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RESEARCH ARTICLE

The Impact of Serum 25-Hydroxyvitamin D Level on Migraine Headache

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ABSTRACT

Objective: To investigate the impact of serum 25-hydroxyvitamin D levels on migraine headache in migraineurs

Patients and Methods: A total of 72 patients were included in the study. Serum vitamin D concentration and its impact on the migraine headache were assessed in migraineurs and migraine subgroups. To assess serum levels of vitamin D, 25(OH) D3 was measured by enzyme-linked immunosorbent assay (ELISA). Patients were categorized as follows based on the results of serum vitamin D measurements. Severity of migraine, average duration and frequency of attacks per month were recorded. The headache diary result (HDR) was determined as: Duration of headache × frequency of headache.

Results: Average vitamin D level was 7.4 ng/ml among patients with migraine with aura group and 8.5 ng/ml in patients with migraine without aura. Severe vitamin D deficiency was detected in 14 (66.7%) patients with migraine with aura and 9 (64.3%) patients with migraine without aura, with no statistically significant difference between the two groups. No significant correlation was found between vitamin D levels and HDR among migraineurs (r=-0.042, p=0.812) as well as in patients with migraine with aura (r=0.044, p=0.842) and in patients with migraine without aura (r=0.059, p=0.842) versus control group with respect to HDR and vitamin D levels. The severity of migraine pain was not associated with vitamin D levels. Serum vitamin D concentration was lower in male patients versus control group.

Conclusion: The impact of vitamin D on the severity and number of migraine attacks is not clear. Further studies are needed to demonstrate the association between vitamin D status and neurological diseases.

Key words: Migraine, 25-hydroxyvitamin D, headache

INTRODUCTION

Migraine is a chronic neurological, incapacitating disease with adverse effects on the daily lives of the affected individuals. Migraine headache, tension-type headaches and medication overuse headaches account for 80% of all headaches. There is a general consensus that migraine pathophysiology involves release of pain-producing inflammatory substances around the nerves and blood vessels of the brain [1,2,3,4]. The lifetime prevalence of migraine varies between 10% and 20%. In Turkey, it is estimated that 16.4% of the population is affected by migraine [5,6].

In recent years, vitamin D deficiency emerged as a global public health problem and became the focus of widespread discussions due to its role in the development of various neurovascular disorders. Despite seasonal changes, the reported prevalence of vitamin D deficiency varies from 30% to 80% in the global population [7,8,9,10]. In a small case-control study, vitamin D receptor polymorphisms were shown to be associated with increased prevalence of migraine as well as the severity of headache [11]. In contrast with previous studies, a case-control study by Zandifar et al. in 2014 showed that there was no significant difference in serum vitamin D

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concentration between migraine patients and control subjects [12].

PATIENTS AND METHODS

Patients were randomly enrolled for the present study. The study was conducted at the neurology department of a university hospital in Gaziantep. A retrospective chart review was performed for each patient. Approval for the study was obtained from the institutional ethics committee.

Biochemical and Headache Assessment

To assess serum levels of vitamin D, 25(OH) D3 was measured by enzyme-linked immunosorbent assay (ELISA). Patients were categorized as follows based on the results of serum vitamin D measurements: deficient (serum vitamin D less than 12 ng/ml); insufficient (serum vitamin D between 12 and 30 ng/ml); and sufficient (serum vitamin D more than 30 ng/ml). Calcium, phosphorus, and albumin levels were measured for the differential diagnosis of primary hyperparathyroidism. Migraine diagnosis was confirmed by the neurologist. Severity, average duration of migraine attacks, and frequency of attacks per month were recorded by the same neurologist. Migraine severity was rated using the Visual Analogue Scale (VAS). The headache diary result (HDR) was determined as: Duration of headache × frequency of headache [13].

Statistical Analysis

Normality of numerical data was tested by the Shapiro-Wilk test and the Mann-Whitney U test was used for non-normally distributed data to compare two independent groups. Relationship between categorical variables was tested by the chi-square test. Frequency, percentage (%) and median [25%-75%] were presented as descriptive statistics. Relationship between numerical variables was investigated using Spearman's rank correlation coefficient. All analyses were performed by SPSS for Windows, Version 24 and a p value less than 0.05 was considered statistically significant.

