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Investigation of the Antiepileptics on Levels of Vitamin D and Calcium

Antiepileptiklerin D vitamini ve kalsiyum düzeylerine etkisi

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ABSTRACT

Aim: We investigated the connection between D vitamin and factors such as the type of antiepileptic agent, patient age and gender.
Methods: This retrospective case-control study enrolled a total of 301 participants, including 141 epilepsy patients with (n= 120) without drug (n=21) regimens followed up in Alanya Alaaddin Keykubat University neurology outpatient clinic and 160 healthy individuals who applied to the neurology outpatient clinic for different reasons from January 2018 to January 2021. Demographics, detailed history, use of medications, duration of antiepileptic use, plasma 25-hydroxy Vitamin D and calcium levels were determined.
Results: The mean level of Vitamin D was 15.46 in the epilepsy group and 16.95 in the control group. Level of D Vitamine did not differ significantly by groups (p>0.05). There were no significant relationship regarding age and vitamin D levels in both groups while decreased Vitamin D levels were detected epileptic women. Vitamin D level was below 20 in 69.6% of healthy control group, 78.9% of carbamazepine users, 62.5% of lacosamide users, all lamotrigine users, 66.7% of levatiracetam users, and 72.4% of sodium valproate users. No significant connection were detected between levels of Vitamin D and the drug used (p>0.05) while a significant association was confirmed only between calcium levels and carbamazepine (p<0.05).
Conclusion: Vitamin D and calcium levels can be found to be low in antiepileptic users; however, except for the calcium levels in the carbamazepine group, this decrease does not constitute a significant difference.

Keywords: Epilepsy, antiepileptic, Ca, vitamin D

ÖZ

Amaç: Çalışmamızın amacı, farklı antiepileptik ajan kullanan epilepsi hastalarında D vitamini ve kalsiyum düzeylerini araştırmak ve D vitamini düzeyleri ile antiepileptik ajanın türü, hastanın yaşı ve cinsiyeti gibi çeşitli faktörler arasındaki ilişkiyi araştırmaktır.
Gereç ve Yöntem: Bu geriye dönük vaka-kontrol çalışmasına Alanya Alaaddin Keykubat Üniversitesi nöroloji polikliniğinde takip edilen ve 21 tanesi ilaç kullanmayan (ilaç kontrol) olmak üzere total 141 epilepsi hastası ve Ocak 2018-Ocak 2021 tarihleri arasında nöroloji polikliniğine farklı nedenlerle başvuran 160 sağlıklı birey (sağlıklı kontrol) olmak üzere toplam 301 katılımcı alındı. Demografi, Tüm katılımcıların ayrıntılı öyküsü, ilaç kullanımı, anti-epileptik kullanım süresi, plazma 25-hidroksi D vitamini ve kalsiyum düzeyleri saptandı.
Bulgular: Ortalama D vitamini düzeyi epilepsi grubunda 15.46, kontrol grubunda 16.95 idi. Gruplara arasında D vitamini düzeyi açısından anlamlı farklılık göstermedi (p>0.05). Her iki grupta da yaş ve D vitamini düzeyleri arasında anlamlı bir ilişki bulunmadı ve epilepsi grubundaki kadınlarda D vitamini düzeyleri istatistiksel olarak anlamlı derecede düşüktü. Sağlıklı kontrol grubunun %69,6'sında, karbamazepin kullanıcılarının %78,9'unun, lakozamid kullanıcılarının %62,5'inin, tüm lamotrijin kullanıcılarının %66,7'sinin ve sodyum valproat kullanıcılarının %72,4'ünün D vitamini düzeyi 20'nin altındaydı. D vitamini düzeyi ile kullanılan ilaç arasında belirgin fark yoktu (p>0.05). Sadece kalsiyum düzeyi ile karbamazepin arasında anlamlı bağlantı vardı (p<0.05).
Sonuç: Antiepileptik kullananlarda D vitamini ve kalsiyum düzeyleri düşük bulunabilir; ancak karbamazepin grubundaki kalsiyum düzeyleri dışında bu düşüş anlamlı bir fark oluşturmamaktadır.

Anahtar Kelimeler: Epilepsi, antiepileptik, Ca, D vitamini

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Introduction

Epilepsy is seen in 0.5-0.8% of cases worldwide. Studies have shown that drugs can keep up to 70% of patients seizure-free, even with monotherapy. There are different types of epilepsy as partial, generalized, absence, tonic, clonic, tonic-clonic,atonic and myoclonic. Although each epilepsy category has its own drug choice, phenytoin, phenobarbital, carbamazepine, sodium valproate, levetiracetam and lamotrigine are the mostcommonly used drugs [1]. Antiepileptic drugs (AED) such as carbamazepine and phenytoin stimulate the Vitamin D catabolism by inducing specific liver enzymes leading to hypocalcemia and secondary hyperparathyroidism by decreasing Vitamin D levels [2-4].

