CLINICAL STUDY

An assessment of the relation between vitamin D levels and electroencephalogram (EEG) changes in migraine patients

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ABSTRACT
BACKGROUND: The present study evaluated vitamin D therapy in migraine patients with vitamin D deficiency and EEG abnormality.
METHODS: 140 patients were divided into four groups: Group A; normal vitamin D and EEG, Group B; low vitamin D and normal EEG, Group C; normal vitamin D and pathological EEG, and Group D; low vitamin D and pathological EEG. Patients with low vitamin D received vitamin D therapy.
RESULTS: Paediatric Migraine Disability Assessment Scale (PedMIDAS) scores and median attack frequencies time-dependent changes in the patients receiving vitamin D therapy in Group B were significant (p <0.05), but not in the untreated patients in the Group A (p >0.05). Interictal EEG was pathological in 41 (29.3 %) patients. The main EEG findings were focal/hemispheric spike/sharp wave activity at 9.3 %, bilateral/generalized spike/sharp wave activity at 8.6 %, focal slowing at 5.8 %, and bilateral slow-wave activity/background rhythm irregularity at 3.6 %. Changes in EEG findings in between the groups C and D were not significant (p >0.05). There was no significant association between vitamin D levels <20 or ≥20 ng/ mL and EEG findings in Group D (p >0.05).
CONCLUSION: Vitamin D therapy positively affects attack frequency and PedMIDAS scores in migraine patients with vitamin D deficiency/insufficiency. No association was determined between EEG findings and vitamin D levels or therapy *(Tab. 6, Ref. 35).* Text in PDF *www.elis.sk*
KEY WORDS: vitamin D, migraine, electroencephalogram.

Introduction

Migraine is the most common cause of chronic and repetitive headache in childhood (1, 2). Despite many conducted studies, it was not possible to explain migraine etiopathogenesis with a single theory. The main pathology in migraine is considered to be the existence of an over-excitable cerebral cortex (2)

Epileptiform abnormalities are detected in EEG of migraine patients due to overexcitable cortex, and this comorbid condition may sometimes cause misdiagnosis (3). Neuronal hyperexcitability and cortical spreading depression (CSD) were considered to be responsible for the relationship between epilepsy and migraine, however, etiopathogenesis has not been fully clarified (3).

It is known that Vitamin D, as a neurosteroid, has a modulating effect on neuronal hyperexcitability and predisposition to convulsion. It is stated that it plays a regulatory role in excitability with its modulating effect on gamma-aminobutyric acid (GABA) (A) receptor (4–6).

Therefore, the present study had been carried out to evaluate vitamin D levels in migraine patients and the efficiency of vitamin D therapy on the patients, who had vitamin D deficiency and EEG abnormalities.

Methods

The present study was approved by Erciyes University Faculty of Medicine Ethical Committee under decision no.2015/489 dated 25.11.2015. It was supported by The Scientific and Technological Research Council of Turkey (TÜBİTAK) with programme code 3001 and project number 116S042. Erciyes University Pediatric Neurology clinic with a headache and diagnosed with migraine with/without aura according to International Classification of Headache Disorders (ICHD)-III beta were included in the study. Informed consent for the study was taken from the guardians of all the patients participating in the study.

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Study design

Patients were divided into four groups according to vitamin D level and EEG findings.

Group A; patients, who had normal vitamin D levels and EEG findings. Classical migraine prophylaxis therapies such as: flunarizine, topiramate and valproate were initiated considering the accompanying clinical findings for the patients, who need migraine prophylaxis therapies.

Group B; patients, who had low vitamin D and normal EEG findings. Initially, vitamin D was applied to patients in Group B for migraine prophylaxis.

Group C; patients, who had normal vitamin D level and pathological EEG findings. Classical migraine prophylaxis therapies were initiated considering the accompanying clinical findings for the patients, who need migraine prophylaxis therapies.

Group D; patients, who had low vitamin D and pathologic EEG findings. Initially, vitamin D was given to the patients in Group D for migraine prophylaxis.

All the patients were examined using the Pediatric Migraine Disability Assessment Scale (PedMIDAS) for migraine disability at the initial diagnosis, at 3, 6 and 12 months (7). The frequency of attacks and response to treatment in the clinical follow-up of patients were evaluated at 1, 3, 6 and 12 months.

In Group B and D, patients, who initially had vitamin D treatment ineffective and who needed migraine prophylaxis despite vitamin D treatment in their follow-ups were given classical migraine prophylaxis therapies.

