZBOG NEDOSTATKA ŽELJEZA POVEZANA S MENSTRUALNOM MIGRENOM? – *POST HOC* ANALIZA OPSERVACIJSKE STUDIJE ZA PROCJENU KLINIČKIH ZNAČAJKA BOLESNICA S MENSTRUALNOM MIGRENOM

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Cilj ove studije bio je utvrditi relativnu učestalost i kliničke značajke bolesnica s isključivo menstrualnom migrenom (IMM) i mentrualno povezanom migrenom (MPM) u odnosu na ostale bolesnice s migrenom. U studiju su bile uključene žene reprodukcijske dobi s migrenom prema kriterijima ICHD-2. Sudionice su zamoljene da vode dnevnik glavobolja tijekom 6 mjeseci u koji su zapisivale karakteristike glavobolja, lijekove koje su uzimale i datume menstruacije. Sideropenična anemija je evidentirana ako su laboratorijski testovi u posljednjih godinu dana ukazivali na niske razine željeza i/ili hemoglobina. U studiju je bilo uključeno 289 žena, 52 (18,0%) s IMM i 116 (40,1%) s MPM, dok 121 (41.9%) žena nije primijetila povezanost između migrene i menstrualnog ciklusa (ne-MM). Trajanje migrenskih napadaja je bilo duže kod bolesnica s IMM/MPM (P<0,0001). Nije zabilježena značajna razlika u odnosu na druge prateće simptome migrenske glavobolje. Žene s IMM/MPM značajno su češće uzimale triptane (P<0,0001). Sideropenična anemija bila je značajno češća kod žena s IMM/MPM (P=0,008). Zaključeno je kako uz duže trajanje glavobolja žene s IMM/MPM imaju i druge slične kliničke značajke kao i ne-MM. Također, sideropenična anemija bila je češća kod žena s IMM/MPM, što može biti potencijalni mehanizam koji pogoršava migrensku glavobolju.

Ključne riječi: *Migrenske bolesti – etiologija; Migrenske bolesti – fiziopatologija; Anemija, željezo – nedostatak; Menstruacijski ciklus; Estrogeni - metabolizam*