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Association between anemia severity and migraine in iron deficiency anemia

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Abstract. – OBJECTIVE: Migraine is an episodic public health problem that usually occurs with a severe headache. Various mechanisms and outcomes have been reported between iron deficiency anemia (IDA) and migraine. We aimed to investigate the effect of the presence and severity of anemia and iron parameters on the frequency and severity of migraine attacks.

PATIENTS AND METHODS: The study included 104 patients with IDA and newly diagnosed migraine in the neurology outpatient clinic and 38 age and gender-matched controls with normal hemoglobin levels. Patients were divided into 3 subgroups (mild, moderate, and severe anemia) to determine a significant relationship between the severity of IDA and migraine attacks. All patients were asked validated questions with the Visual Analogue Scale (VAS), Headache Impact Test-6 (HIT-6), and the Hamilton Anxiety Rating Scale (HAM-A) face-to-face.

RESULTS: In this study, 85.6% of the participants were female, and 22 (14.6%) of them were male. Thirty-two mild anemia patients' mean age was 36.6 ± 12.5, 41 with moderate anemia was 46 ± 14.2, and 31 with severe anemia patients' mean age was 48 ± 14.1. There was no significant difference between the subgroups in VAS, HIT-6 score, headache type, and headache frequency. Menstrual migraine is associated with low hemoglobin levels. A significant increase was found in VAS and HIT-6 scores with low ferritin levels.

CONCLUSIONS: The presence and severity of anemia and iron deficiency do not affect the frequency and severity of migraine attacks in groups other than menstruation-related migraine. An inverse relationship was found between VAS, HIT-6, and ferritin levels. VAS was found to be more effective than HIT-6.

Key Words:
Iron deficiency anemia, Ferritin, Migraine.

Introduction

Migraine is a chronic neurological disorder characterized by usually unilateral throbbing head pain attacks associated with phonophobia, photophobia, nausea, and vomiting. The headache attacks are usually aggravated by physical activity and may persist for 4-72 hours[1]. Migraine is a common cause of primary headaches and is considered a public health priority by the World Health Organization (WHO) due to the widespread socioeconomic losses due to the disability it causes. It is more common in women, and its worldwide prevalence ranges from 5% to 12%[2]. Menstrual migraine is a subset of migraine in women observed without aura, usually starting in the twenties, and continuing until menopause, and includes both pure menstrual migraine (PMM) and menstrual-related migraine (MRM)[3].

There are various tests that evaluate the severity of pain in migraine headaches and its effect on daily life. Headache Impact Test-6 (HIT-6) is a simple, straightforward self-report questionnaire that assesses the burden and impact of headaches on quality of life in daily life, including pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. The patient responds to each of the six questions as "never", "rarely", "sometimes", "very often" or "always"[4]. HIT-6 is scored between 36 and 78; the higher the score, the greater the impact of headache on the person's daily life[5]. VAS is a scale developed by Price et al[6] in 1983 to quantify the intensity and level of pain between no pain (0) and the most severe pain (10). VAS is a proven and easy-to-use scale that has been used as a pain scale in many studies[7,8], in addition to migraine headaches.

Migraine is closely associated with anxiety and depression in relation to high levels of 5-HT2A receptors in the prefrontal cortex and hippocampus. Studies[9] have shown that hormonal irregularities and headache-related factors lead to anxiety and depression, which may affect sleep quality and lead to a decrease in quality of life. The Hamilton Anxiety Rating Scale (HAM-A) is an easy-to-use scale that helps to objectify and rate

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the severity of a person's anxiety by assessing the level of anxiety based on clinical questions. The 14-item scale measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored from 0 (not present) to 4 (very severe); the total score range is 0-56, and a score of 17 and below is considered mild severity; 18-24 is mild to moderate severity; 25-30 is moderate-severe, and over 30 is severe[10].

