

An Evaluation of Magnesium Levels in Pediatric Migraine Patients

Stellenwert des Magnesiumspiegels bei Kindern mit Migräneanfällen

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ABSTRACT

Background The purpose of this study is to compare serum magnesium levels between migraine patients and the control group and to examine the relationship between attack frequency and duration and average serum magnesium level.

Patients and Methods Patients diagnosed with migraine were included in the study retrospectively. Patients diagnosed with migraine were included as the study group and healthy children presenting to the pediatric neurology clinic in the same period as the control group. The demographic, clinical and laboratory characteristics were recorded.

Results Sixty-one pediatric migraine patients and 50 healthy controls were included in the study. The mean age of the mi-

graine patients was 13.39 ± 3.47 years. Mean magnesium levels were 2.02 ± 0.12 (1.7–2.3) mg/dl in the patient group and 2.05 ± 0.13 (1.8–2.5) mg/dl in the control group, and the difference was not statistically significant ($p = 0.17$). No significant association was determined between attack frequencies and durations and magnesium ($p = 0.89$ and $p = 0.061$, respectively). **Conclusions** The role of magnesium among the triggering factors in the etiopathogenesis and in the treatment of migraine is well-established. However, very few previous studies have reported magnesium levels in pediatric migraine patients, and the present research determined no significant difference in serum levels between patients with migraine and a control group.

ZUSAMMENFASSUNG

Zielsetzung Ziel dieser Studie ist es, den Magnesiumgehalt im Blutserum von Migränepatienten im Vergleich zur Kontrollgruppe zu analysieren und einen Zusammenhang zwischen der Häufigkeit und Dauer der Anfälle, sowie den durchschnittlichen Magnesiumwert festzustellen.

Methode Patienten mit diagnostizierter Migräne wurden nachträglich in die Studie mit einbezogen. An der Studie beteiligten sich diagnostizierte Migränepatienten, sowie die Kontrollgruppe (gesunde Kinder, die sich im gleichen Zeitraum in der Klinik für neurologische Untersuchungen vorstellten). Die demographischen und klinischen Merkmale, sowie die Laborwerte wurden dokumentiert.

Ergebnisse 61 Kinder mit nachgewiesenen Migräneanfällen und 50 gesunde Kinder aus der Kontrollgruppe nahmen an der Studie teil. Das Durchschnittsalter der Migränepatienten betrug 13,39 ± 3,47 Jahre. Der durchschnittliche Magnesiumspiegel der Patienten betrug 2,02 ± 0,12 (1,7–2,3) mg/dl. Der Durchschnittswert der Kontrollgruppe lag bei 2,05 ± 0,13 (1,8–2,5) mg/dl, was keinen auffälligen Unterschied darstellte ($p = 0,17$). Es wurde kein signifikanter Zusammenhang zwischen der Häufigkeit, der Dauer und des Magnesiumwertes festgestellt ($p = 0,89$, $p = 0,061$).

Schlussfolgerung Schlussendlich lässt sich sagen, dass im Rahmen der Ätiopathogenese und der Behandlung, Magnesium eine Rolle als auslösenden Faktor für Migräneanfälle spielen kann. Allerdings liegen bisher nur wenige Studien über Migränepatienten im Kindesalter vor. Die aktuelle Studie ergab, dass kein signifikanter Unterschied zwischen dem Magnesiumgehalt im Blutserum der Migränepatienten und der Kontrollgruppe festzustellen war.

Introduction

Migraine is characterized by moderate-to-severe episodic, throbbing, unilateral headaches usually accompanied by nausea, vomiting, photophobia, and phonophobia [1]. It is one of the most important neurological disorders in all age groups, with a prevalence in children and adolescents of 7.7% [2, 3].

