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Research Article

Is There a Relation Between Vitamin B_{12} Levels and Headaches in Children and Adolescents?

Çocuk ve Ergenlerdeki Baş Ağrılarının Vitamin B_{12} Düzeyleri ile İlişkisi var mı?

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ABSTRACT

Objective: *Primary headaches are common and benign discomforts both in children and adolescents. However, they have a negative influence on the quality of life. This retrospective study aimed to determine the relationship between vitamin B_{12} results and primary headaches in Turkish children.*
Methods: *Demographical features, headache types, laboratory results, including vitamin B_{12}, were assessed retrospectively. Headache types were categorized as tension-type headache, migraine, and unclassified headache according to the International Classification of Headache Disorders-beta version (ICD-3 beta). Patients with seconder headaches, anemia, and macrocytosis were excluded.*
Results: *The study group consisted of 133 (86 female, 47 male) patients with headache and a control group of 103 (57 female, 46 male) healthy children. There was no significant difference in terms of age and gender between groups ($p>0.05$). Vitamin B_{12} levels in tension-type headache, migraine, and unclassified headache groups were significantly lower ($p<0.0001$) than in the control group. Logistic regression has identified lower vitamin B_{12} levels than 400 pg/ml as an independent risk factor for headache (OR: 3.212, 95% CI: 1.850-5.576).*
Conclusion: *We conclude that lower vitamin B_{12} levels than 400 pg/mL may be associated with tension-type headache, migraine, and unclassified headache.*

Keywords: *Vitamin B_{12} levels, unclassified headache, migraine, tension-type headache, cobalamin deficiency, the pain-reducer effect of vitamin B_{12}*

ÖZ

Amaç: *Primer baş ağrıları, çocuk ve ergenlerde sık görülen benign patolojiler olmalarına rağmen, yaşam kalitesi üzerine olumsuz etki gösterirler. Bu retrospektif çalışma, çocuk ve ergenlerde vitamin B_{12} düzeyleri ile primer baş ağrıları arasındaki ilişkiyi incelemeyi amaçlamıştır.*
Yöntem: *Demografik özellikler, baş ağrısı tipleri ve vitamin B_{12} düzeylerini içeren laboratuvar sonuçları retrospektif olarak kaydedildi. Baş ağrısı tipleri International Classification of Headache Disorders-beta version (ICD-3 beta) kriterlerine göre; gerilim tipi, migren ve sınıflandırılamayan tipte baş ağrısı olarak sınıflandırıldı. Sekonder baş ağrısı, anemisi ve makrositozu olan olgular dışlandı.*
Bulgular: *Çalışma grubu; 133 hasta (86'si kız, 47'si erkek) ve 103 (57'si kız, 46'sı erkek) sağlıklı kontrol olmak üzere toplam 236 kişiden oluşmaktaydı. Hasta ve kontrol grupları arasında yaş ve cinsiyet açısından anlamlı farklılık saptanmadı ($p>0.05$). Vitamin B_{12} düzeyleri gerilim tipi, migren tipi ve sınıflandırılamayan tipte baş ağrısı gruplarının tamamında kontrol grubuna göre anlamlı olarak düşük saptandı ($p<0.0001$). Lojistik regresyon analizi sonrasında vitamin B_{12} düzeyinin 400 pg/ml'nin altında olmasının baş ağrısı için bağımsız bir risk faktörü olduğu saptandı (OR: 3.212, 95% CI: 1.850-5.576).*
Sonuç: *Vitamin B_{12} düzeylerinin 400 pg/mL'nin altında olmasının gerilim tipi, migren tipi ve sınıflandırılamayan baş ağrıları ile ilişkili olabileceğini düşünmekteyiz.*

Anahtar kelimeler: *Vitamin B_{12} seviyeleri, sınıflandırılamayan baş ağrısı, gerilim tipi baş ağrısı, kobalamin eksikliği, vitamin B_{12}'nin ağrı kesici etkisi*