Although the common mechanisms with many diseases, such as cardiovascular diseases, stroke, and depression, are not fully understood, iron deficiency anemia (IDA) has been associated with the frequency and severity of migraine attacks through several mechanisms. Iron deficiency anemia is one of the most significant conditions contributing to the global burden of disease, particularly affecting children, pre-menopausal women, and people in low-and middle-income countries, with clinical and functional impairments caused by iron deficiency[11]. According to the World Health Organization (WHO), anemia is defined as hemoglobin (Hb) levels < 12.0 g/dL in women and < 13.0 g/dL in men and affects 1.62 million people[12].

It is widely accepted that the relationship between IDA and migraine implicates iron in the peripheral and central activation of various neurotransmitters and the trigeminovascular system involved in the pathogenesis of migraine. In iron deficiency, which plays an important role in the synthesis and metabolism of serotonin, dopamine, and norepinephrine, the decrease in the serotonin system in the central nervous system and the loss in neuronal activities due to this decrease lead to an increase in migraine attacks[13]. IDA has also been associated with reduced monoamine oxidase activity in humans, which promotes impaired metabolism of monoamines, including dopamine and serotonin. In addition to iron's role in the monoaminergic system, it also regulates the balance between inhibitory and excitatory neurotransmitters, γ-aminobutyric acid (GABA) and glutamate, respectively. Furthermore, iron has been shown to interact with other metals, such as zinc, and to be involved in processes such as dendritogenesis, neuro-metabolism, gene profiles, and protein profiles[14].

In the brain, astrocytes and microglia can secrete ferritin. Ferritin is involved in the production of oligodendrocyte precursor cells. The central nervous system is responsible for the synthesis and maintenance of myelin sheaths. It has been reported that neuronal loss and oxidative damage develop when ferritin levels decreases[15].

In studies[16,17] examining the relationship between migraine and IDA, the relationship between the presence and severity of anemia or iron parameters has been investigated, and different results have been revealed. In this study, we aimed to investigate the relationship between the level of iron parameters and severity of anemia and the frequency and severity of migraine attacks in patients with newly diagnosed migraine and treatment-naive iron deficiency anemia.

Patients and Methods

In this study, the data were obtained from patients who had been diagnosed with migraine and applied to the Balikesir University Faculty of Medicine, Department of Neurology, outpatient clinic between January 2022 and April 2023. Written informed consent was obtained from the patients, and ethical clearance was obtained from the institutional ethics committee. An equal number of age and sex-matched controls without anemia were included in the study.

Study Design

In this retrospective cross-sectional study, a sample size of 104 cases with iron deficiency anemia was divided into 3 subgroups, and 38 age and sex-matched controls were estimated to detect a significant association between the severity of iron deficiency anemia and migraine attacks. Patients with anemia were separated into three groups: mild, moderate, and severe, according to hemoglobin levels. Power of 95% and a 5% level of significance, assuming the migraine prevalence among chronic daily headaches (CDH) as 16% in Turkey[18].

Inclusion Criteria

Patients over the age of 18 who were newly diagnosed according to the 3rd edition criteria of the International Classification of Headache Disorders (ICHD-3) and HIT-6 or who had not yet received treatment for migraine were evaluated[19,20]. The inclusion criteria of the study were having treatment-naive migraine and a confirmed iron deficiency anemia.

Visual Analogue Scale (VAS) consists of a vertical line of 100 millimeters. At the bottom end of the line is a value of 0, meaning "no pain", while at the top is a value of 10, meaning "very severe pain". The patient was asked to determine the level of pain on this line. The severity of the headache was assessed by a VAS ranging from 0 to 10, with 0

denoting "no headache at all" and 10 denoting "the worst possible headache." The participants were also assessed with HAM-A. Menstrual migraine was questioned in female pre-menopausal patients.

