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Decreased serum magnesium levels patients with migraine: a case control study

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Sedat YASİN[1,a], Erman ALTUNIŞIK[2,b]

[1] Department of Neurology, Gaziantep University Faculty of Medicine, Gaziantep, Turkey.
[2] Department of Neurology, Adiyaman University Faculty of Medicine, Adiyaman, Turkey.
[a]*ORCID:* 0000-0001-8067-8388, [b]*ORCID:* 0000-0002-5996-2090

Abstract

Objective: *Migraine is a common neurological syndrome that affects 15% of the population. The pathogenesis of migraines is not fully understood. In the nervous system; magnesium plays critical roles such as nerve conduction, neuromuscular coordination and protection against excitotoxicity.*

Method: *In this retrospective study, patients were diagnosed with migraine according to the International Classification of Headache Disorders-3 beta criteria were included. Patients were divided into three groups as migraine with aura, migraine without aura and chronic migraine.*

Results: *A total of 168 participant, 71 patients and 97 controls, were included in the study. Serum Mg values were measured as 1.98 mg/dl in the patient group and 2.04 mg/dl in the control group and were found to be significantly lower in the patient group (p=0.021). No significant difference was found in terms of mean serum Mg values in migraine subgroups.*

Conclusion: *We found that serum Mg levels are low in migraine patients and we think that this vital cation may be one of the factors playing a role in the pathogenesis of migraine. Evaluation of serum Mg level in migraine patients may help in predicting migraine attacks and symptoms, as well as in appropriate therapeutic planning for patients.*

Keywords: Migraine, magnesium, headache, measurement, level, pathogenesis.

Introduction

Migraine is a recurrent, usually unilateral common primary headache type characterized by moderate to severe headache attacks. Headache duration varies from hours to days and tends to worsen with routine physical activity. It is often accompanied by nausea, vomiting, photophobia and phonophobia . It is known to affect 15 percent of the general population[1,2]. About 18% of women and 6.5% of men suffer from migraine[3]. The group with 14 or less headaches per month is

Corresponding author: E-mail: ermanaltunisik@gmail.com

defined as episodic migraine, while chronic migraine (CM) defines patients with migraine who experience headaches 15 or more days per month. Episodic migraine is also divided into two subgroups as migraine with aura (MwA or classic migraine) and migraine without aura (MwoA or common migraine)[4] .

Magnesium (Mg) is a very important dietary macromineral that acts as a cofactor in more than 300 enzymatic reactions in the human body. In the nervous system; plays critical roles such as nerve conduction, neuromuscular coordination and protection against excitotoxicity[5]. Inadequate intake of Mg, due to its wide-ranging functions, may predispose individuals to many health problems, including those related to neurological conditions. In the previous studies, it has been reported that Mg may have a role in the mechanism of diseases such as migraine, chronic pain, epilepsy, Alzheimer's disease, Parkinson's disease, stroke, anxiety and depression[6].

The high incidence and prevalence of migraine and its crippling nature necessitate the elucidation of the underlying mechanism. The pathophysiological mechanisms underlying migraine attacks are not fully understood. Many factors have been blamed for the emergence of attacks. Sex hormones, cortisol, thyroxine, melatonin, hypothalamic axle, autonomic system, ions such as calcium and magnesium are among the factors that play a role in the pathogenesis of migraine headaches[7].

So far, no concrete answer has been found to the question of whether the decrease in Mg serum concentration is a factor that causes migraine headaches. The aim of this study is to compare the serum Mg levels of migraine patients and healthy individuals , to question the role of Mg in the pathogenesis of migraine and to contribute to the diagnosis and treatment planning of the disease.

Materials and Method

In this retrospective, cross-sectional, observational and comparative study, a total of 71 patients between the ages of 18 and 60 who applied to the neurology headache outpatient clinic of a tertiary university hospital and were diagnosed with migraine according to the International Classification of Headache Disorders (ICHD)-3 beta criteria were included. According to these criteria, patients were divided into three groups as MwA, MwoA and CM. Migraine severity evaluated with Migraine Disability assessment (MIDAS) score[8]. Detailed clinical history, sociodemographic characteristics, frequency of migraine attacks, duration of attacks, number of headache days per month, presence of aura were obtained from medical records for each patient.

Those with chronic diseases (such as chronic kidney failure, chronic liver failure, congestive heart failure), gastrointestinal system disease and malnutrition, and those receiving Mg-containing

drug therapy were not included in the study. In addition, patients with a history of drug use such as cyclosporine, cisplatin, aminoglycoside , amphotericin B, furosemide , acetazolamide and thiazide that affect serum levels of Mg were excluded from the study. In addition to the selection criteria used for the patient group, the control group consisted of healthy individuals who did not have a history of any type of headache, and whose blood samples were taken for routine health control.
Using a disposable injector, venous blood sample from the antecubital vein was taken between 8 am and 10 am after an overnight fast, into silicone-coated plastic tubes and centrifuged at 5000 rpm for 10 minutes.

The study was conducted in accordance with the Declaration of Helsinki guidelines and approval was obtained from the local ethics committee.

