The Role of Serum Ferritin, Vitamin B12 and Vitamin D Levels in Childhood Primary Headaches

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Abstract

Aim: In this study, it was aimed to investigate the relationship between headache components and serum ferritin, vitamin B12 and vitamin D levels in pediatric patients with migraine and tension-type headache (TTH).

Methods: The data of patients aged 7-17 years who applied to the outpatient pediatric neurology clinic with a complaint of headache and were diagnosed with migraine and TTH based on the International Classification of Headache Disorder (ICHD)-3 beta criteria were evaluated retrospectively.

Results: The mean age of the patients was 13.80 ± 3.89 years in the migraine group and 14.10± 4.17 years in the TTH group. In the migraine group, the duration of the attack was longer and the pain intensity was higher. Unilateral headache, throbbing character, nausea, vomiting, discomfort from light and sound were statistically significantly higher in the migraine group. In patients with migraine, low vitamin D and low ferritin levels were associated with a prolongation of the disease duration and an increase in the frequency of attacks. A decrease in serum iron level was associated with an increase in pain severity and a decrease in vitamin D levels was associated with an increase in attack duration. It was observed that there was an increase in the frequency of attacks with a decrease in serum ferritin levels in the TTH group. No statistically significant correlation was found between headache characteristics and vitamin B12.

Conclusions: Our study shows the necessity of routine evaluation of vitamin D and ferritin levels in childhood primary headaches.

Keywords: *Migraine, Tension-type headache, iron deficiency anemia, vitamin D, vitamin B12*

1. Introduction

Headache is among the most common reasons for referral to pediatric neurology outpatient clinics. In recent years, the frequency of childhood migraine and recurrent headache has increased due to undesirable changes in children's lifestyles.[1] The frequency of headaches in childhood ranges from 26.6% to 93.3%.[2,3] The majority of headaches in children are primary headaches, including migraine and tension-type headaches (TTH)[1]. The etiology of headache can usually be revealed with a detailed history and a careful neurological examination. It is the most important point that the clinician should not miss the secondary headaches that require urgent treatment in a patient with headache. Detailed history and neurological examination play an important role in excluding secondary causes, classifying headaches and relieving families concerns.[4] Neuroimaging techniques should be used in differential diagnosis when necessary to exclude secondary causes. An accurate definition and classification of the headache symptom is an important factor influencing patient management. Neuroimaging techniques should be used in differential diagnosis when necessary to exclude secondary causes. An accurate definition and classification of the headache symptom is an important factor influencing patient management. The International Classification of Headache Disorder (ICHD-3 beta version) has been proposed to support and prove this common neurological problem.[5] Chronic headaches prevent school attendance, cause loss of daily activities, insufficient participation in regular activities, loss of productivity and significant deterioration in quality of life.[4]

In this study, we aimed to compare the headache components and scores, including the number of attacks, duration of attacks, frequency, severity and accompanying symptoms, between the two groups, and to reveal their effects on daily life in pediatric patients with migraine and TTH. At the same time, it was aimed to investigate the relationship between headache characteristics and serum ferritin, vitamin B12 and vitamin D levels.