The participants were excluded from the study due to the following conditions:

- Having a secondary daily headache.
- Having had migraine treatment or iron supplementation in the last six months.
- Having minor or major anxiety, according to HAM-A.
- Having a confirmed hypochromic microcyte anemia, except for iron-deficiency anemia such as thalassemia.
- Suspicion of thalassemia in the absence of a known history of hemoglobinopathy (Mentzer index below 13, target cells in peripheral smear... etc.).
- Infectious, auto-inflammatory, 3etc., clinic that may increase acute phase reactants.

Study Protocol

Patients presenting with headache were subjected to a detailed history, clinical examination, computed tomography (CT) scan / magnetic resonance imaging (MRI) of the brain and evaluation for structural abnormalities or other causative lesions. Those diagnosed with migraines were randomly selected for the study to avoid any bias. The patients with anemia were further evaluated for IDA.

Those with anemia were assessed with a complete hemogram, serum iron, ferritin level, total iron-binding capacity (TIBC), stool examination (routine and for occult blood), serum vitamin B12, serum folate, transferrin saturation, kidney function tests, liver enzymes, peripheral blood smear (if there is a suspicion for thalassemia), C-reactive protein, and erythrocyte sedimentation rate.

Anemia was defined as a low level of hemoglobin in the blood and was classified into mild anemia (11-12.9 g/dl), moderate anemia (8-10.9 mg/dl), and severe anemia (< 8 mg/dl) according to WHO criteria[21].

IDA was defined as hemoglobin < 13 g/dl in males and < 12 g/dl in females, and percent transferrin saturation < 20, and serum ferritin < 20 mg/L[22].

Statistical Analysis

In the analysis, continuous variables were performed for Kolmogorov-Smirnov's test of normality. Descriptive statistics are shown as mean ± standard deviation for variables with a normal distribution, median (interquartile range) for non-normal distributions, and the number of cases and percentage (%) for nominal variables.

The correlations between continuous variables were assessed by the Spearman or Pearson correlation test. Rho correlation coefficients were used. Because the number of groups was more than two, the significance of differences between the groups in terms of averages was investigated by the ANOVA variance analysis test, and the significance of medians was determined by the Kruskal-Wallis test.

In the variables with two groups, parameters with a normal distribution were evaluated with the Student's *t*-test. The Mann-Whitney U test was used for continuous, and the Chi-square test was used for categorical variables in paired groups with a normal distribution. Binominal logistic regression analysis was performed on significant variables. The significance of differences between the post-hoc test was performed within anemia subgroups. Nominal variables were assessed by Pearson Chi-square or Fisher Exact test.

The correlations between the analysis of the data were done with the SPSS 25 (IBM Corp., Armonk, NY, USA) package program. Results with $p < 0.05$ were considered statistically significant. The required number of samples was calculated to be at least 43 patients with an acceptable error of 5% and a 95% confidence level.

Results

In this study, 85.6% of the 142 participants were female, and 22 (14.6%) of them were male. Patients were divided into four subgroups based on the severity of their anemia, according to the WHO classification. The mean age of 32 patients with mild anemia was 36.6 ± 12.5, 41 patients with moderate anemia had a mean age of 46 ± 14.2, and 31 patients with severe anemia had a mean age of 52.4 ± 13.7.

The mean hemoglobin level of the patients was 10.5 ± 2.45 g/dl. Eight point five percent of the patients have migraine with aura. The mean frequency of headaches in a month was 5.7 ± 3.5. Menstrual migraine was present in 38.5% of female patients. Demographic variables, IDA parameters, characteristics of migraine (type and frequency of attacks), VAS, HIT-6, and HAM, as well as outcomes of the subgroups, were summarized in Table I.

There was no significant difference between the subgroups in VAS, HIT-6 score for migraine severity, headache type, and headache frequency. Menstrual migraine is associated with low hemoglobin levels ($p = 0.03$). Regardless of the

Table I. The relationship between demographic variables, migraine attacks and IDA subgroups.