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INTRODUCTION

Headaches are common chronic neurological disorders, both in children and adolescents [1]. Intracranial mass, trauma, infection, metabolic, or vascular diseases should be considered as they may be life-threatening conditions for secondary headache [2]. Although primary headaches are benign, they may have negative impacts on patients' quality life [3]. Tension-type headache (TTH) is a common cause of primary headaches in children. Though the exact pathological mechanism of TTH is unclear, both muscular and psychogenic factors are thought to be related to TTH. Migraine is another common cause of recurrent primary headaches in children and has a significant impact on school attendance and family dynamics [4]. Pediatric migraine differentiates from adult migraine in response to treatment and its presentation. Under the new classification, bilateral location and shorter duration of attacks are currently revised for children in the diagnosis of migraine headaches [5]. Although migraines are divided into six categories, migraine with aura and migraine without aura are the most important and frequently seen subtypes. Headaches that differ from almost all types of headaches are classified as unclassified headaches.

There is some evidence supporting the use of comprehensive elimination diets in the prevention of migraine and other headache types. Various comprehensive elimination diets have been discussed in the literature including diets containing high folate, low fat, ketogenic diets, modified Atkins diets, and high omega-3 / low omega-6 diets [6]. There are also some reports supporting folate, vitamin B_2, vitamin B_6, vitamin B_{12} supplements in the treatment of migraine. Evidence exists that diets rich in folate and vitamin B_6/B_{12} supplements may prevent attacks of migraines, especially in people with certain gene variants of enzymes involved in homocysteine metabolism [7].

Anemia is a common health problem. Numerous studies exist regarding the negative impact of iron deficiency anemia (IDA) on psychomotor development [8]. Moreover, some reports have pointed out the association between headache and anemia [9]. Vitamin B_{12} is a water-soluble vitamin B that participates in DNA synthesis and plays a role in cell division, proliferation, and nerve myelination. Vitamin B_{12} deficiency is a common nutritional problem, especially in developing countries. Developmental delay, irritability, weakness, failure to thrive, paresthesia, sensory deficits, loss of deep tendon reflexes, movement disorders, hypotonia, seizures, and paralysis are the manifestations of vitamin B_{12} deficiency [10]. The prevalence may be as high as 40% in children in developing countries due to malnutrition, and inadequate intake is the most common cause of vitamin B_{12} deficiency [11]. The main systems of the human body affected by vitamin B_{12} deficiency are the hematological system, nervous system, skin, and mucous membranes. Numerous neurological disorders have been reported related to vitamin B_{12} deficiency. Moreover, studies on the relationship between headache and vitamin B_{12} deficiency have been increasing [12-15]. In the current study, we aimed to determine the relationship between vitamin B_{12} levels, and headache types in Turkish children and adolescents.

MATERIAL and METHOD

Study design and subject

We have obtained the approval of the local ethics committee (Date: 03/20/2019 No:2019-03/03) in line with the principles outlined in the Second Declaration of Helsinki. Due to the retrospective design of the study, the waiver of consent was not required by the ethics committee. This retrospective study was conducted from January 2018 to July 2018 in the department of pediatric neurology clinic of a state hospital, and included 133 cases aged between 5-18 with complaints of headache. Headache types, demographic features, and laboratory results were assessed retrospectively. Since the most frequent headache types in children were migraines, TTH, and unclassified headache, headache types were specified in these categories and categorized according to the International Classification of Headache Disorders-beta version (ICDH-3 beta).

Patients were excluded if they had a chronic disease, secondary headache with specific pathology detected on examination such as hypertension or detected on magnetic resonance imaging (MRI) like an intracranial mass or hydrocephalus. The control group consisted of 103 healthy children aged between 5-18 years without a headache or history of a chronic disease or drug use. The control group was chosen from the healthy children outpatient clinic among those who had no history of headache and underwent complete blood count (CBC), vitamin B_{12} analyses in the previous two weeks. The results were extracted from the electronic database. Demographic features and laboratory results of the patients and the healthy controls were compared according to headache types. Serum vitamin B_{12} levels were analyzed by electrochemiluminescence (ECLIA) immunoassay. Serum vitamin B_{12} level <400 pg/ml was defined as deficiency. Patients with anemia and macrocytosis were excluded from the study.