Statistical analysis

Statistical analyzes were performed with the SPSS version 21.0 program. The conformity of the variables to the normal distribution was tested with kurtosis and skewness analyses. Mean and standard deviation values were used for descriptive analyses. Categorical variables were compared with the Chi-Square Test. The Mann Whitney U Test was used to compare non-normally distributed quantitative variables, and the independent T -test was used to compare normally-distributed quantitative variables. Comparisons between multiple groups was done with one way ANOVA test. The correlation of quantitative data with each other was analyzed with Spearman and Pearson correlation tests. Cases with a P-value below 0.05 were considered as statistically significant results.

Results

A total of 168 participant, 71 patients and 97 controls, were included in the study. Of the migraine patients included in the study, 13 were in the MwA, 34 in the MwoA and 24 in the CM subgroup. The clinical features of migraine patients are shown in Table 1.

Table 1: Clinical features of migraine patients

Frequency of attacks (per month)	5.70
Duration of attacks (hours)	48.22
Headache days (per month)	11.87
MIDAS score	17.78
Episodic migraine (n) Migraine without aura (n) Migraine with aura (n) Chronic migraine (n)	47 34 13 24

While there were 53 (83.1 %) women in the patient group, 81 (83.5 %) of the control group were women. The mean age of the patient group was 35.12, and the mean age of the control group

was 33.74. The patient and control groups are similar in terms of age and gender distribution. Serum Mg values were measured as 1.98 mg/dl in the patient group and 2.04 mg/dl in the control group and were found to be significantly lower in the patient group (p=0.021). The characteristics of age, gender and serum Mg levels of the patient and control groups are shown in Table 2. No significant difference was found in terms of mean serum Mg values in migraine subgroups.

Table 2: Gender distribution and mean ages of the control and migraine groups

		Control		Migraine		p
		n	%	n	%	
Gender	Male	16	(16.5)	12	(16.9)	0.944[1]
	Female	81	(83.5)	59	(83.1)	
Age (year)	mean±Sd	33.74±8.71		35.12±9.87		0.338[2]
Magnesium serum level (mg/dl)	mean±Sd	2.04±0.14		1.98±0.15		0.021[2]

[1]Chi-square test, [2]Independent sample T test

The patients were divided into 4 groups according to their MIDAS scores in terms of migraine severity. The number of patients with Grade 1 was 10, the number of patients with Grade 2 was 22, the number of patients with Grade 3 was 23, and the number of patients with Grade 4 was 16. No significant difference was found in terms of mean serum Mg values in disease severity subgroups.

In the correlation analysis, no significant correlation was found between serum Mg values and frequency of migraine attacks, duration of attacks, number of headache days per month and MIDAS scores.

Discussion and Conclusion

In this study, we found that serum Mg levels were significantly lower in migraine patients compared to the healthy control group. We think that low Mg levels may be one of the physiopathological factors underlying migraine.

Mg plays an important role in the active transport of ions across neuronal membranes. It has been known for many years that Mg is associated with serotonin and N-methyl-D-aspartate (NMDA) receptors and affects nitric oxide synthesis and release[9]. Mg plays a vital role in controlling vascular tonicity and the reaction of vascular membranes to hormones and neuromediators by blocking NMDA channels[10]. It is also necessary for the release of nitric oxide trapped inside the cell. In Mg deficiency, nitric oxide remains in the cell and combines with superoxide to produce a peroxynitrite free radical that induces oxidative stress, lipid peroxidation

and myelin destruction, and neuronal irritability increases[7]. It has been thought that decreased Mg levels may cause cortical spreading depression leading to migraine by opening calcium channels, increasing intracellular calcium with glutamate release, and increasing extracellular potassium[11,12]. In addition, low Mg may be associated with increased platelet aggregation and vasoconstriction, which may be an important underlying etiology for triggering migraine because it affects serotonin receptors[13]. All these mechanisms support the view that Mg is one of the factors playing a role in the pathogenesis of migraine. Low Mg levels in migraine patients, which we found in the results of our study, may have led to migraine attacks by activating mechanisms such as free radical production, neurotoxicity and vasoconstriction.

Conflicting results have been obtained in studies investigating the relationship between migraine and Mg. In a study, it was reported that serum Mg levels were significantly lower in migraine patients compared to controls, and they were similar at the time of attack and between attacks[14]. In a different study , serum Mg levels of women with menstrual migraine were found to be significantly lower than the control group[15]. Our results seem consistent with these studies. On the other hand, there are also studies reporting that there is no significant difference between the serum Mg values of migraineurs and healthy individuals[16,17]. In a different study, it was reported that although Mg serum levels were within physiological limits both during the attack and between attacks, its concentrations during acute migraine attacks were lower than the period between attacks[18]. The inconsistencies found between the studies can be attributed to the presence of modifier factors such as smoking, drug use, intense exercise, nutritional differences, the difference in the number of patients in the study, and the serum Mg measurement method used.