Demographic Variables	Normal (N = 38)	Mild (11-12.9 mg/dl) (N = 32)	Modarate (8-11 mg/dl) (N = 41)	Severe (< 8 mg/dl) (N = 31)	*p* (< 0.05)
Age					
n (Mean)	41.6 ± 12.1	36.6 ± 12.5	46 ± 14.2	48 ± 14.1	0.12
Sex					0.66
• Female	30	31	37	24	
• Male	8	3	4	7	
Headache					0.34
• with Aura	2	2	1	0	
• without Aura	31	24	36	29	
• Aura+TTH	3	4	0	0	
• Without Aura+TTH	2	2	4	2	
Menstrual Migraine	5	14	16	12	0.03
Headache Frequency N (Mean)	5.47 ± 3.75	6.4 ± 4.16	5.53 ± 2.91	5.70 ± 3.65	0.34
BMI	25.2 ± 0.6	25.6 ± 0.6	23.9 ± 0.4	25.9 ± 0.7	0.30
VAS	5.8 ± 0.2	5.8 ± 0.2	5.73 ± 0.1	6.16 ± 0.3	0.97
HIT-6	50.2 ± 2.1	52.7 ± 2.2	55.3 ± 1.9	55.0 ± 1.8	0.08
HAM-A	2.7 ± 0.1	2.2 ± 0.2	2.6 ± 0.1	2.8 ± 0.1	0.35
Iron µg/dl	69.2 ± 4.2	41.4 ± 4.7	25.7 ± 2.0	22.2 ± 1.8	0.000
TIBC	259.5 ± 9.6	372.2 ± 11.9	393.8 ± 13.0	408.6 ± 9.7	0.000
Ferritin	28.3 ± 3.2	13.6 ± 2.0	14.3 ± 3.8	10.4 ± 1.0	0.000
Hemoglobin (g/dl)	13.5 ± 1.06	11.5 ± 0.3	9.5 ± 0.7	7.2 ± 0.8	0.000
Rbc	4.5 ± 0.05	4.5 ± 0.1	4.1 ± 0.05	4.1 ± 0.01	0.006
MCV	79.1 ± 0.7	79.4 ± 0.6	77.8 ± 0.4	77.5 ± 1.0	0.79
RDW	12.1 ± 0.3	16.4 ± 0.1	17.6 ± 0.09	16.7 ± 0.37	0.000

IDA = Iron deficiency anemia; TTH = Tension-Type Headache; HIT-6 = Headache Impact Test-6; VAS = Visual Analogue Scale; HAM-A = Hamilton Anxiety Rating Scale; BMI = Body Mass Index; TIBC = Total iron binding capacity; Rbc = Red blood cell; MCV = Mean cell volume; RDW = Red cell distribution with.

severity of anemia, no significant difference was observed in the frequency and severity of migraine when the data of patients with and without anemia were compared (Table II).

Finally, the association between ferritin levels and migraine was analyzed, as shown in Table II. A significant increase was found in menstrual migraine, VAS and HIT-6 scores with low ferritin levels. The association was statistically significant when adjusted for age and gender with logistic regression analysis. VAS [$R^2 = 0.224$, Odds Ratio (OR) = 1.57 (1.14-2.18), $p = 0.006$] was more favorable than HIT-6 (Table III).

Discussion

Iron deficiency is a common public health problem in developing countries, with symptoms ranging in severity from isolated low ferritin to severe hemoglobin decrease. In our study, the majority of the study population were female patients. In a study examining the relationship between gender and migraine in Turkey, the incidence of migraine in women was found to be 2.8 times higher than in men[23]. It is also known that the prevalence of iron deficiency anemia is higher in women than in men, which is found in a study[24] from Turkey as 7.4% of men and 25% of women.