The mechanism involved in the development of migraine is not yet fully understood. However, research investigating the underlying mechanism has implicated activation of the trigeminovascular system as the principal factor. Both genetic and environmental factors play important roles in the development of migraine [4]. In the light of previous studies indicating a decrease in serum magnesium (Mg) in patients with migraine as one such factor, Mg deficiency has been reported to be capable of playing a significant role in the pathogenesis [5–8]. Mg plays a key role in various physiological and biochemical processes in the brain, and deficiency leads to the impairment of important neuronal functions [9]. The element acts as a cofactor for adenosine triphosphate (ATP) synthase involved in ATP production. In addition, Mg plays important role in providing neuronal excitability and in the regulation of vascular tone [10]. Low Mg levels induce cerebral arterial vasoconstriction, increase platelet aggregation, and thus support serotonin release. Magnesium enhances the vasoactive effect of serotonin and reduces the effect of 'prostacyclin'-mediated vascular smooth muscle vasodilation [11, 12]. Additionally, decreasing Mg levels facilitate the development of cortical spreading depression by enhancing the sensitivity to glutamate of N-methyl-D-aspartate receptors [13]. Although Mg deficiency is seen in children and adolescents with migraine, for which reason it has been suggested that Mg support may play a role in the treatment of the disease, other studies have espoused a contradictory view. The role of Mg in the treatment of both acute and prophylactic pediatric migraine therefore remains unclear [14–17].

Although numerous publications have investigated the therapeutic role of Mg in migraine, very few studies have evaluated migraine patients' serum Mg levels [18]. The purpose of this study was to compare serum Mg levels in patients with migraine and a control group and to examine the relationship with the frequency and duration of attacks.

Materials and Methods

Patients diagnosed presenting to the Balıkesir University Faculty of Medicine pediatric neurology outpatient clinic, Balıkesir, between 01.09.2019 and 01.04.2023 and diagnosed with migraine were included retrospectively. The study was approved by the institutional clinical research ethics committee (decision no. 2023/68 dated 10.05.2023).

Patients diagnosed with migraine were included as the study group and control group presenting to the pediatric neurology clinic at the same times for neuromotor development follow-up checks were enrolled as the control group. The demographic characteristics (age, sex, and body mass index) of the patient group and their clinical (attack durations and frequencies, symptoms during attacks, and treatments) and laboratory [hemoglobin (Hb), hemato-

crit (Hct), platelet, glucose, calcium (Ca), Mg, vitamin D, folate, and ferritin levels] characteristics were recorded.

Patients and controls in whom Mg therapy was contraindicated (renal failure or nephrolithiasis), with non-migraine headaches, with substance/drug addiction (abuse), with psychiatric and/or chronic systemic diseases, and cases with histories of drug use (antidepressants, neuroleptics, tranquilizer group, antiepileptic medications (lithium and carbamazepine), using headache prophylaxis (beta blockers and calcium antagonists), and patients with deficient file data were excluded from the study.

Statistical analysis

Descriptive characteristics (mean, number, and percentage) were determined for the study variables. Normality of distribution of numerical variables was checked. Normality of distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. The independent sample t test was applied for normally distributed continuous variables. The Kruskal Wallis test was used to determine the significance of differences between the means of three or more non-normally distributed groups. Qualitative data were given as absolute reference and percentage distributions, and quantitative variables as mean and standard deviation (SD) in case of normal distribution. Categorical variables were compared using the chi-square test. Analyses were performed on Statistical Package for Social Sciences version 25 software. p values < 0.05 were considered significant.

Results

Sixty-one pediatric migraineurs and 50 control groups were included in the study. Twenty-one (34.4%) of the migraine patients were boys and 40 (65.6%) were girls. The mean age of the migraineurs was 13.39 ± 3.47 years. The cases' descriptive demographic and clinical data are shown in ► **Table 1**.

Mean Mg levels were 2.01 ± 0.12 (1.7–2.3) mg/dl in the patient group and 2.05 ± 0.13 (1.8–2.5) mg/dl in the control group, the difference not being statistically significant ($p = 0.17$, ► **Table 2**). No significant difference was also observed in terms of Hb, Hct, platelet, calcium, folate, or ferritin levels investigated simultaneously with Mg values in the patient and control groups, although a statistically significant difference was observed in their vitamin D levels ($p = 0.013$) (► **Table 2**).

No significant relationship was determined between the patient's sex nor frequency or duration attacks and Mg levels in the migraineur group ($p = 0.130$, $p = 0.843$ and $p = 0.119$, respectively, ► **Table 3, 4**).