Statistical analysis

SPSS-22 (Statistical Package for Social Sciences) was used for statistics of the study. The Kolmogorov-Smirnov test was applied to quantitative data to detect conformity to the normal distribution, and values were stated as median and interquartile range. The differences among four groups regarding numerical variables were estimated by Kruskal-Wallis test and pairwise comparisons were compared using Tamhane tests. Chi-square test was applied to compare the categorical variables between groups, and a value of $p<0.05$ was accepted as statistically significant.

RESULTS

The study group comprised 133 patients (86 female, 47 male) and 103 (57 female, 46 male) healthy children. The most frequent headache types in the study group were TTH (42.1%), unclassified headache (30%), and migraine (27.8%). Demographic results are summarized in Table 1. Vitamin B_{12} results of 133 patients were extracted from the electronic database. Serum median vitamin B_{12} levels in the children with TTH, migraine, unclassified headache, and control groups were 315 (162.7) pg/ml, 313 (132) pg/ml, 284.7 (154.85) pg/ml, and 405 (238) pg/ml respectively. Vitamin B_{12} levels were significantly lower in TTH, migraine, and unclassified headache groups than in the control group. ($p<0.0001$) (Table 1). The logistic regression analysis has demonstrated vitamin B_{12} deficiency (<400 pg/ml) as an independent risk factor in children for headache (OR: 3.276, 95% CI:1.889-5.683, Table 2).

Table 1. Demographics, hemoglobin, MCV and vitamin B_{12} results of the headache and control groups.

	Tension-type headache (n=66, 25%)	Migraine (n=46, 17.4%)	Unclassified headache (n=48, 18.2%)	Control Group (n=103, 39.1%)	Pα-value
Age (years)*	11 (3)	12 (5)	12 (5)	13 (6)	0.151
Female	46 (69.7%)	25 (54.3%)	25 (56.3%)	57 (55.3%)	0.236
Male	20 (30.3%)	21 (45.7%)	21 (43.8%)	46 (44.7%)	0.343
Hemoglobin*	13.9 (1.15) mg/dL	13.9 (1.2) mg/dL	13.8 (1.5) mg/dL	13.6 (1.5) mg/dL	0.761
MCV*	81.45 (6.78) fL	81.7 (5.20) fL	81.8 (6.10) fL	82.7 (5.6) fL	<0.0001
Vitamin B_{12}*	300 (188) pg/ml**	313 (131) pg/ml**	278 (152.6) pg/ml**	405 (238) pg/ml	

**Median, (interquartile range), α: the difference of numerical variables between four groups obtained by Kruska Wallis and pairwise comparisons by Tamhane test*

***Vitamin B_{12} levels were significantly lower in tension-type, migraine, and unclassified headache groups than in the control group (pα<0.0001)*

p1α=0.001, difference between control and tension-type headache groups

p2α=0.005, difference between control and migraine groups,

p3α=0.01, difference between control and unclassified headache group,

p4α=0.999 difference between tension-type headache and migraine groups,

p5α=0.767 difference between tension-type headache and unclassified headache groups.

Table 2. Multiple logistic regression model for vitamin B_{12} deficiency.

		95% CI		
	Odds Ratio	Lower limit	Upper Limit	p-value
Vitamin B_{12} deficiency (<400 pg/ml)	3.276	1.889	5.683	<0.0001

The logistic regression has demonstrated vitamin B_{12} deficiency (<400 pg/ml) as an independent risk factor in children for headache (OR: 3.276, 95% CI:1.889-5.683).