Different results have been obtained in studies on the relationship between IDA and migraine in the literature. Iron deposition was shown in the periaductal gray matter, red nucleus, globus pallidus, and putamen in migraine patients, although the level varied with age[25]. These regions associated with migraine are the basis of the dopaminergic pathway and iron accumulation in the brain leads to altered expression of genes involved in dopamine functioning in this pathway, which has been linked to neurological disorders such as restless legs syndrome, with loss of dopaminergic function and alterations in cortical excitability[26]. On the other hand, it has been reported that high iron levels in migraine patients may lead to an increase in attacks by lowering the pain threshold through inflammatory mediators such as nitric oxide, neurotransmitter pathways in the central nervous system, and low Hb levels may lead to a decrease

Table II. The relationship between severity and frequency of migraine attacks and IDA.

Demographic Variables	Without Anemia	Anemia	*p* (< 0.05)	Ferritin (> 20 ng/ml)	Ferritin (< 20 ng/ml)	*p* (< 0.05)
Headache			0.60			0.23
• with Aura	2	2		1	0	
• without Aura	31	24		36	29	
• Aura+TTH	3	4		0	0	
• Without Aura+TTH	2	2		4	2	
Menstrual Migraine	5	42	0.02	4	43	0.015
Headache Frequency N (Mean)	5.47 ± 3.75	6.40 ± 4.16	0.34	5.53 ± 2.91	5.70 ± 3.65	
HIT-6	25.2 ± 0.6	25.6 ± 0.6	0.74	47.7 ± 2.1	55.0 ± 1.1	0.006
VAS	5.8 ± 0.2	5.8 ± 0.2	0.97	5.1 ± 0.1	6.1 ± 0.1	0.000
HAM-A	50.2 ± 2.1	52.7 ± 2.2	0.086	2.6 ± 0.1	2.8 ± 0.1	0.61
BMI	2.7 ± 0.1	2.2 ± 0.2	0.35	23.9 ± 0.4	25.9 ± 0.7	0.32
Iron µg/dl	69.2 ± 4.2	41.4 ± 4.7	0.00	25.7 ± 2.0	22.2 ± 1.8	0.00
TIBC	259.5 ± 9.6	372.2 ± 11.9	0.00	393.8 ± 13.0	408.6 ± 9.7	0.00
Ferritin	28.3 ± 3.2	13.6 ± 2.0	0.00	14.3 ± 3.8	10.4 ± 1.0	0.00
Hemoglobin (g/dl)	13.5 ± 1.06	11.5 ± 0.3	0.00	9.5 ± 0.7	7.2 ± 0.8	0.00
Rbc	4.5 ± 0.05	4.5 ± 0.1	0.006	4.1 ± 0.05	4.1 ± 0.01	0.02
MCV	79.1 ± 0.7	79.4 ± 0.6	0.79	77.8 ± 0.4	77.5 ± 1.0	0.19
RDW	12.1 ± 0.3	16.4 ± 0.1	0.00	17.6 ± 0.09	16.7 ± 0.37	0.00

TTH= Tension Type Headache; HIT-6= Headache Impact Test– 6; VAS= Visual Analogue Scale; HAM-A= Hamilton Anxiety Rating Scale; BMI= Body Mass Index; TIBC= Total iron binding capacity; Rbc= Red blood cell; MCV= Mean cell volume; RDW= Red cell distribution with.

in the number of migraine attacks[27]. However, it was shown that women with anemia had more severe migraine episodes[28]. Gür-Özmen et al[29] found that the frequency of IDA in women with migraine was higher than in the healthy control group. Hemoglobin levels were found to be associated with menstrual migraine prevalence, whereas no significant difference was found between iron parameters and migraine features. Another study[30], similar to ours, found low ferritin levels in the serum of women with recurrent migraine attacks during or toward the end of menstruation.