Despite no association found between serum Vitamin D and long-term treatment with phenobarbital, carbamazepine, sodium valproate, and levetiracetam [5], a study of 111 patients taking antiepileptics showed that 24 patients (22%) had Vitamin D failure and 45 patients (41%) had Vitamin D deficiency. Vitamin D deficiency [6]. Another study conducted with 198 patients showed that 124 patients had Vitamin D deficiency (62.6%) [7]. Although there are different results about whether antiepileptics cause Vitamin D deficiency, there is no clearity in the literature. Also the effect of the course of epilepsy itself on Vitamin D is still interesting research area.

Our aim was to evaluate Vitamin D and total calcium (Ca) status in epilepsy patients taking antiepileptics while also determining the link between levels of Vitamin D and the type of antiepileptic used, patient age and gender.

Materıal and Methods

This study enrolled a total of 291 participants, including 141 epilepsy patients followed up in AlanyaAlaaddinKeykubat University neurology outpatient clinic and 150 healthy individuals who applied to the neurology outpatient clinic for different reasons from January 2018 to January 2021. This study, designed as a retrospective case-control study (Ethics Committee of AlanyaAlaaddinKeykubat University with the decision no. 14-05 of September 22, 2021). Demographics, detailed history, use of medications, duration of antiepileptic use, plasma 25-hydroxy Vitamin D and calcium levels of all participants were recorded. The differences between the epilepsy group and the control group were compared statistically. Inclusion criteria were as follows: The study group included epilepsy patients aged 18-65 years, who received monotherapy with the same antiepileptic agent for at least 1 year. The healthy group included individuals in the same age group who were not diagnosed with epilepsy and did not receive antiepileptic treatment (n= 150) while the drug control group included epilepsy patients without a current drug regimen (n= 23). Exclusion criteria were as follows: Individuals with a history of severe central nervous system disease, intracranial mass, surgery, trauma, dementia; individuals with chronic liver and kidney disease, alcohol and substance abuse, and malignancy; individuals with endocrinological diseases such as hypothyroidism, hyperthyroidism, hypoparathyroidism; individuals with a history of gout, and individuals who took calcium and/or Vitamin D supplements were excluded from the study.

Statistical Analysis

Our analyzes were performed with the SPSS 21.0 program at a 95% confidence level. The coefficients of kurtosis and skewness from the measurements were between +3 and -3, which was considered sufficient for a normal distribution. Intergroup comparisons were made through independent 2-sample T-test and chi-square test. A p value less than 0.05 was deemed statistical significance.

Results

Demographic features of patients with epilepsy and healthy controls

In our study, the gender distribution was 36.9% men and 63.1% women in the epilepsy group and 27.5% men and 72.5% women in the control group. There was no significant difference in gender distribution between the groups ($p>0.05$). The rate of participants with vitamin D level below 20 was 71.6% in the epilepsy group and 63.8% in the healthy control group. There was no significant relationship between the group and Vitamin D levels ($p>0.05$). The rate of participants

with calcium levels between 8.6-10 was 88.7% in the epilepsy group and 91.3% in the healthy control group. There was a significant relationship between the group and calcium level (p<0.05). The rate of participants with 8.5 and below is higher in the epilepsy group, and the rate of participants between 8.6-10 and over 10 is higher in the healthy control group (Table 1a).

Table 1a: Demographic features of participants

		Groups				Chi-square	p
		Epilepsy		Healthy Control			
		N	%	n	%		
Age	<50 age	111	78,7	96	60,0	12,234	,000*
	>51 age	30	21,3	64	40,0		
Ort±ss		36,29±16,35		44,36±14,10			
Sex	Men	52	36,9	44	27,5	3,036	0,081
	Women	89	63,1	116	72,5		
25_oh_vitd_level	>20	101	71,6	102	63,8	3,319	,190
	20-29	27	19,1	45	28,1		
	>30	13	9,2	13	8,1		
Ca level	<8,5	16	11,3	10	6,3	5,505	,050*
	8,6-10	125	88,7	146	91,3		
		0	0,0	4	2,5		

*p<0.05: Indicates a significance level of 0.05

Relationships Between Vitamin D Levels and Antiepileptics Used Compared With Control Patients Without Drug

Vitamin D level was below 20 in 69.6% of drug control group, 78.9% of carbamazepine users, 62.5% of lacosamide users, all lamotrigine users, 66.7% of levetiracetam users, and 72.4% of sodium valproate users. There was no significant relationship between Vitamin D level and the drug used (p>0.05) (Table 1b).