Another entity that supports the role of Mg in the pathogenesis of migraine is the use of this mineral in the treatment of migraine. It is known that agents containing Mg are effective in migraine prophylaxis[19]. It has also been reported that Mg supplementation helps to reduce the dose of valproate in migraine patients treated with valproate[20]. It has been observed that the prophylactic use of oral Mg or the therapeutic administration of intravenous Mg during the attack is a useful approach and reduces migraine attacks. It is thought that this effect occurs as a result of the interaction of Mg with serotonin receptors[21]. Reports on the benefits of Mg use in both exacerbation and prophylactic treatment of migraine support the view that Mg deficiency is one of the factors that play a role in the pathogenesis of migraine.

Our study has some limitations. First of all, our study was designed retrospectively . The results of our study, which included a small patient population from a single center, cannot be generalized. Evaluations were based on a single measurement result and serum analyzes were not

performed during an acute migraine attack. Therefore, dynamic changes in ion levels may have been ignored.

Conclusion

We found that serum Mg levels are low in migraine patients and we think that this vital cation may be one of the factors playing a role in the pathogenesis of migraine. Evaluation of serum Mg level in migraine patients may help in predicting migraine attacks and symptoms, as well as in appropriate therapeutic planning for patients. We think that longitudinal studies with a large patient population are needed to better elucidate its diagnostic and therapeutic role.

References

1. Panconesi A, Bartolozzi ML, Guidi L. Migraine pain: reflections against vasodilatation. J Headache Pain 2009; 10: 317–325.
2. Altunisik E, Oren B. Retinal Neurovascular Structural Changes in Optical Coherence Tomography and the Relationship between These Changes and White Matter Hyperintensities in Patients with Migraine. *Eur Neurol*. 2021; 84(6): 460-471
3. Chiristiaopher J, David J, Capobian co. Headache and facial pain. In: Walter G, Bradly, Robert Daroff. Neurology in clinical practice, Vol. 2, Fifth edition, Philadelphia, Elsevier, 2008; 2011-2063
4. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013; 33(9): 629-808
5. Grober, U.; Schmidt, J.; Kisters, K. Magnesium in prevention and therapy. Nutrients 2015; 7: 8199–8226
6. Kirkland AE, Sarlo GL, Holton KF. The Role of Magnesium in Neurological Disorders. *Nutrients*. 2018; 10(6): 730.
7. Dhillon KS, Singh J, Lyall JS. A new horizon into the pathobiology, etiology and treatment of migraine. Med Hypotheses 2011; 77:147–151
8. Stewart WF, Lipton RB, Downson AJ, et al. Development and testing of the migraine disability assessment (MIDAS) questionnaire to assess headache related disability. Neurology 2001; 56: 20–28.
9. Modyl, Lambert JDC, Heinemann B: Low extra cellular magnesium induce epileptiform activity and spreading depression in rate hypocampal slices. J Neurophysical 1987; 57: 869-888.

10. Samsam M. Central nervous system acting drugs in treatment of migraine headache. Cent Nerv Syst Agents Med Chem 2012; 12:158–172.
11. Dolati S, Rikhtegar R, Mehdizadeh A, Yousefi M. The Role of Magnesium in Pathophysiology and Migraine Treatment. Biol Trace Elem Res. 2020; 196: 375-383.
12. Bussone G. Pathophysiology of migraine. Neurol Sci. 2004; 25: 239-241.
13. Tepper SJ, Rapoport A, Sheftell F. The pathophysiology of migraine. Neurologist. 2001 ;7(5): 279-286.
14. Samaie A, Asghari N, Ghorbani R, Arda J. Blood Magnesium levels in migraineurs within and between the headache attacks: a case control study. Pan Afr Med J. 2012; 11: 46.
15. Mauskop A, Altura BT, Altura BM. Serum ionized magnesium levels and serum ionized calcium/ionized magnesium ratios in women with menstrual migraine. Headache 2002; 42(4): 242-248
16. Trauninger A, Pfund Z, Koszegi T, Czopf J. Oral magnesium load test in patients with migraine. Headache 2002; 42(2): 114-9.
17. Assarzadegan F, Asadollahi M, Derakhshanfar H, Kashefizadeh A, Aryani O, Khorshidi M. Measuring Serum Level of Ionized Magnesium in Patients with Migraine. *Iran J Child Neurol*. 2015; 9(3): 13-16.
18. Masoud A. A study on relation between attacks of migraine headache and serum-magnesium level. Iranian J Publ Health 2003; 32: 27–30.
19. Miller AC, K Pfeffer B, Lawson MR, et al. Intravenous magnesium sulfate to treat acute headaches in the emergency department: A systematic review. Headache. 2019; 59: 1674-686.
20. Khani S, Hejazi SA, Yaghoubi M, Sharifipour E. Comparative study of magnesium, sodium valproate, and concurrent magnesium-sodium valproate therapy in the prevention of migraine headaches: A randomized controlled double-blind trial. J Headache Pain. 2021; 22: 21.
21. Christina Sun-Edelstein, Alexander Mauskop. Role of magnesium in the pathogenesis and treatment of migraine. Expert Review of Neurotherapeutic 2009; 9(3): 369-379.