At the end of the study, the effects of vitamin D on attack frequency and clinical findings were evaluated by comparing the attack frequency and clinical findings of the group A and group B. The effects of vitamin D on EEG findings were evaluated by comparing EEG findings and treatment responses of group C and group D.

Determining Vitamin D levels

At baseline, plasma 25 (OH) D levels of all the patients were evaluated with HPLC (high-pressure liquid chromatography) method using ClinRep Kit (IRIS Technologies International GmbH, Cursdorf, Germany). Both vitamin D levels and clinical responses to treatment of patients, who had vitamin D deficiency were evaluated at 1, 3, 6 and 12 months.

Tab. 1. Comparison of patients who completed the study according to patient groups, gender, age, Vitamin D, Ca, P, PTH values according to groups at baseline and migraine type variables.

Parameters	Patient groups				p
	A	B	C	D	
Gender					0.039
Female	17 (39.5)[a]	38 (67.9)[a]	8 (53.3)[a]	16 (61.5)[a]	
Male	26 (60.5)[b]	18 (32.1)[b]	7 (46.7)[a]	10 (38.5)[a]	
Age	12.80±2.87	13.05±2.98	12.15±3.13	12.74±2.09	0.744
Vitamin D (ng/mL)	26.55±6.50[a] (20.21–48.97)	13.13±3.82[b] (3.82–19.94)	27.31±5.58[a] (20.54–39.49)	13.84±4.19[b] (4.66–19.84)	< 0.001
Ca (mg/dL)	9.81±0.38 (8.99–10.67)	9.81±0.28 (9.18–10.39)	9.83±0.36 (9.32–10.59)	9.84±0.43 (9.01–10.67)	0.974
P (mg/dL)	4.49±0.73 (2.86–5.68)	4.55±0.69 (3.19–6.03)	4.48±0.70 (3.30–5.80)	4.69±0.71 (3.24–6.15)	0.685
PTH (pg/mL)	41.61±17.14 (9.97–103.90)	45.52±21.10 (15.02–101.90)	36.29±9.97 (24.82–57.92)	52.70±49.86 (15.04–264.90)	0.236
Migraine type					0.268
With aura	11 (25.6)	21 (37.5)	6 (40.0)	12 (46.2)	
Without aura	32 (74.4)	35 (62.5)	9 (60.0)	14 (53.8)	

Data are given as mean ± standard deviation and n (%). * * Values in the parentheses represent minimum and maximum values. According to the multiple comparison test, the same letters in the same column express the similarity between the groups and the different letters express a difference.

Tab. 2. Comparison of PedMIDAS scores and attack frequencies between groups and by time.

Variables	Groups				p*
	A (n=43)	B (n=56)	C (n=15)	D (n=26)	
Baseline PedMIDAS	11.0 (3.0–24.0)[a]	14.5 (6.0–33.8)[a]	9.0 (6.0–24.0)[a]	13.5 (0.8–35.5)[a]	0.425
3rd month PedMIDAS	5.0 (2.0–12.0)[ab]	9.5 (0.0–20.8)[ab]	0.0 (0.0–4.0)[ab]	6.0 (0.0–16.5)[ab]	0.114
6th month PedMIDAS	4.0 (1.0–20.0)[ab]	4.0 (0.0–14.0)[b]	1.0 (0.0–14.0)[ab]	2.5 (0.0–14.0)[b]	0.235
12th month PedMIDAS	4.0 (0.0–11.0)[b]	8.0 (0.0–13.0)[b]	1.0 (0.0–8.0)[b]	1.0 (0.0–6.0)[b]	0.140
p	**0.003**	**< 0.001**	**0.023**	**< 0.001**	
Variables	Groups				p*
	A (n=43)	B (n=56)	C (n=15)	D (n=26)	
Baseline frequency of attacks	4.0 (3.0–10.0)[a]	6.5 (4.0–12.0)[a]	4.0 (2.0–12.0)	4.0 (2.8–10.0)[a]	0.116
1st month frequency of attacks	3.0 (1.0–6.0)[b]	4.0 (2.0–6.8)[b]	2.0 (1.0–10.0)	3.0 (1.0–4.0)[ab]	0.343
3rd month frequency of attacks	3.0 (1.0–4.0)[b]	3.5 (2.0–7.8)[b]	2.0 (0.0–4.0)	3.0 (1.8–5.3)[ab]	0.092
6th month frequency of attacks	3.0 (1.0–5.0)[b]	3.0 (1.0–6.0)[b]	1.0 (1.0–3.0)	3.0 (1.0–4.0)[ab]	0.328
12th month frequency of attacks	3.0 (1.0–4.0)[b]	3.0 (1.0–4.8)[b]	2.0 (1.0–6.0)	1.5 (1.0–3.3)[b]	0.622
p	**0.002**	**< 0.001**	0.124	**0.001**	

Data are expressed as median (1st quarter–3rd quarter). According to the multiple comparison test, the same letters in the same column express the similarity between the groups and the different letters express a difference. p; shows the significance of difference between time periods and p* shows the significance of difference between groups.