DISCUSSION

Headache is one of the most common symptoms among children and adolescents who are admitted to emergency services, pediatrics, and pediatric neurology clinics [16]. There is a high prevalence of psychological comorbidity related to headache disorders, which significantly decreases the quality of life, with the severity of impairment being dependent on headache type [3]. Therefore, this issue is an important public problem. Although there are studies regarding the relationship between vitamin B12 deficiency and various neurological manifestations [10,17-20], studies on the relationship between vitamin B_{12} deficiency and headaches should be conducted. Hence, the present study hypothesizes that there may be an association between headache and vitamin B_{12} deficiency. The major outcomes of the current study were i) TTH was the most frequent headache type (42.1%) of the study group ii) vitamin B_{12} levels were significantly lower in TTH, migraine, and unclassified headache groups than in the control group (p<0.0001) (Table 1). iii) Vitamin B12 level lower than 400 pg/ml is an independent risk factor for headache (OR: 3.212, 95% CI:1.850-5.576) (Table 2). In the present study, the most frequent headache type was TTH. Tension-type headaches recurred at intervals of more (n=38), and less than 15 days (n=18) a month. Among migraineurs, the history of aura was present in 14 cases. Unclassified headache differed as for all headache features from both migraine and TTH. The common features were mild intensity and short duration (<1 hour) in patients who were categorized as unclassified headaches. These symptoms were similar to undifferentiated headaches, which were previously described by Wöber et al. [21].

Although there is generally no sex difference in prepubertal children, adult women suffer from migraines more frequently than adult men [22]. Some epidemiological studies have shown that the prevalence of migraine increases with age until a peak is reached during the fourth decade of life; thereafter, the prevalence declines [23,24]. According to a study performed in school children between the ages of 7 and 17 years in Kayseri, the prevalence of recurrent headache was 47.5%, and the estimated prevalence rates of unclassified headache, migraine and TTH were 4.6%, 7.2%, and 7.8%, retrospectively. In children older than 15 years, the frequency of migraine and TTH significantly increased [25]. Jin et al. [26] found a higher prevalence of headaches in the 12 and 15 year age groups. In the current study, headache episodes recurred in 42.1%, 27.8%, and 30% of children with TTH, migraine, and unclassified headache groups, respectively (Table 1). There were no statistically significant differences between headache types and age.

Vitamin B_{12} deficiency can present with various neurological manifestations during infancy, childhood, and adulthood. Neurological symptoms are attributable to pathology in the peripheral nerves, posterior, and lateral columns of the spinal cord and brain. When we browse through the symptomatology in infancy, slowly progressive manifestations such as motor delay, apathy, and developmental regression, and acute neurological events such as seizure or involuntary movement disorders may also be seen [27]. Besides, vitamin B_{12} has antinociceptive effects with some resultant clinical outcomes [28,29]. A possible explanation of the antinociceptive mechanism of vitamin B_{12} comes from interactions with prostaglandin synthesis, including cyclooxygenase (COX) enzymes. Although animal studies exploring the direct effects of vitamin B_{12} on COX enzyme are lacking, in murine models dextran sodium sulfate-induced colitis showed that a methyl-deficient diet (excluding vitamin B_{12}, folate, and choline) leads to a significant upregulation of COX_2 in the intestines after exposure