In this study, we homogenized the isolated IDA patients according to their hemoglobin levels to evaluate the relationship between the severity of anemia, the depth of iron deficiency, and ferritin levels with migraine symptoms. Therefore, we selected a control group with a similar mean for the subgroups. The frequency of menstrual migraine was associated with both hemoglobin and ferritin levels. VAS for severity of headache, HIT-6 for the effect of migraine on the patient's quality of life, and the number of attacks in a month were used. As a matter of fact, we found no significant difference between the subgroups in terms of monthly headache frequency, VAS, and HIT-6. Pamuk et al[16] found a higher prevalence of migraine in patients with iron deficiency but did not find a relation between migraine severity and anemia. Tayyebi et al[17] found a high frequency of iron deficiency in migraine patients, and when they grouped the patients by gender, they did not find any relationship between hemoglobin, ferritin levels and migraine symptoms in men, and they concluded that iron deficiency triggers migraine more in women.

Table III. Univariate relations (ORs) between migraine scales and ferritin levels.

Variable	R^2	OR (C.I. 95%)	*p* (< 0.05)
VAS	0.224	1.57 (1.14-2.18)	0.006
HIT-6	0.205	1.04 (1.01-1.08)	0.01

VAS = Visual Analogue Scale; HIT-6 = Headache Impact Test-6; OR = Odds Ratio; C.I. = Confidental Interval.

In a national cross-sectional age-stratified analytical study in adults in the USA, it was found that there was an inverse correlation between dietary iron and severe headache or migraine in women aged 20-50 years and serum ferritin levels in women over 50 years. The mean serum ferritin level between 20 and 50 years of age was 49.27 µg/L and 82.68 µg/L in women over 50 years of age, and it was emphasized that a threshold value should be reached for its effect on migraine attacks[28]. In our study, we finally divided the patients into two groups according to ferritin level

(< 20 ng/dl). Although local guidelines accept 15 ng/dl and below for low ferritin, we increased the target because similar studies have suggested a cut-off value between 15-80 ng/dl[17,28]. VAS and HIT-6 are inversely related to ferritin levels. VAS values showing headache severity were found to be more effective than HIT-6 values showing frequency and impact on daily life. This emphasizes the importance of VAS, which is a simple, easy, and inexpensive test.

We encountered limitations in our study, with one being the restricted number of patients and controls. Additionally, a notable limitation was the predominantly female composition of our study population. Recent studies[29,31] have shown a gender-variable association between IDA and migraine. Although we found a relationship between ferritin and migraine pain severity, different tests could have been added because the VAS score may vary according to the pain threshold of the patients. On the other hand, studies[17,29] on the effect of iron on migraine prevalence have intensified in the literature. Conflicting results such as dietary iron intake decreasing migraine and iron accumulation in the brain in migraine patients have been obtained, and there is still no definite consensus. Our study aimed to make a difference by evaluating the effect of the presence of anemia, severity of anemia, and ferritin level on migraine patients.

Conclusions

The presence and severity of anemia and iron deficiency do not affect the frequency and severity of migraine attacks in groups other than menstruation-related migraine. An inverse relationship was found between VAS, HIT-6, and ferritin levels. VAS was found to be more effective than HIT-6. Serum ferritin level may affect the clinic and treatment response in migraine, especially menstrual migraine, as in patients with restless legs syndrome. In these patients, the ferritin level target can be increased regardless of anemia.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contributions

Conceptualization by U.S.S., O.K.B.; Methodology by U.S.S., O.K.B.; Software by U.S.S.; Validation by U.S.S, O.K.B.; Formal Analysis by O.K.B.; Investigation by U.S.S., O.K.B.; Resources by U.S.S.; Data curation by U.S.S.; Writing-Original Draft Preparation by O.K.B.; Visialization by U.S.S.; Supervision by O.K.B.; Project Administration by U.S.S. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Balikesir University (date of approval: 10.05.2023, protocol code: 2023/63).

Informed Consent

Written informed consent was obtained from all participants involved in the study before entry into the study.

Availability of Data and Materials

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy reasons.

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