Vitamin D therapy

Patients with a plasma 25 (OH) D level below <12ng/mL were evaluated as vitamin D deficiency, and those found between 12–20 ng/mL as vitamin D insufficiency (8). After the routine etiological evaluation, 150.000 IU single-dose oral vitamin D

Tab. 3. Comparison of PedMIDAS scores and frequency of attacks between the patients who received treatment in group A and those who received vitamin D in group B, and those who + the treatment in the group A and those who received the vitamin D in the group B, according to the time and frequency of attacks.

Variables	Groups		p*
	Patients who received treatment* in group A (n=26)	Patients who received Vitamin D in group B (n=56)	
Baseline PedMIDAS	18.5 (9.5–29.3)[a]	14.5 (6.0–33.8)[a]	0.716
3rd month PedMIDAS	5.0 (1.8–12.3)[b]	9.5 (0.0–20.8)[ab]	0.597
6th month PedMIDAS	6.5 (1.8–12.3)[b]	4.0 (0.0–14.0)[b]	0.371
12th month PedMIDAS	3.0 (0.0–11.3)[b]	8.0 (0.0–13.0)[b]	0.730
p	**< 0.001**	**< 0.001**	
Baseline frequency of attacks	8.0 (4.0–12.0)[a]	6.5 (4.0–12.0)[a]	0.684
1st month frequency of attack	3.5 (1.0–6.5)[b]	4.0 (2.0–6.8)[b]	0.362
3rd month frequency of attack	3.0 (1.0–4.0)[b]	3.5 (2.0–7.8)[b]	0.103
6th month frequency of attack	3.0 (1.0–6.5)[b]	3.0 (1.0–6.0)[b]	0.868
12th month frequency of attack	3.0 (1.0–4.0)[b]	3.0 (1.0–4.8)[b]	0.940
p	**< 0.001**	**< 0.001**	

Variables	Groups		p*
	Patients who did not received treatment* in group A (n=17)	Patients who received vitamin D in group B (n=56)	
Baseline PedMIDAS	5.0 (3.0–10.5)	14.5 (6.0–33.8)[a]	**0.004**
3rd month PedMIDAS	5.0 (2.0–14.0)	9.5 (0.0–20.8)[ab]	0.509
6th month PedMIDAS	4.0 (0.0–16.0)	4.0 (0.0–14.0)[b]	0.947
12th month PedMIDAS	5.0 (0.0–7.5)	8.0 (0.0–13.0)[b]	0.545
p	0.908	**< 0.001**	
Baseline frequency of attack	3.0 (2.0–4.0)	6.5 (4.0–12.0)[a]	**0.001**
1st month frequency of attack	3.0 (1.0–6.0)	4.0 (2.0–6.8)[b]	0.458
3rd month frequency of attack	3.0 (1.5–4.0)	3.5 (2.0–7.8)[b]	0.169
6th month frequency of attack	4.0 (1.0–4.5)	3.0 (1.0–6.0)[b]	0.757
12th month frequency of attack	3.0 (1.0–6.5)	3.0 (1.0–4.8)[b]	0.777
p	0.996	**< 0.001**	

Data are expressed as median (1st quarter–3rd quarter). According to the multiple comparison test, the same letters in the same column express the similarity between the groups and the different letters express a difference. p; shows the significance of difference between time periods and p* shows the significancy of difference between groups. Treatment* Drug treatments such as flunarizine, topiramate, valproate used in the treatment of migraine prophylaxis.

(stoss therapy) was applied and vitamin D levels were increased to 20 ng/mL (8).

EEG

All scans were performed using 21 electrodes and 10–20 system adhered to the scalp with paste with Grass (R) AS40 and/or AS40 Plus (Astro-Med, U.S.A.) and/or Nihon Kohden EEG-1200K (Nihon Kohden Corporation, Japan) and/or Natus Nicolet EEG v32 (Natus Neurology Incorporated, U.S.A) EEG devices. According to EEG findings, patients were defined as with normal EEG findings and with pathological EEG findings.