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2. Materials and methods

This single-center, cross-sectional, clinical-based and retrospective study was conducted on patients who applied to the outpatient neurology outpatient clinic with headache complaints between January 2021 and January 2023 and were diagnosed with migraine and TTH based on the "International Classification of Headache Disorder (ICHD-3 beta)" criteria was included in the study. Patients with secondary headaches who could not be classified according to the criteria were not included in the study[5]. As the control group, 100 healthy children aged 7-17 years, who applied to the pediatric health and diseases polyclinics for routine control, did not have acute and chronic diseases and did not use drugs, and whose demographic characteristics were similar to the patient group, were included. Although there is no standard approach in the evaluation of patients who apply to pediatric neurology outpatient clinics with the complaint of outpatient headache, a detailed history is taken from all patients and a detailed neurological examination including blood pressure measurement and ophthalmological examination is performed. All these data are recorded in the electronic hospital database by the pediatric neurologist at each control. Demographic characteristics such as age, gender, neurological examinations, headache characteristics, laboratory findings (hematological parameters, routine biochemistry, serum ferritin, vitamin B12 and vitamin D), neuroimaging results, if any, were recorded. Patients who were diagnosed with migraine and TTH and kept a complete headache diary for the last 3 months were included in the study in the order of admission to the hospital, without any other selection. In the headache diary; days of headache, duration of pain, severity of pain (out of 10), accompanying nausea-vomiting during pain, being disturbed by light and/or sound, pain, taking painkillers, not being able to go to school, having to return home from school, not being able to study at home or whether it caused the inability to attend a social event. These diaries were kept by the patients with parental control. Pediatric Migraine Disability Assessment (PedMIDAS) scores of each patient were calculated with the help of diaries[6]. Today, the determination of the effects of headache, the decision of prophylaxis, the follow-up of the chronicity process is done with the PedMIDAS scoring system. While evaluating the PedMİDAS scale; Those with a score of 1-10 were classified as none, between 11-30 as mild, 31-50 as moderate, and above 50 as severe[6]. Written informed consent was obtained from the patients and parents participating in the study. Medical Ethics Committee approval was obtained for the study protocol and the study was conducted within the scope of the Declaration of Helsinki (Number. 2023/4904)

2.1. Statistical analyses

The variables used in the study were summarized with mean, standard deviation, median, minimum and maximum values, frequency and percentage according to measurement levels. The assumption of normal distribution for numerical variables was examined using the Shapiro-Wilk test. The comparison of continuous variables that did not conform to normal distribution between more than two groups was compared with the Kruskal-Wallis H test and then with the Dunn test as a Post Hoc test. Comparisons of continuous variables that did not fit normal distribution between two independent groups were compared with the Mann Whitney U test. Pearson chi-square and Fisher's Exact tests were used for categorical variables. Spearman rho correlation coefficient was used to determine the relationship between two independent variables with continuous measurement values that did not conform to the normal distribution. $p \leq 0.05$ was accepted as statistical significance level. IBM SPSS Statistics 22 program was used in the analysis.

3. Results

A total of 264 patients (100 migraine, 64 TTH and 100 controls), 169 (64%) girls, aged 7-17 years, were included in the study. There was no difference between migraine, TTH and control patients in terms of age and gender. The demographic characteristics of the patients and their comparison between the three groups are summarized in Table 1.

Table 1

Demographic and clinical information of the patients

		Migraine (n=100)	TTH (n= 64)	Control (n=100)	P
Age /year (Mean±SD)		13.80 ±3.89 (7.16-17.00)	14.10±4.17 (7.35-17.00)	13.60±3.21 (8.31-17.00)	0.868
Gender	F (%)	64 (%64.00)	42 (%65.60)	63 (%63.00)	0.782
	M(%)	36 (%36.00)	22 (%34.40)	37 (%37.00)	
Disease duration month median (min-max)		26 (6-82)	18 (8-61)	—	0.038

TTH, Tension-type headache; SD, standard deviation

Table 2

Comparison of headache characteristics in migraine and TTH groups

	Migraine (n, %)	TTH (n, %)	P
Headache attack frequency			
• 1-3 times a month	16 (%16.00)	8 (%12.50)	
• 1 time per week	14 (%14.00)	8 (%12.50)	
• 2-3 times a week	45 (%45.00)	31 (%48.43)	0.734
• 4 times a week	25 (%25.00)	17 (%26.56)	
Headache attack duration			
• 0.5-1 hour	22 (%22.00)	22 (%34.37)	
• 1-3 hours	42 (%42.00)	36 (%56.25)	
• 4-24 hours	31 (%31.00)	6 (%9.37)	0.032
• 24-72 hours	5 (%5.00)	0 (%0.00)	
Shape of the headache			
• Pulsating	65 (%65.00)	4 (% 6.25)	
• Printmaker	15 (%15.00)	50 (%78.12)	<0.001
• Both of them	20 (%20.00)	10 (%15.62)	
Headache severity			
• Mild	1 (%1.00)	0 (%0.00)	
• Middle	34 (%34.00)	40 (%62.50)	0.022
• Severe	65 (%65.00)	24 (%37.50)	
Headache localization			
• One sided	64 (%64.00)	21 (%32.81)	
• Bilateral	27 (%27.00)	34 (%53.12)	0.044
• Uncertain	9 (%9.00)	9 (%14.06)	