Discussion

This study was planned because the etiopathogenesis of migraine is both very complex and multifactorial, research on the subject is limited, and because studies linking Mg values to the etiopathogenesis of the disease may also contribute to the therapeutic process. Magnesium levels were compared between pediatric patients with migraine and control groups, and no statistically significant difference was determined. However, no significant relationship

was determined between the patient's sex or frequency or duration of attacks and Mg levels in the migraineur group.

Although the main pathogenesis of migraine remains unclear, studies have emphasized that migraine emerges as a result of brain irritability as a result of various causes, particularly low Mg levels, mitochondrial abnormalities, or dysfunction associated with increased nitric oxide or calcium channels [19]. Several studies have also emphasized the importance of Mg among triggering factors in the pathogenesis and treatment of migraine. Magnesium is the most abundant mineral in the body and functions as a cofactor for several enzymatic reactions [20]. Magnesium performs numerous functions in the human body [21]. Deficiency can lead to an increased disposition to migraine by affecting calcium channels and neuroinflammation [9, 22]. At the same time, low Mg levels have been linked to cortical spreading depression, neurotransmitter release, and platelet cohesion and vasoconstriction [11, 23–25]. The interruption of

any one of these functions can facilitate the development of migraine by increasing brain irritability. Magnesium deficiency can be associated with the stimulation of excitatory neurotransmitters such as acetylcholine and serotonin. Neurotransmitters such as serotonin also play a critical role in the pathophysiology and treatment of migraine [4].

The factors that trigger migraine attacks include internal and/or external agents such as electrolyte disorders (e. g. hypomagnesemia), emotional and environmental factors (e. g., bright or flickering lights such as sunlight, fluorescent or LED lights, powerful aromas, noise, and substances contained in some foods. A low Mg concentration is an independent risk factor for migraine attacks [26]. Some studies have reported lower Mg levels in migraine patients with severe headache compared to those with mild and moderate severity, although others have determined normal serum Mg levels in migraine patients [27–32]. Adult studies have reported lower Mg levels in women with menstrual migraine [33]. Samaie et al. [31] reported significantly lower mean serum Mg levels in adult migraine patients compared to those in control group, but found no significant differences in total serum Mg levels within and between attacks in migraine patients. Boska et al. [34] reported low levels of Mg in migraine patients. Alshehri et al. [35] compared the serum Mg levels of 91 migraine patients aged 19–65 and a 54-member control group and observed no statistically significant difference between the groups. Talebi et al. observed a significant linear association between Mg levels and frequency of headache in adult migraineurs and control group. That study also showed that attacks increased in patients with low serum Mg levels, while a significant decrease was observed in serum Mg levels in the migraine patients compared to the control group ($p = 0.00$) [30]. Those authors also reported no significant relationship in that study between serum Mg levels and the patients' sex, duration of headache, or time of onset of headache [30]. Masoud [18] observed a significant difference in serum Mg levels during attacks in an adolescent subgroup, and reported that serum levels subsequently rose following the migraine attack. That author emphasized that the significant relationship determined between migraine and low serum Mg levels in adolescents (aged 10–18 years) could be explained in terms of adult migraine pathogenic mechanisms. Bhurat et al. [36] reported no statistically significant difference in the Mg levels of 35 patients ranging in age between five and 18 years and diagnosed with migraine and those of a control group. We also observed no significant difference in serum Mg values between migraine patients aged 7–18 and the control group in the present study. Although Mg occupies an important place in the pathogenesis of migraine, no clear relationship was determined between serum Mg levels and attack duration and frequency in the migraine patient group.

Magnesium absorption and excretion are affected by different hormones. 1,25-dihydroxyvitamin D [1,25(OH)₂D] has been shown to be capable of stimulating intestinal Mg absorption. Mg is a cofactor required for the binding of vitamin D to its transport protein, vitamin D binding protein (VDBP). Moreover, the conversion of vitamin D by hepatic 25-hydroxylation and renal 1 α -hydroxylation into the active, hormonal form 1,25(OH)₂D is Mg-dependent. Mg deficiency, which leads to reduced 1,25(OH)₂D levels and impaired parathyroid hormone response, has been implicated in "Mg-de-

► **Table 1** The migraine patients' general characteristics.