to dextran sulfate. Probably, vitamin B_{12} may have a role in the regulation of COX_2 levels during inflammatory challenges [30]. Hosseinzadeh et al. [31] performed a hot plate and abdominal pain studies. In these studies, mice showed mild and moderate reduction in pain in response to the administration of vitamin B_{12}. Hot plate pain study testing involves central COX mechanism, whereas abdominal writhing measures peripheral COX enzyme effects, suggesting that vitamin B_{12} may have both central and peripheral COX inhibitory features. Another possible antinociceptive mechanism of vitamin B_{12} involves neurotransmitters. Evidence shows that homocysteine decreases noradrenaline and 5-hydroxytryptamine synthesis. Additionally, it is well known that vitamin B reduces homocysteine levels. Lowering homocysteine levels with vitamin B might regulate neurotransmitter synthesis in individuals with high homocysteine levels, which may contribute to neurotransmitter-moderated antinociceptive effects [32]. In the current literature, the pain-reducing effect of vitamin B_{12} is observed in conditions of chronic pain including diabetic neuropathy, postherpetic neuralgia, low back pain, and aphthous ulcers with significant beneficial results [33,34]. Some studies have exhibited the relationship between vitamin B_{12} and headaches. Çalik et al. [12] performed a prospective study with 75 TTH patients and a control group of 49 healthy children. Serum vitamin B_{12} levels were significantly lower in patients with TTH than in the control group. Moreover, 66.6 % of the patients in the headache group with vitamin B_{12} deficiency also had an anxiety disorder. They suggested that there was a high incidence of vitamin B_{12} deficiency in those with TTH and anxiety disorder. Furthermore, some reports have shown the relationship between neuropsychiatric disorders such as depression and vitamin B_{12} deficiency. In the previous studies a possible mechanism has been suggested indicating the role of vitamin B_{12} in the synthesis of S-adenosyl methionine, which is an important methyl donor for the production of monoamine transmitters [35]. Togha et al. [13] performed a case-control study in 70 adult patients with migraine and 70 healthy adult cases. Serum vitamin B_{12} levels were significantly lower in patients with migraine than in the control group ($p=0.07$), whereas migraineurs had higher levels of MMA ($p=0.027$). They suggested that patients with lower levels of vitamin B_{12} and higher levels of MMA had higher odds of migraine. Aydın et al. [14] performed a retrospective study in children and adolescents, including 65 migraineurs and 87 healthy cases. They found a statistically significant difference between the migraine group and the control group, in terms of levels of vitamin B_{12} and folic acid ($p=0.008$, $p<0.0001$). Abu-Shanab et al. [15] performed a study in 485 patients and found that recurrent headaches were significantly related to lower vitamin B_{12} levels.

The reference range for vitamin B_{12} was 201-1100 pg/ml. Nevertheless, serum vitamin B_{12} levels between 201-400 pg/ml have frequently been found in both metabolically and clinically significant vitamin B_{12} deficiency due to frank depletion of B_{12} stores [36]. Thus, we accepted the adequate level for serum vitamin B_{12} as ≥400 pg/ml. In the current study, the median vitamin B_{12} levels were <400 pg/ml in all types of headache groups, and we also observed significantly lower vitamin B_{12} levels in TTH, migraine, and unclassified headache groups when compared to the control group ($p<0.0001$). The probable mechanisms of the linkage between headache and vitamin B_{12} deficiency involve the neurotransmitter-moderated antinociceptive effect of vitamin B_{12}, and the role of vitamin B_{12} to control COX_2 levels during the inflammatory challenges. The results of the present study regarding the relationship between TTH, migraines, and lower vitamin B_{12} levels support the results of the previous studies mentioned. Moreover, we also found an association between the unclassified headache, and lower vitamin B_{12} levels.

One of the limitations of our study was its retrospective design. The other limitations were the lack of clinical results regarding post-treatment follow-up and a small number of study patients. Randomized double-blind placebo-controlled studies are needed on this issue.

The current study, one of the few studies in this field, has shown not only the relationship between vitamin B_{12} deficiency and TTH but also the linkage

between migraine, unclassified headache, and lower vitamin B_{12} levels. We suggest that vitamin B_{12} levels lower than 400 pg/ml are significant independent risk factors for headache. The probable mechanism might be related to neurotransmitter-moderated pathways and interactions with prostaglandin synthesis, as found in previous investigations. Therefore, vitamin B_{12} should be analyzed in patients with TTH, migraine, and unclassified headache.

Ethics Committee Approval: Cumhuriyet University Non-Interventional Clinical Research Ethics Committee approval was obtained (20.03.2019/03/03).

Conflict of Interest: The authors declare no competing interest.

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