TTH, Tension-type headache

When the subgroups of migraine patients were evaluated according to ICHD-3 beta classification; 80 (80%) patients were diagnosed as migraine without aura, 11 (10%) migraine with aura, 9 (9%) chronic migraine. When patients with migraine are evaluated in terms of visual, auditory and sensory auras; Auras were detected in 14 patients (14%), color vision in 6 patients (6%), linear shapes in 17 patients (17%), numbness in the arms and legs in 10 patients

(10%). Migraine history in the family (mother, father, sibling, first degree relatives) was found in 49 (49%) migraine group and 16 (25%) in TTH group (p=0.001). When we look at the headache characteristics of the patients; There was no statistically significant difference between the groups in terms of attack frequency. In the group of patients diagnosed with migraine, the duration of attacks was statistically significantly longer and the severity of headache was higher (p=0.032; p=0.022, respectively). Unilateral, throbbing, nausea, vomiting, and discomfort from light and sound were statistically significantly higher in the migraine group (respectively- p=0.044; p <0.001; p < 0.001; p=0.003; p <0.001; p=0.047). Triggering/increasing pain with both physical and mental activity was significantly higher in the migraine group (p=0.006; 0.086, respectively). In addition, the increase in pain with hunger, insomnia, cold weather and smoking environment was significantly higher in this group (p=0.087; p= 0.008; p=0.006; p=0.035). The comparison of headache characteristics between the two groups is summarized in Tables 2 and Table 3.

When patients were asked to determine the severity of pain according to Visual Analogue Scoring (out of 10), it was significantly higher in the migraine group (p=0.038). There was no statistical significance between the two groups in terms of the pedMIDAS score used to show the severity of pain (p=0.138) (Table 4). In the migraine patient group, a positive and significant relationship was found between prolongation of the disease duration and an increase in the frequency of attacks and an increase in the duration of attacks (p=0.032; p=0.013, respectively). There was no statistically significant difference in hematological parameters, iron, ferritin, vitamin B12 and vitamin D levels between the three groups (p> 0.05) (Table 5). The relationship between headache characteristics and laboratory parameters was also evaluated in the study. It was found that low vitamin D and ferritin levels in patients with migraine were significantly associated with longer disease duration (p= 0.032; p=0.004, respectively). The frequency of migraine headache attacks was increased in children with iron deficiency anemia (IDA) and vitamin D deficiency (p= 0.004; p=0.003, respectively). At the same time, a decrease in serum iron was associated with an increase in headache severity (p= 0.001) and a decrease in vitamin D levels with an increase in attack duration (p= 0.042). No statistically significant correlation was found between headache characteristics and vitamin B12. No statistically significant correlation was found between the Visual Analogue Scale (VAS) values, in which the severity of headache was measured, and the pedMIDAS score and laboratory parameters. There was no statistically significant relationship between disease duration, attack frequency, headache severity and attack duration in the patient group with TTH. A correlation was observed between a decrease in serum ferritin level and an increase in the frequency of attacks (p= 0.026). No statistically significant correlation was found between headache characteristics and other laboratory parameters in children with TTH.In migraine patients, 52% of cranial magnetic resonance imaging (MRI) were normal and 48% of them had benign changes. In TTH patients, 33 (51.5%) of the cranial MRIs were normal and 31 (48.4%) had benign changes.