Statistical analysis

The suitability of data for normal distribution was evaluated by histogram and Q–Q plots and Shapiro-Wilk test. The homogeneity of the variances was tested with Levene's test. Mann-Whitney *U* test and two-sample independent t-test were used to compare the quantitative parameters between the groups. Kruskal Wallis test was used for the comparisons between more than two groups. Friedman test was applied for comparison of quantitative para-

meters between the measurements. For multiple comparisons, Dunn-Bonferroni and Adjusted Bonferroni tests were applied. Pearson χ2 analysis was used for comparison of categorical data. Cochran's Q test was used for qualitative variables in comparisons between measurements. Analysis of data was performed in TURCOSA (Turcosa Ltd Co,) statistical software. Significance level was set as $p < 0.05$.

Results

There was a total of 140 patients, 79 (56.4 %) girls and 61 (43.6 %) boys, who completed the study. Fifty of the patients (35.7 %) had migraine with aura while 90 patients (64.3 %) had migraine without aura. Ninety-nine of the patients (70.7 %) had normal EEG findings while 41 of the patients (29.3 %) had pathological EEG findings.

No statistically significant difference was found between the patient groups for age and migraine type ($p > 0.05$). Statistically significant difference was found between the patient group and gender ($p < 0.05$). In group A, the number of male patients was significantly higher than the number of female patients. In group B, the number of female patients was significantly higher than the number of male patients. Table 1 shows the distribution of age, gender and migraine type parameters between the study groups. At baseline, a statistically significant difference was found between the mean values of vitamin D levels of patients in all the groups ($p < 0.05$) (Tab. 1).

In Table 2, PedMIDAS scores and the comparison of the frequency of attacks between groups and periods are presented. PedMIDAS score was not statistically significant between groups at baseline, 3rd month, 6th month and 12th month ($p > 0.05$). While the change of attack frequency in the group over time was not statistically significant in group C ($p > 0.05$), the change of PedMIDAS scores over time was significant ($p < 0.05$).

No statistically significant difference was found within the groups over time for patients, who received treatment in group A and patients, who received vitamin D in group B for baseline, 3, 6 and 12 months PedMIDAS scores and for the frequency of attack at baseline, 1, 3, 6 and 12 months ($p > 0.05$) (Tab. 3). A statistically significant difference was found between the groups, who did not receive treatment in the A group at the beginning and who received vitamin D in the group B for the frequency of attacks at baseline ($p < 0.05$). Time-dependent changes in the frequency of attack at baseline, 1st, 3rd, 6th and 12th months of the group, who did not receive treatment in group A at the beginning were not statistically

Tab. 4. Comparison of PedMIDAS scores and attack frequencies of patients in group B who completed the study between subgroups of vitamin D.