Patient characteristics	
Age (years) mean \pm SD	13.39 \pm 3.47
Age at onset of migraine (years) mean \pm SD (min.-max.)	10.78 \pm 3.35 (5–17)
Gender n (%)	
Male	21 (34.4)
Female	40 (65.6)
*BMI	
< 17	8 (13.1)
17–25	16 (26.2)
25–30	6 (9.8)
> 30	3 (4.9)
N/A	28 (45.9)
Attack duration	
< 30 min	11 (18)
30–60 min	14 (23)
1–4 hours	23 (37.7)
4–24 hours	7 (11.5)
> 24 hours	6 (9.8)
Attack frequency	
Every day in a week	20 (32.8)
2–3 times a week	25 (41)
Once weekly	9 (14.8)
Once monthly	7 (11.5)
Nausea n (%)	14 (23)
Vomiting n (%)	8 (13.1)
Nausea + Vomiting n (%)	16 (26.2)
Photophobia n (%)	4 (6.6)
Phonophobia n	5 (8.2)
Photophobia + phonophobia n (%)	33 (54.1)
Presence of a family history of migraine, n (%)	39 (63.9)
Rate of benefit from elimination of triggering factors	25 (41)
Patients receiving migraine treatment, n (%)	18 (29.5)
Flunarizine	16 (26.2)
Levetiracetam	2 (3.3)
*Body mass index	

► **Table 2** Laboratory results in children with migraine and controls.

	Study group	Control group	
Gender n (%)			
Girls	21 (34.4)	25 (50)	
Boys	40 (65.6)	25 (50)	
	Study group mean ± SD (minimum-maximum)	Control group mean ± SD (minimum-maximum)	p
Age (years)	13.39 ± 3.47	12.34 ± 3.69	0.125
Hemoglobin (g/dl)	13.22 ± 0.97 (10.1–15.4)	13.2 ± 1.28 (10.3–15.9)	0.93
Hematocrit (%)	39.74 ± 3.14 (32.6–52.5)	39.82 ± 3.50 (32.4–46.4)	0.89
Platelet (/ml)	303.95 ± 80.46 (140–539)	302.46 ± 102.73 (127–733)	0.93
Calcium (mg/dl)	9.86 ± 0.38 (9–10.7)	9.82 ± 0.33 (8.9–10.6)	0.57
Magnesium (mg/dl)	2.01 ± 0.12 (1.7–2.3)	2.05 ± 0.13 (1.8–2.5)	0.17
Magnesium (mg/dl)			0.296
Girls	2.0 ± 0.1 (1.7–2.3)	2.0 ± 0.2 (1.8–2.5)	
Boys	2.1 ± 0.1 (1.9–2.3)	2.1 ± 0.1 (1.8–2.3)	
Vitamin D (µg/L)	20.62 ± 8.16 (9–42.3)	16.26 ± 6.19 (5.1–29.9)	0.013
Folate (µg/L)	7.99 ± 3.50 (3.2–19.1)	8.56 ± 3.47 (3.7–17.3)	0.41
Ferritin (µg/L)	27.20 ± 43.43 (1.9–340.8)	28.51 ± 28.12 (3.4–160.6)	0.85

► **Table 3** Magnesium levels and attack frequency in patients with migraine according to gender.

	Female n (%)	Male n (%)	p
Gender	40 (65.6)	21 (34.4)	
Magnesium (mg/dl)	1.99 ± 0.12 (1.7–2.3)	2.07 ± 0.12 (1.9–2.3)	0.119
Attack Frequency			0.130
Every day in a week	15 (75)	5 (25)	
2–3 times a week	16 (64)	9 (36)	
Once weekly	7 (77.8)	2 (22.2)	
Once monthly	2 (28.6)	5 (71.4)	

► **Table 4** Magnesium levels and attack duration in migraine patients according to gender.

