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The Association of Menstrual Migraine with Iron Deficiency and Its Induced Anemia

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ABSTRACT

Background: Menstrual Migraine (MM) is a subgroup of migraine headache that affect the quality of life of patients in menstrual age. Iron Deficiency Anemia (IDA) is the most common cause of anemia, especially in women of reproductive age.

Objectives: To determine the association of iron deficiency anemia with menstrual migraine.

Materials and Methods: This descriptive-analytic study was conducted on women with migraine visiting neurology clinics affiliated to Isfahan University of Medical Sciences in late 2015 and early 2016. The demographic data and characteristics of migraine headache were registered in a designed questionnaire. The patients underwent laboratory tests for iron deficiency and anemia. Data were analyzed in SPSS-20 using Chi-square test and independent t-test. Significance level was considered at $p<0.05$.

Results: Of the 93 migraine patients, 47.3% had Pure MM (31.9% with premenstrual migraine and 15.4% with true menstrual migraine), 40.6% had Menstrual-Related Migraines, and 12.1% had non-menstrual migraines. The frequency of iron deficiency anemia was 51.1%, 40.5% and36.4% in PMM, MRM and non-menstrual migraines ($p=0.18$). Total frequency of iron deficiency anemia in PMM and MRM groups was 46.2%, which was not significantly different from non-menstrual migraine group ($p=0.82$). Iron deficiency anemia was significantly higher in migraine patients with aura compared to those without aura (53% *vs.* 43.2%) ($p=0.04$).

Conclusion: Although iron deficiency anemia was more prevalent among patients with menstrual migraine, but it is not associated menstrual migraine.

Keywords: Migraine; Menstrual Migraine; Anemia, Iron Deficiency

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Introduction

As a highly prevalent headache, migraine has dramatic effects on the lives of affected people. The highest and the lowest prevalence of migraine have been reported in Europe (15%) and Africa (5%), respectively [1]. Migraine is a periodic

and hereditary headache that begins in childhood, adolescence or early middle age, with greater prevalence in women. The pain is moderate to severe and may be associated with photophobia, phonophobia, throbbing, nausea and vomiting [2].

Many women with migraine have frequently experienced menstrual-related headaches [3,4], known as Menstrual Migraine (MM). MM is divided into two groups: Menstrual-Related Migraine (MRM), which occurs during menstruation as well as other times during the cycle, and Pure Menstrual Migraine (PMM), which occurs only during menstruation with ±2 days of onset [5,6]. The prevalence of MRM and PMM have been reported up to 60% and 7% respectively [4,7-11]. Some recent studies have indicated the significantly higher prevalence of iron deficiency anemia (IDA) in women with PMM [12].

IDA is the most common type of anemia and nutritional disorder in the world [13]. A nationwide study conducted in 1995 on 1600 15-49 year-old rural and urban women revealed that according to serum ferritin level that shows body iron reserves, 50% of women suffered from mild to severe iron deficiency, of whom, 34% had severe iron deficiency [14].

Previous studies have shown that iron has a major role in the synthesis of serotonin, dopamine, and epinephrine [15]. While, as a chemical mediator, serum serotonin level reduces in migraine headaches [16], and in IDA the serum iron is consumed [17]. Previous studies indicate that monoamine oxidase (MAO) activity reduces with both migraine and IDA [18]. It has been observed that iron is essential to MAO synthesis [19].Iron is necessary in the synthesis of monoamine oxidase apoenzyme or as a cofactor of the enzyme which binds flavin-adenine dinucleitide to monoamine oxidase apoenzyme covalently, and that iron-therapy increases this enzyme [20]. Decreased blood ions including iron following hormonal changes is considered to be involved in MM [21].

The reported differences between patients with MM and patients with other types of migraine include changes in aldosterone, intracellular magnesium, platelet hemostasis, nitric oxide synthesis, prostaglandin secretion, and prolactin level [15,22]. A study showed that high levels of prolactin are involved in chronicity of migraine [23].