RESULTS

A total of 72 subjects were enrolled in the study including 35 migraine patients and 37 controls. Migraine group was divided into two subgroups as patients with migraine with aura and patients with migraine without aura. Within the migraine with aura group, there were 18 (85.7%) females and 3 males and migraine without aura group included 10 (71.4%) females and 4 males. The mean age of the two subgroups was comparable (37 and 34.5 years, respectively). Average vitamin D level was 7.4 ng/ml among patients with migraine with aura group and 8.5 ng/ml in patients with migraine without aura. Severe vitamin D deficiency was detected in 14 (66.7%) patients with migraine with aura and 9 (64.3%) patients with migraine without aura, with no statistically significant difference between the two groups.

Average duration of migraine attacks was statistically significantly longer in patients with migraine with aura (48 hours) in comparison to patients with migraine without aura (18 hours). No difference was observed between the migraine subgroups with respect to the frequency of pain and HDR (Table 1).

Table 1. Comparison between migraine subgroups

Variables	Migraine with Aura (n=21)	Migraine without Aura (n=14)	P
Gender†			
Female	18 (85.7)	10 (71.4)	0.305
Male	3 (14.3)	4 (28.6)	
Age (years)‡	37 (31 -42)	34.5 (28-45)	0.829
Vitamin D concentration (ng/mL)‡	7.4 (5.8 -10.5)	8.5 (6.6 -13.7)	0.249
Vitamin D status†			
Insufficiency	1 (4.8)	2 (21.4)	0.944
Deficiency	6 (28.6)	2 (14.3)	
Severe Deficiency	14 (66.7)	9 (64.3)	
Severity of pain†			
Moderate	5 (23.8)	4 (28.6)	0.753
Severe	16 (76.2)	10 (71.4)	
Duration of pain‡	48 (14 -72)	18 (5 -24)	0.040*
Frequency of pain‡	4 (3 -6)	4 (3 -8)	0.960
HDR‡	192 (64 -240)	54 (15 -192)	0.096

*Significant at 0.05 level, † n (%); Chi-square test HDR: Headache Diary Result
‡ Median (25%-75%); Mann-Whitney U test

Comparing the entire sample of migraine patients with the control group showed that migraineurs were mostly female, whereas control group had an even distribution of gender. Vitamin D levels did not differ significantly between migraineurs and control group (Table 2). Comparing the migraine with aura subgroup with the control group showed a statistically significantly greater number of female patients within the migraine with aura subgroup. Other variables showed no significant differences (Table 3). Age, gender and vitamin D concentration were not significantly different between patients with migraine without aura in comparison to control subjects (Table 4).No significant correlation was found between vitamin D levels and HDR among migraineurs (r=-0.042, p=0.812) as well as in patients with migraine with aura (r=0.044, p=0.842) and in patients with migraine without aura (r=0.059, p=0.842) versus control group with respect to HDR and vitamin D levels. There was no difference between males and females with regard to vitamin D levels within the migraine group (p=0.300), whereas vitamin D levels were significantly higher in the control group (p=0.012). Vitamin D levels did not significantly differ between female migraineurs and female controls (p=0.210). Vitamin D levels were also not significantly different between male migraineurs and male controls (p=0.725) (Table 5).

Table 2. Comparison between migraineurs and control group

Variables	Migraineurs (n=35)	Controls (n=37)	P
Gender†			
Female	28 (80)	17 (45.9)	0.003*
Male	7 (20)	20 (54.1)	
Age (years)‡	37 (28 -45)	45 (28 -56)	0.107
Vitamin D concentration (ng/mL)‡	8.1 (6.3 -12.4)	8.1 (6.1 -11.8)	0.128
Vitamin D status†			
Insufficiency	4 (11.4)	5 (13.5)	0.944
Deficiency	8 (22.9)	9 (24.3)	
Severe Deficiency	23 (65.7)	23 (62.2)	

† n (%); Chi-square test.
‡ Median (25%-75%); Mann-Whitney U test
*Significant at 0.05 level.