	Female n (%)	Male n (%)	p
Gender	40 (65.6)	21 (34.4)	
Magnesium level	1.99 ± 0.12 (1.7–2.3)	2.07 ± 0.12 (1.9–2.3)	0.119
Attack Duration			
<30 min	7 (7.2)	4 (3.8)	0.843
30–60 min	8 (9.2)	6 (4.8)	
1–4 hours	15 (15.1)	8 (7.9)	
4–24 hours	5 (4.6)	2 (2.4)	
>24 hours	5 (4.6)	2 (2.4)	
Total	40 (65.6)	21 (34.4)	

pendent vitamin-D-resistant rickets". Mg supplementation has been shown to substantially reverse resistance to vitamin D treatment [37, 38]. Several other factors, such as oestrogen or parathyroid hormone (PTH), are involved in the magnesium excretion [39]. In the present study, vitamin D levels were significantly lower in the

control group than in the migraine group. This may be associated with the high prevalence of vitamin D deficiency and insufficiency (42.9%) in children in Türkiye and the fact that this rises significantly with age [40]. In addition, seasonality (particularly winter and fall), age, sex, dark skin pigmentation, and limited exposure to sunlight are all potential causes of vitamin D deficiency. The present study was conducted in Balıkesir in Türkiye, and vitamin D deficiency in the control group may be associated with their living between 39.20° and 40.30° North [41].

Magnesium oxide is commonly recommended for migraine prophylaxis in the pediatric population at a daily dose of 400 mg [42]. At present, while several studies have reported an effective result in the use of intravenous magnesium in acute migraine attacks, there are still no randomized studies in the literature involving pediatric patients [43]. However, there are also studies reporting the effectiveness of Mg prophylaxis in adolescents. For example, Facchinetti et al. reported a decrease in the number of days with headache in patients with menstrual migraine using Mg pyrrolidone carboxylic acid [44]. Taubert also observed a significant reduction in the incidence of migraine attacks with the administration of 600 mg Mg/day in the form of trimagnesium dicitrate [45]. Peikert et al. showed that the number of days with migraine and drug consumption for treatment per patient decreased significantly with the daily use of 600 mg Mg (trimagnesium dicitrate) for 12 weeks; however, the reduction in intensity of migraine attacks was not significant [46].

In their review study from 2019 titled 'Intravenous Magnesium Sulfate to Treat Acute Headaches in the Emergency Department,' Miller et al. reached no definitive conclusion concerning the efficacy and usefulness of intravenous magnesium sulfate in the treatment of acute non-traumatic headaches. However, they nevertheless suggested that the existing evidence shows that it may be beneficial in terms of pain control beyond one hour, aura duration, and rescue analgesia requirements [47]. In another meta-analysis,

Okoli et al. reported that, due to insufficient evidence, it is unclear whether Mg is effective for migraine prophylaxis in adults [48]. In the present study, 19 patients were using flunarizine and two lev-
etiracetam.

Studies have shown that Mg levels fall during migraine attacks in 50% of patients [49]. One limitation of the present study is that Mg levels during migraine attacks could not be investigated due to its retrospective design. Another is that Mg levels can be affected during measurement. Hemolysis during blood collection can lead to falsely elevated serum Mg levels, since red blood cells contain higher concentrations of Mg than serum [50]. In addition, the measurements were performed without a structured protocol, Mg levels were measured only once in each patient between seizures and at control visits. Finally, the sample size was small, with a wide age range.

Conclusions

In conclusion, although the role of Mg among the triggering factors in the etiopathogenesis and treatment of migraine is well-established, there are also studies in the literature espousing the opposite view. While studies have evaluated serum Mg levels in adults with migraine, the number reporting serum levels in the pediatric age group is very small. No significant difference in serum Mg levels between the patients with migraine and the control group was observed in this study, and no association was found with attack durations or numbers. Further studies involving more centers and larger patient numbers are now needed.

Data Availability Statement

The study data are available from the authors upon reasonable request.

Contributor's Statement

H. Aydin – concept and design, acquisition of data, drafting or revising the manuscript; A.Orman – drafting or revising manuscript; B. Caliskan – acquisition of data.

Conflict of Interest

The authors declare that they have no conflict of interest.

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