Variables	Frequency of attacks of patients in group B at 1st month		
	Vitamin D level <20 ng/mL (n=17)	Vitamin D level ≥20 ng/mL (n=39)	p*
Baseline frequency of attacks	8.0 (3.5–13.5)[a]	5.0 (4.0–12.0)[a]	0.726
1st month frequency of attacks	5.0 (3.0–11.0)[ab]	3.0 (2.0–6.0)[b]	**0.041**
3rd month frequency of attacks	5.0 (2.0–9.0)[ab]	3.0 (2.0–6.0)[ab]	0.374
6th month frequency of attacks	4.0 (1.5–11.0)[ab]	2.0 (1.0–5.0)[b]	0.102
12th month frequency of attacks	3.0 (1.0–4.5)[b]	3.0 (1.0–5.0)[b]	0.607
p	**0.003**	**< 0.001**	
Variables	Frequency of attacks and PedMIDAS scores of patients in group B at 3rd month		
	Vitamin D level <20ng/mL (n=18)	Vitamin D level ≥20 ng/mL (n=38)	p*
Baseline PedMIDAS	16.0 (6.8–30.0)	13.0 (5.0–35.0)[a]	0.550
3rd month PedMIDAS	13.5 (2.3–21.8)	7.0 (0.0–18.0)[ab]	0.179
6th month PedMIDAS	4.0 (0.0–15.0)	4.0 (0.0–13.0)[b]	0.283
12th month PedMIDAS	1.0 (0.0–10.0)	9.0 (0.015.8)[b]	0.105
P	0.054	**< 0.001**	
Baseline frequency of attack	5.0 (4.0–12.8)[a]	7.5 (3.8–12)[a]	0.958
1st month frequency of attack	4.0 (2.8–10.0)[ab]	3.0 (2.0–6.0)[ab]	0.479
3rd month frequency of attack	3.5 (2.8–7.3)[ab]	3.5 (2.0–8.0)[ab]	0.791
6th month frequency of attack	3.0 (1.0–5.0)[b]	3.0 (1.0–6.5)[b]	0.811
12th month frequency of attack	2.5 (0.0–7.5)[b]	3.0 (1.0–4.0)[b]	0.122
p	**0.001**	**< 0.001**	
Variables	Frequency of attacks and PedMIDAS scores of patients in group B at 6th month		
	Vitamin D level <20 ng/mL (n=19)	Vitamin D level ≥20 ng/mL (n=37)	p*
Baseline PedMIDAS	7.0 (3.0–34.0)	15.0 (10.0–34.0)[a]	0.077
3rd month PedMIDAS	18.0 (0.0–24.0)	19.0 (0.0–15.0)[a]	0.334
6th month PedMIDAS	4.0 (0.0–15.0)	4.0 (0.0–13.0)[b]	0.707
12th month PedMIDAS	2.0 (0.0–14.0)	8.0 (0.0–13.0)[b]	0.698
p	0.129	**< 0.001**	
Baseline frequency of attacks	4.0 (3.0–12.0)[a]	8.0 (4.0–12.5)[a]	0.253
1st month frequency of attacks	3.0 (2.0–13.0)[ab]	4.0 (2.0–6.0)[b]	0.965
3rd month frequency of attacks	6.0 (2.0–10.0)[ab]	3.0 (2.0–5.5)[b]	0.226
6th month frequency of attacks	3.0 (1.0–5.0)[b]	3.0 (1.0–6.5)[b]	0.583
12th month frequency of attacks	4.0 (0.0–10.0)[b]	3.0 (1.0–4.0)[b]	0.500
p	**0.010**	**< 0.001**	
Variables	Frequency of attacks and PedMIDAS scores of patients in group B at 12th month		
	Vitamin D level <20 ng/mL (n=16)	Vitamin D level ≥20 ng/mL (n=40)	p*
Baseline PedMIDAS	13.0 (7.3–23.5)[a]	15.0 (6.0–35.0)[a]	0.580
3rd month PedMIDAS	10.0 (0.0–20.8)[ab]	9.5 (0.5–20.3)[ab]	0.568
6th month PedMIDAS	3.0 (2.0–12.5)[ab]	4.5 (0.3–14.8)[b]	0.318
12th PedMIDAS	1.0 (0.0–10.0)[b]	9.0 (0.0–15.8)[b]	0.073
p	**0.009**	**< 0.001**	
Baseline frequency of attacks	4.5 (3.3–8.0)[a]	10.5 (4.0–12.8)[a]	0.107
1st month frequency of attacks	3.0 (2.0–4.8)[ab]	4.0 (2.0–9.0)[bc]	0.125
3rd month frequency of attacks	2.5 (1.3–6.0)[b]	4.0 (3.0–8.0)[ab]	0.125
6th month frequency of attacks	3.0 (0.3–5.8)[ab]	3.0 (1.3–7.0)[bc]	0.443
12th month frequency of attacks	2.5 (0.0–7.5)[ab]	3.0 (1.0–4.0)[c]	0.862
p	**0.046**	**< 0.001**	

Data are expressed as median (1st quarter–3rd quarter) p; shows the significance of difference between time periods and p* shows the significancy of difference between groups. According to the multiple comparison test, the same letters in the same column express the similarity between the groups and the different letters express difference.

significant (p >0.05). Baseline, 1, 3, 6 and 12 month attack frequency changes of the patients in group B receiving vitamin D at the beginning were statistically significant (p <0.05).

In Table 4, the comparison results of the attack frequency and PedMIDAS scores of the patients in group B are given in the subgroups of vitamin D. In the patients with vitamin D level ≥20 ng/mL, the change in the frequency of attacks at 3 months, 6 months and 12 months and PedMIDAS scores in the group were found to be statistically significant (p <0.001).

Descriptive statistics of pathological and normal EEG findings of the patients in the group C and the group D in Table 5 and the comparison results of EEG findings by groups and time are given in Table 6. In the group C and the group D, considering 140 patients, there were focal or hemispheric spike or sharp wave activity in 13 patients (9.3 %) and bilateral or generalized spike or sharp wave activity in 12 patients (8.6 %), focal slowdown in 8 patients (5.8 %), bilateral slow-wave activity or ground rhythm irregularity in 5 patients (3.6 %).

In Table 6, EEG findings at 1st, 3rd, 6th and 12th months between the groups and the change depending on time was not statistically significant (p >0.05). Since there were no patients with normal baseline EEG findings in groups C and D, they were not included in the analysis in C and D group comparisons and time-dependent changes.