Table 3. Comparison of patients with migraine with aura versus control group

Variables	Migraine with Aura (n=21)	Controls (n=37)	P
Gender†			
Female	18 (85.7)	17 (45.9)	0.003*
Male	3 (14.3)	20 (54.1)	
Age‡	37 (31 -42)	45 (28 -56)	0.159
Vitamin D concentration (ng/mL)‡	7.4 (5.8 -10.5)	8.1 (6.1 -11.8)	0.544
Vitamin D status†			
Insufficiency	1 (4.8)	5 (13.5)	0.534
Deficiency	6 (28.6)	9 (24.3)	
Severe Deficiency	14 (66.7)	23 (62.2)	

*Significant at 0.05 level, † n (%); Chi-square test.
‡ Median (25%-75%); Mann-Whitney U test.

Table 4. Comparison between patients with migraine without aura and control group

Variables	Migraine without Aura (n=14)	Controls (n=37)	P
Gender†			
Female	10 (71.4)	17 (45.9)	0.104
Male	4 (28.6)	20 (54.1)	
Age‡	34.5 (28-45)	45 (28 -56)	0.237
Vitamin D concentration (ng/mL)‡	8.5 (6.6 -13.7)	8.1 (6.1 -11.8)	0.533
Vitamin D status†			
Insufficiency	2 (21.4)	5 (13.5)	0.636
Deficiency	2 (14.3)	9 (24.3)	
Severe Deficiency	9 (64.3)	23 (62.2)	

*Significant at 0.05 level, † n (%); Chi-square test.
‡ Median (25%-75%); Mann-Whitney U test.

Table 5. Comparison of migraine subgroups with control group with respect to gender

	Groups											
	Migraineurs						Controls					
	Female			Male			Female			Male		
	Median	%25	%75	Median	%25	%75	Median	%25	%75	Median	%25	%75
Vitamin D concentration (ng/mL)	7.75	5.95	11.55	8.70	6.40	13.70	6.10	5.20	8.80	9.85	7.45	13.25

DISCUSSION

In the current study, we showed that male migraine patients had low vitamin D levels and the duration of pain was longer in patients with migraine with aura. While these results are consistent with those reported by some previous studies, we did not find any significant association between vitamin D concentration and the severity of migraine, the duration of migraine or the frequency of pain. This may have resulted from the fact that almost all study patients had low vitamin D levels and that the study was conducted during the winter months. This may also be related to the high prevalence of vitamin D deficiency in Gaziantep where the study was conducted. Kjaergaard et al. found an association between non-migraine headache and low levels of serum 25(OH) D but did not determine a significant relation between migraine and serum 25(OH)D [14,15]. One study demonstrated a significant positive association between serum levels of vitamin D and HDR but we did not observe such relationship in the present study [16]. In the same study, no significant association was found between serum vitamin D concentration and migraine severity or among different vitamin D subgroups and our study lends support to this finding. In a cross-sectional study including 11,614 participants in the sixth survey of Tromso study, a significant relationship was not observed between serum levels of vitamin D and migraine, and the association between nonmigraine headache and vitamin D levels was only significant in nonsmokers group and adjustments were performed for age, BMI, sex, season, chronic diseases, education level, physical activity, and alcohol consumption [17]. A case report study was conducted in two female patients with migraine associated with menstruation and premenstrual syndrome. These patients had low levels of vitamin D and significant reduction in migraine attacks and premenstrual symptoms were observed with consumption of vitamin D and calcium supplement (1600-1200 IU per day) during 2-month treatment [18]. Another study conducted among postmenopausal patients with migraine and low levels of vitamin D showed that the use of vitamin D and calcium supplements reduced the frequency and duration of migraine attacks [19]. Although the exact role and mechanism of vitamin D deficiency in headache is still unknown, some theories have been suggested to explain potential mechanisms; one possible mechanism involves the abnormal metabolism and low serum levels of magnesium and another one includes the vitamin D binding protein in the brain, particularly the hypothalamus. The role of these two mechanisms were demonstrated in patients with tension-type headache [20].

A relatively small sample of patients residing in the same region was examined in this study and this is the primary limitation of our study. Other limitations include the inability to study vitamin D gene polymorphisms and to perform a reassessment

of migraine attacks of patients after administration of vitamin D.

In conclusion, the impact of vitamin D on the severity and number of migraine attacks is not clear. While the role of vitamin D in several neurological conditions has been widely investigated, further prospective, controlled studies with a larger sample size are needed to ascertain the exact mechanisms involved because vitamin D deficiency is highly prevalent in the general population.

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