Table 3

Comparison of headache accompanying symptoms in migraine and TTH groups

	Migraine (n, %)	TTH (n, %)	P
Symptoms accompanying headache			
• Photophobia	80 (%80.00)	28 (%43.75)	< 0.001
• Phonophobia	91 (%91.00)	47 (%73.43)	0.047
• Discomfort with odor	40 (%40.00)	15 (%23.44)	0.126
• Nausea	65 (%65.00)	0 (%0.00)	< 0.001
• Vomiting	27 (%27.00)	0 (%0.00)	0.003
• Dizziness	63 (%63.00)	31(%48.44)	0.074
• Tears in the eyes	42 (%42.00)	17 (%26.56)	0.127
• Stomachache	26 (%26.00)	15 (%23.44)	0.936
Causes of headache			
• Physical fatigue	42 (%42.00)	9 (%14.06)	0.006
• Mental work	56 (%56.00)	23 (%35.93)	0.086
• Extreme excitement	17 (%17.00)	10 (%15.62)	0.862
• Stress	76 (%76.00)	47 (%73.43)	0.538
• Hunger	65 (%65.00)	28 (%43.75)	0.087
• Thirst	34 (%34.00)	13 (%20.31)	0.151
• Insomnia	80 (%80.00)	29 (%45.31)	0.008
• Going to school	37(%37.00)	18 (%28.12)	0.621
• Watching television	31 (%31.00)	14 (%21.87)	0.391
• Using a computer	37 (%37.00)	20 (%31.25)	0.623
• Cold weather	45 (%45.00)	10 (%15.62)	0.006
• Hot weather	32 (%32.00)	16 (%25.00)	0.812
• Smoking environment	30 (%30.00)	6 (%9.37)	0.035
Causes of headache relief			
• To relax	80 (%80.00)	43 (%67.18)	0.367
• Cold application	7 (%7.00)	6 (%9.37)	0.728
• Eating	27 (%27.00)	15 (%23.43)	0.855
• Vomiting	14 (%14.00)	0 (%0.00)	0.074
• Medication intake	56 (%56.00)	33 (%51.56)	0.631

TTH, Tension-type headache

Table 4

Comparison of VAS and PedMIDAS Scores in migraine and TTH patient groups

	Migraine Median (min-max)	TTH Median (min-max)	P
Visual Analoque Scoring	8.00 (4-10)	7.00 (4-10)	0.038
Pediatric Migraine Disability Assesment	19.00 (0-155)	15.00 (0-77)	0.138
Rating according to the PedMIDAS scale			
• Very little-none	25 (%25.00)	18 (%28.10)	0.342
• Mild	47 (%47.00)	35 (%54.70)	
• Middle	13 (%13.00)	9 (%14.10)	
• Severe	15 (%15.00)	2 (%3.10)	

TTH, Tension-type headache, PedMIDAS, Pediatric Migraine Disability Assesment

Table 5

Comparison of laboratory parameters in migraine, TTH and control patient groups

	Migraine n=100	TTH n=64	Control n=100	P
Hb (g/dl)	13.70±1.35 (11.20-16.60)	13.81±1.40 (10.90-16.60)	13.80 ±1.38 (8.60-17.80)	0.931
MCV (fl)	84.65 ±2.74 (60.90-96.40)	83.80±2.80 (74.70-91.80)	83.50 ±3.52 (64.20-96.30)	0.405
Serum iron (ug/dl)	69.50 ±22.10 (3.00-165.00)	64.00±20.32 (12.00-135.00)	58.50±20.80 (6.00-168.00)	0.091
Ferritin (ng/ml)	25.60±16.38 (5.70-247.40)	23.45 ±12.44 (3.90-96.40)	25.90±14.51 (3.90-161.80)	0.792
Vitamin B12 (pg/ml)	278.50±105.34 (135.00-748.00)	283.50 ±95.54 (147.00-419.00)	278.00 ±124.50 (131.00-907.00)	0.428
Vitamin D (ng/ml)	17.40 ±18.56 (3.30-123.00)	13.85±5.64 (1.10-56.00)	18.30±9.28 (1.00-89.00)	0.629

Hb, Hemoglobine; MCV, Mean Corpusculer Volume; TTH, Tension-type headache

4. Discussions

This study shows that low vitamin D and serum ferritin levels are associated with longer disease duration and increased frequency of attacks in childhood migraine patients. While a decrease in serum iron level was associated with higher headache severity, a decrease in vitamin D level was associated with increased attack duration. It was found that low ferritin level was associated with increased attack frequency in children with TTH diagnosis.