Migraine is most prevalent at ages when people are the most active and productive, and it incurs huge medical costs and harms community health. Given the above and its higher prevalence during menstruation, and that few studies have been conducted on this subject, we decided to investigate the prevalence of IDA in patients with menstrual migraine and compare it with non-menstrual migraine for the first time in Iran. If these two diseases are associated, we should consider treatment of this type IDA in patients with menstrual migraine, and thus reduce severity of migraine, improve the quality of life of these patients, and reduce costs incurred.

Materials and Methods

The present descriptive-analytic study was conducted in late 2015 and early 2016 on women in their reproductive age presenting with migraine to neurology clinics affiliated to Isfahan University of Medical Sciences. The present study was approved by the ethics committee of Isfahan University of Medical Sciences, and conducted after obtaining informed consents of patients. Participants were informed that their answers to questions

and test results would remain confidential. Sampling was conducted according to non-random convenient method. First, patients with migraine were identified by a neurologist according to the International Classification of Headache Disorders (ICHD-III-β). Then, patients were divided into three groups according to the association of their migraine with menstruation, including non-Menstrual Migraine (non-MM), Menstrual-Related Migraine (MRM) and Pure Menstrual Migraine (PMM). In sub-classification, PMM was itself divided into *premenstrual migraine* (headache, 3 to 7 days before menstruation) and *true menstrual migraine* (headache 2 to 3 days after menstruation) [24]. A checklist was also completed during examination by the neurologist containing participants' personal details and characteristics of migraine headache. It should be noted that patients undergoing prophylactic therapy for migraine or receiving iron therapy were excluded. Patients could use only ordinary analgesics such as acetaminophen or NSAID in acute attacks.

Blood samples (2cc) were taken from patients and assessed for hemoglobin level (Hb), serum iron and Total Iron Binding Capacity (TIBC) using spectrophotometry and also for serum Ferritin using radioimmunoassay (RIA) method. The criteria for IDA were Hb≤12 and Ferritin≤30 ng/mL[25,26]. Patients with Ferritin≤30 ng/mL but Hb>12 were considered as non-anemic iron deficiency (non-anemic ID) group [27]. Given the role of ferritin as the acute phase reactant, data related to Ferritin>306 ng/mL in patients with anemia were excluded from the study [28,29].

Data obtained from the questionnaire and test results were analyzed in SPSS-20 using Chi-square test and independent t-test. The prevalence of iron deficiency and its induced anemia in patients with and without menstrual migraine were determined and compared. Significance level was considered at $p<0.05$.

Results

General characteristics

Participants included 93 patients with a mean age 34.5 years (range: 15-51 years), of whom, 25 (26.9%) had migraine with aura and 68 (73.1%) migraine without aura.

Mean duration of migraine was 8.7 years in patients with anemia, 7.7 years in patients with iron deficiency and without anemia, and 7.9 years in patients with normal Hb. One-way variance analysis showed no significant relationship between duration of migraine and anemia ($p=0.082$).

The association of migraine with menstruation

According to table 1, only in 12.1% of cases migraine had no relationship with menstruation. However, 45 patients (47.3%) included in PMM group [30patients (31.9%) with premenstrual migraine, and 14patients (15.4%) with true menstrual migraine)], and 37 (40.6%) in MRM group.

Table 1. Frequency distribution of the different migrainetype in association with menstruation

Migraine		N (%)
Pure Menstrual Migraine	Premenstrual Migraine	29 (31.9)
	True Menstrual Migraine	14 (15.4)
Menstrual Related Migraine		37 (40.6)
Non- Menstrual Related Migraine		11 (12.1)

Anemia state

According to reference values, 41 (45.1%) patients had IDA, and 29 (31.8%) had non-anemic ID. Only 21 (23.1%) patients had no anemia or iron deficiency.

In assessing TIBC, 28 patients from PMM group (66.7%), 20 (60.6%) from MRM, and 5 (45.5%) from non-MM had values higher than the normal reference, with no significant difference (p=0.21).