Comparison of EEG findings in the group C and the group D according to migraine type and time, there was no statistically significant difference between the groups with and without aura in C and D groups for 1st, 3rd, 6th and 12th month EEG findings (p >0.05).

In the comparison of EEG findings in the group D (whether normal or pathological) for periods (1st, 3rd, 6th and 12th month) and vitamin D level (vitamin D level <20 ng/mL and vitamin D level ≥20 ng/ mL), no statistically significant difference was found both in and between the groups (p >0.05).

Tab. 5. Descriptive statistics of pathological and normal EEG findings of patients in group C and D.

Variables	Descriptive statistics	
Group C	Baseline	12th month
Focal slowdown	4 (26.7)	–
Focal or hemispheric spike and sharp wave activity	5 (33.3)	1 (6.7)
Bilateral or generalized spike or sharp wave activity	2 (13.3)	–
Bilateral slow–wave activity or background rhythm irregulation	4 (26.7)	–
Normal	–	14 (93.3)
Group D	Baseline	12th month
Focal slowdown	4 (15.4)	–
Alpha asymmetry	1 (3.8)	–
Focal or hemispheric spike or sharp wave activity	8 (30.8)	1 (3.8)
Bilateral or generalized spike or sharp wave activity	10 (38.5)	2 (7.7)
Photoparoxysmal response	1 (3.8)	–
Bilateral slow wave activity or background rhytm irregularity	1 (3.8)	–
Diffuse slow wave activity	1 (3.8)	1 (3.8)
Normal	–	22 (84.6)

Data are given as n (%).

Tab. 6. Comparison of EEG findings by groups and time.

Variables			Group C	Group D	p*
EEG	Baseline	Pathological	15 (100.0)	26 (100.0)	–
		Normal	–	–	
	1st month	Pathological	2 (13.3)	5 (19.2)	0.958
		Normal	13 (86.7)	21 (80.8)	
	3rd month	Pathological	4 (26.7)	7 (26.9)	0.999
		Normal	11 (73.3)	19 (73.1)	
	6th month	Pathological	4 (26.7)	2 (7.7)	0.231
		Normal	11 (73.3)	24 (92.3)	
	12th month	Pathological	1 (6.7)	4 (15.4)	0.744
		Normal	14 (93.3)	22 (84.6)	
p			0.234	0.158	

Data are given as n (%). p; shows the significance of difference between time periods and p* shows the significancy of difference between groups

Discussion

Headache is one of the most common neurological problems among children (9). Poyrazoğlu et al (10) reported that recurrent headache was detected in 5027 (47.5 %) of 10584 school children aged between 7 and 17. Primary recurrent headache frequency was reported as 21 %. They reported that migraine prevalence was 7.2 % among primary recurrent headaches, and that 68 % of the patients diagnosed with migraine were girls and 32 % were boys (10). Song et al (11) evaluated 157 migraine patients in their study. They also reported that 75.2 % of all the patients were girls, and the rate of vitamin D deficiency in girls was 94/118 (79.7 %), while this ratio was 27/39 (69.2 %) in boys.

In the present study, there was no statistically significant difference between the groups for age and migraine types (Tab. 1). However, there was a statistically significant difference between study groups for gender. In accordance with literature, 67.9 % of the patients in the group B and 61.5 % of the patients in the D group were girls. Besides, this finding may be related to the fact that vitamin D deficiency is more common in girls than boys due to our preservative society structure. These findings may also support the view that the prevalence of migraine in adolescent girls

is a risk factor in the etiopathogenesis of vitamin D deficiency.

Guidetti et al (12) highlighted that migraine should not only be related to genetic and environmental factors and it is multifactorial. This multifactorial disease may have negative effects on children's school, family and social life. Therefore, studies on both pathogenesis and treatment of the disease continue. Many studies were conducted to assess the relationship between vitamin D and migraine. It was reported on vitamin D deficiency or insufficiency in migraine and headache patients. In the literature review by Ghorbani et al (13), it was stated that these rates vary between 45–100 %. In addition, vitamin D deficiency of migraine patients and the effectiveness of vitamin D in the treatment had been evaluated in recent years. It was reported that vitamin D improves the quality of life and improves headache scores in various studies (14).

Kilic and Kilic (15) evaluated 92 paediatric migraine patients in their study and divided the patients into two subgroups as low-level vitamin D and normal level vitamin D groups. In conclusion, they emphasized that there was a significant relationship between migraine in paediatric patients and vitamin D level. They also emphasized that vitamin D treatment is beneficial in migraine patients.