In previous studies investigating migraine and vitamin D deficiency, it was reported that migraine attacks increase in cold seasons and high latitudes, and the increase in the frequency of attacks may be due to low vitamin D.[7,8] A negative correlation was shown between vitamin D level and the frequency of headache attacks. In a study evaluating 300 children with migraine, it was reported that vitamin D deficiency was common in children and the prevalence of recurrent headache was higher in the vitamin D deficiency group than in the control group.[9] Vitamin D levels were found to be low in children with primary headache, both migraine with and without aura, and children with TTH.[10] In a study conducted in our country, the vitamin D level was found to be lower in the migraine patient group than in the TTH group.[11] On the contrary, several studies reported that no relationship was found between vitamin D level and migraine attack frequency, duration and severity.[12,13] In our study, vitamin D deficiency was detected in migraine, TTH and healthy control group. This result supports that vitamin D deficiency is a common health problem in our society. When evaluated in terms of headache characteristics, a decrease in vitamin D levels in patients with migraine was found to be associated with a prolongation of the disease duration and an increase in the frequency of attacks. No relationship was found between headache characteristics and vitamin D levels in children with TTH.

Previous studies investigating migraine and IDA reported that IDA was common in patients with menstrual migraine, and the severity and duration of headache increased in this group[14]. In a study conducted in children with IDA accompanying migraine, it was found that the frequency of headache attacks and pain severity were higher, and the pedMIDAS score was higher than those without anemia[15]. This study reported that when migraine children with anemia were re-evaluated after three months of iron treatment, the frequency, severity and duration of headache attacks decreased, and the pedMIDAS score also decreased[15]. A similar study supported that IDA was more common in children with migraine than the control group, and that low levels of hemoglobin, iron, and ferritin had an effect on the frequency, severity and duration of headache attacks.[16] While the increase in the frequency of pain in the TTH patient group was related to the decrease in serum ferritin and hemoglobin, it was shown that it did not affect the severity and duration of headache.[17] In another study, it was reported that the ferritin level was found to be significantly lower during an attack than during the attack-free period, but this situation was not associated with the frequency of headache.[18] In our study, it was shown that the decrease in ferritin level in patients with migraine was associated with the duration of the disease and an increase in the frequency of attacks. While the decrease in ferritin level was associated with the prolongation of the disease duration in the TTH patient group, it was not found to be associated with the severity of headache and the duration of the attack.

There are differences between studies examining the relationship between migraine and vitamin B12 or homocysteine levels in the literature. In a population-based study, it was stated that low vitamin B12 and high homocysteine levels were found in children with recurrent headaches.[19] In another study, although homocysteine levels were increased in children with migraine compared to healthy children, vitamin B12 levels were found to be similar.[20] A few studies reported that the mean homocysteine level in patients with migraine was higher than the general population, however, the vitamin B12 level was within normal limits. When these patients were re-evaluated six months after B12 and folic acid supplementation, they reported that the frequency of migraine attacks and the severity of pain decreased with a decrease in homocysteine levels.[21,22] In our study, no statistically significant difference was found between the migraine, TTH and healthy control groups in terms of vitamin B12 levels. One of the limiting factors of our study is that homocysteine, which is an indicator of functional vitamin B12 deficiency, and serum and urine methylmalonic acid levels were not measured in our study.

5. Conclusions

Recurrent headaches in children constitute an important patient burden for pediatric and pediatric neurology outpatient clinics. A detailed history and careful general and neurological examination can be diagnosed in the majority of patients. Iron deficiency anemia, vitamin D and vitamin B12 deficiency should be routinely screened and treated in these patients.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Inönü University Faculty of Medicine Ethics Committee with the decision no. 2023/4904.

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

Concept/Design, Data acquisition, Data analysis and interpretation, Drafting manuscript, Critical revision of manuscript and Final approval and accountability: GY.

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