Migraine association with IDA

The frequencies of IDA and non-anemic ID and also patients with no anemia or iron deficiency in all three groups are shown in Table 2. The highest IDA was observed in PMM group. However, chi-square test showed no significant relationship between anemia and menstrual migraine (p=0.18).

Table 2. Frequency distribution of anemia by migraine association with menstruation

	Pure Menstrual Migraine	Menstrual Related Migraine	Non- Menstrual Related Migraine	*p-value*
	N (%)	N (%)	N (%)	
Iron deficiency anemia	36.4 (4)	40.5 (15)	51.2 (22)	0.18
Iron deficiency without anemia	36.4 (4)	27 (10)	34.8 (15)	
Healthy	27.2 (3)	32.5 (12)	14 (6)	

In another assessment, Chi-square test showed no significant relationship between migraine and combined anemia and non-anemic ID rate in all three groups (PMM=86%), non-MM=72.2%, MRM=67.6%) (p=0.14).

Moreover, separate independent-test showed no significant relationship between serum iron (p=0.64) or ferritin (p=0.59) and menstrual migraine.

However, Chi-square test showed a significant relationship between anemia state and type of migraine, and that IDA was higher in migraine patients with aura than patients without aura (53% *vs.* 43.2%) (p=0.04).

Discussion

Given the higher prevalence of migraine in females after puberty [12], the present study was conducted in this group of patients.

In the present study, 47.3% of patients had PMM and 40.6% suffered from MRM. These results agree with those of previous studies that reported the prevalence of 26% to 60% for PMM and 33% to 60% for MRM [9,30].

The present study showed the prevalence of IDA as 45.1% and Iron deficiency as 30.8%, which are much higher than those found in a comprehensive study conducted by Sheikhaleslam *et al.* in rural and urban communities in Iran on 15-49 year-old women. A prevalence of 16.6% was reported for IDA in women of reproductive age in Iran [14], which is higher compared to IDA prevalence reported in European countries (IDA=1.5%-14%, and ID=10%-30%) [24]. Sucha significant difference with the present study is probably due to small sample size.

The present study results indicate that despite high prevalence of IDA among patients with PMM and MRM compared to non-MM group, no significant relationship was observed between migraine and menstruation (p=0.18). Few studies have investigated the relationship of IDA with MRM, PMM, and non-MM groups. In one study, the prevalence of IDA was significantly higher in women with PMM and MRM compared to non-MM group [12]. This difference may be attributed to the small sample size in the present study and definitions used in two studies. Since in the present study, PMM group was divided into premenstrual migraine (headache 3 to 7 days before menstruation) and true menstrual

migraine (headache 2 days before to 3 days after menstruation) groups, and the above study (2010) only investigated true MM group [12]. Contrary to the present study result, a study conducted by Gür-Özmen *et al.* showed a significant relationship between IDA and MRM/PMM group [26].

In the present study, IDA and non-anemic ID in PMM, MRM, and non-MM groups were compared, and no significant relationships were found. Serum iron and ferritin (as the best serum iron marker [27]) were assessed in non-MM and MM groups, and again no significant relationship was observed. In a study conducted by Kesler *et al.*, anemia and hemoglobin were found to have no obvious relationship with headache [29]. In the guidelines for treatment of primary headache, IDA is not considered a major factor in treatment [12].

An important point investigated in the present study was the relationship of anemia with aura in migraine, which was found to be significant in patients with anemia.

In the present study, credible diagnostic tools were used to detect migraine and IDA, which is considered a strong point. In addition to assessing IDA, non-anemic ID was also investigated, which showed no significant relationship with migraine either.

Study samples may not represent the general population because they were selected from a third degree clinic, and considering higher prevalence of IDA in the present study, further studies with larger sample size appear necessary in order to confirm the above results or find a significant relationship in this field.

Conclusion

The present study showed that although the prevalence of IDA in patients with menstrual migraine is higher than in non-menstrual migraine patients, given the absence of a significant difference, iron deficiency and its induced anemia are not associated with migraine.

Conflict of Interest

The authors have no conflict of interest.

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