In the present study, a comparison of attack frequency and PedMIDAS scores of the patients within the groups A and B and between the two groups themselves are given in Table 2. Results similar to time-related improvement in the group A were also obtained in the group B. As it can be seen in Table 3, the comparison of PedMIDAS scores and attack frequencies of the patients, who did not receive treatment in the group A and those, who received vitamin D treatment in the group B were compared between the groups and by time. The median values of initial PedMIDAS scores and attack frequencies were 5.0 (3.0–10.5), 3.0 (2.0–4.0) in the group A, and 14.5 (6.0–33.8), 6.5 (4.0–12.0) respectively in the group B, and these values were in the group B. It was significantly higher (p <0.05). While the temporal change of these values in the group B was also statistically significant (p <0.05), there was no statistically significant change in the group A (p >0.05). These findings support the view that the effect of vitamin D treatment on PedMIDAS scores and attack frequency is as effective as classical migraine treatment in the long term, similar to the studies of Kilic and Kilic (15). In addition, these findings support the view that clinical findings will be more severe in the patients with vitamin D deficiency.

Togha et al (16) reported that that vitamin D level should be evaluated in migraine patients and that every 5 ng/mL increase in

serum vitamin D level would lead to a 22 % proportional decrease in migraine frequency. They also emphasized that vitamin D level should be kept above 20 ng/mL in the patients. In the present study, in the patients with vitamin D $\geq$20 ng/mL, it was observed that the change of attack frequency and PedMIDAS scores over time in the group was statistically significant (p <0.001) and showed a continuous change (Tab. 4). Considering the literature data, these results may not be associated with migraine alone, but it suggests that deficiency or insufficiency of vitamin D may be a risk factor for migraine pathophysiology. Migraine patients should be followed up for vitamin D deficiency or insufficiency, vitamin D treatment should be given to the patients with deficiency and vitamin D level should be kept at a sufficient level ($\geq$20 ng/mL). The patients, who need migraine prophylaxis despite previous vitamin D treatment should also be evaluated for migraine prophylaxis treatment.

The association between migraine and epilepsy is a controversial topic. These two paroxysmal disorders may trigger one another or sometimes show a coexistence (17). The use of EEG as a diagnostic test in the patients presenting with headache is still a controversial issue. Dow and Whitty (18) reported dysrhythmia showing fluctuation in migraine phases in EEG of 51 migraine patients in 1947. This dysrhythmia has been reported to be associated with neuronal dysfunction of the trigeminovascular system (19). EEG abnormality in migraine patients had been reported in approximately 20 % in the following years (20). Sand (21) reported in the review that focal slow-wave activity was detected in 0–15 % of migraine patients with or without aura in the interictal period, and spike-wave activity in 0.2–9 % of the patients. He stated that it was not different from the EEG findings in the control group. However, spike-wave activity was more common in migraine patients than in the control groups. In his study, slow-wave activity and background activity in migraine patients with aura indicated a depression in amplitude, unilateral or bilateral delta activity or a slowdown in hemiplegic migraine and basilar migraine patients. De Carlo et al (22) showed the EEG findings in the ictal phase in 32 (80 %) of 40 migraine patients and found that 29 patients had migraine with aura. The most common EEG findings were focal, hemispheric, or bilateral slowing. They reported that rapid beta activity was observed in the ictal period in 7.5 % of the patients. In the interictal period, 357 (86.6 %) of 412 patients had normal EEG, 18 had 4.4 % interictal period slow-wave activity, 30 patients (7.3 %) had epileptic activity. Also, rolandic spikes were detected in 4 of 30 patients with interictal epileptic activity. It was reported that 11 patients had normalized EEG findings, 8 patients had still EEG findings, and 4 of 8 patients were diagnosed with epilepsy and two patients had epilepsy history in their families. Golla and Winter (23) reported that the persistence of the photic drift response (H response) can be seen in the patients with migraine-like headaches. Piccinelli et al (24) reported that they detected pathology in EEG at the rate of 43.5 % in the interictal period of migraine patients with aura and 5.4% of migraine patients without aura. The most frequent interictal EEG findings were spike, sharp-wave, slow-wave, spike-slow-wave complex or multiple spike-wave activities (20, 24).

In the present study, similar to literature data, interictal EEG disorder was found in 41 (29.3 %) patients of the initial EEGs (Tab. 1). Descriptive statistics of the pathological and normal EEG findings of the patients in the groups C and D are given in Table 5. There were focal or hemispheric spike or sharp wave activity in 13 patients (9.3 %), bilateral or generalized spike or sharp wave activity in 12 patients (8.6 %), focal slowdown in 8 patients (5.8 %), bilateral slow-wave activity or ground rhythm irregularity in 5 patients (3.6 %). In the group D, photoparoxysmal response was detected in interictal EEG at the beginning of the study in one patient. At the end of the study, EEG was pathological in one patient (6.7 %) in group C and four patients (15.3 %) in group D (5 of 140 patients, 3.6 %). The comparison results of the EEG findings by groups and time are given in Table 6 (p >0.05). In this study, 40 % of the patients in group C and 46.2 % of the patients in group D were migraines with aura. The temporal change in the EEG findings of migraine patients with and without aura was not statistically significant (p > 0.05).

Considering this information, interictal EEG is not routinely recommended in the diagnostic evaluation of the patients with headache (21). However, it is stated that if the clinical findings of the patients cause a suspicion of epilepsy, it may have a diagnostic contribution (21). EEG scan is recommended in the patients with a suspected alternative hemiplegia, prolonged migraine aura and basillary migraine (21). In addition, if clinical history is suspected in terms of epilepsy, EEG may be performed for differential diagnosis (25).

The relationship between vitamin D and epilepsy is versatile (4). Sönmez et al (26) evaluated the patients with idiopathic epilepsy. They reported that 25-OH vitamin-D3 levels were significantly lower in the patient group compared to the control group (14.07±8.12 and 23.38±12.80 ng/mL).

Holló et al (27) measured vitamin D levels in 13 resistant epilepsy patients and normalized the vitamin D level with treatment. They reported that the frequency of seizures decreased by an average of 40 % with vitamin D treatment and the normalization of serum vitamin D level had an anticonvulsant effect. It is emphasized that low vitamin D levels are associated with an increase in the frequency of seizures in the patients with epilepsy. Teagarden et al (28) evaluated vitamin D levels in 596 epilepsy patients in their study. They reported that vitamin D level was <20 ng/mL in 45 % of patients and <10 ng/mL in 11 %. For this reason, in the patients using antiepileptics, it is recommended that vitamin D levels are routinely measured 2 or 3 times a year according to age groups (27, 28).

Rarely, there are reports that there is no correlation between vitamin D level and frequency of seizures (29). However, the general belief in literature is that vitamin D treatment has positive effects on decreasing seizure frequency (30). In recent years, it has been focused on the antiepileptic effects of vitamin D. It is stated that GABA (A) receptor modulation is also important in the antiepileptic effects of vitamin D (4). However, it is also noted that vitamin D is not as potent as a classic anticonvulsant (eg lorazepam) (31).

We did not find a study evaluating the relationship between vitamin D deficiency and EEG findings in literature search. How-

ever, Danesi (32) suggested that photoparoxysmal changes in epilepsy patients were higher in the winter than in the summer, which may be related to seasonal changes in the amount of sunlight and strengthened this theory with the study of British and Nigerian Grand Mal epilepsy patients. In Nigerian patients, spike-wave discharges, photoparoxysmal changes, and non-specific EEG changes were seen by 15.7 %, whereas British patients with similar diagnoses reported this rate to be 52.9 % (33). This finding supports the view that vitamin D deficiency or insufficiency may be associated with EEG findings in epilepsy patients. However, vitamin D level was not studied in the study of Danesi (33).

In the present study, we evaluated the relationship between EEG findings and vitamin D level in migraine patients. There was no statistically significant difference in the interictal EEG findings of the patients in the groups C and D during baseline, follow-up, and treatment (p > 0.05). EEG findings of migraine patients with and without aura in groups C and D were not statistically significant between groups (p > 0.05). There was no statistical relationship between vitamin D level (< 20 ng/mL and ≥ 20 ng/mL) and EEG findings in group D (p > 0.05).

Conclusions

In conclusion, considering that literature highlights that vitamin D may play a role in both epilepsy and migraine pathogenesis as a neurosteroid and the pathophysiology of EEG changes, it should be taken into consideration. However, in the present study, no relation was found between interictal EEG findings and vitamin D level in migraine patients. In larger case series, the threshold value should be determined in migraine patients for vitamin D level, and it should be studied in the larger patient groups with EEG disorder and migraine coexistence, especially on attack frequency, PedMIDAS scores and EEG findings (26,34,35).

Highlights

- Vitamin D deficiency is higher in girls compared to boys in migraine patients.
- The most common EEG findings was a focal or generalized spike/sharp wave activity.
- There was no statistical relationship between EEG findings and vitamin D levels.

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