Relationships Between Calcium Level and the Drug Used Compared With Control Patients Without Drug

Calcium level was between 8.6-10 mg/dl in 95.7% of drug control group, 63.2% of carbamazepine users, 87.5% of lacosamide users, all lamotrigine users, 94.7% of levetiracetam users, and 82.8% of sodium valproate users. There was a significant relationship only between calcium level and carbamazepine (p<0.05). The use of carbamazepine is highest in patients with a calcium level of less than 8.5 mg/dl and the use of levetiracetam is highest in patients with a calcium level of 8.6-10 (Table 2).

Table 1b: Relationship Between Vitamin D Levels and AED Used Compared With Control Patients Without Drug

		25_oh_vitd_level (ng/dl)						Chi-square	P
		below 20		20-29		30 and over			
		n	%	n	%	n	%		
AED	Drug Control group	16	69.6	4	26.1	1	4.3	6.176	.794
	Carbamazepine	15	78.9	2	10.5	2	10.5		
	Lacosamide	5	62.5	2	25.0	1	12.5		
	Lamotrigine	7	100.0	0	0.0	0	0.0		
	Levetiracetam	38	66.7	13	22.8	6	10.5		
	Sodium valproate	21	72.4	4	13.8	4	13.8		

*p<0.05: Indicates a significance level of 0.05

Table 2: Relationship Between Calcium Levels and the AED Used Compared With Control Patients Without Drug

		calcium level				Chi-square	P
		8.5 and below		8.6-10			
		N	%	N	%		
AED	Control group	1	4.3	20	95.2	13.263	.009*
	Carbamazepine	7	36.8	12	63.2		
	Lacosamide	1	12.5	7	87.5		
	Lamotrigine	0	0.0	7	100.0		
	Levetiracetam	3	5.3	54	94.7		
	Sodium valproate	5	17.2	24	82.8		

*p<0.05: Indicates a significance level of 0.05

Intergroup comparison of Vitamin D and calcium levels Compared With Control Patients Without Drug

The average Vitamin D level was 15.46 in the epilepsy group and 16.95 in the drug control group. Vitamin D level did not differ significantly by groups (p>0.05). No significant relationship was found between age and vitamin D levels in both groups, and Vitamin D levels were statistically significantly lower in women in the epilepsy group (p<0.05).

Discussion

Vitamin D has a primary function in calcium and bone metabolism. In addition, recent studies indicated that it plays a critical role in diabetes mellitus, autoimmune diseases, obesity and cardiovascular diseases. Vitamin D2 (ergocalciferol) obtained

only from plant-derived foods by the exogenous route and vitamin D3 (cholecalciferol) synthesized in the skin by the endogenous way, with the help of UV radiation, as well as foods of animal origin. Both forms are converted in the liver to 25-OH cholecalciferol, the main circulating form of vitamin D. 25-OH cholecalciferol is catabolized by enzymes in the cytochrome P450 enzyme system (CYP24, CYP 3A4). It has been shown that antiepileptics may cause Vitamin D deficiency andbone-mineral metabolism such as hypocalcemia, hypophosphatemia, secondary osteoporosis, osteomalacia, and rickets[8,9]. To the best of ourknowledge, there is not enough data in the literature comparing the effects of antiepileptics on Vitamin D and calcium levels in patients receiving monotherapy. In our study, we compared 5 different antiepileptic agents in patients receiving monotherapy with the control group to investigate their effects on levels of Vitamin D and calcium. Antiepileptics - including phenytoin, carbamazepine, phenobarbital - are metabolized in the liver and cause cytochrome P450 enzyme induction, thereby increasing Vitamin D metabolism by upregulating the enzymes that convert Vitamin D to its inactive form. Consequently, the Vitamin D deficiency is thought to indirectly cause secondary hyperparathyroidism, hypocalcemia and, therefore, loss in bone mineral densitometry [10-12]. In a study on 596 epileptic patients, 54% of Vitamin D deficiency was observed in enzyme-inducing antiepileptics [13]. In accord with this, in our study, in patients using carbamazepine, 78.9% had Vitamin D deficiency and 63.2% had hypocalcemia. Also, in a recent on 58 epileptic patients in the young adult age group, Kulak et al. suggested that the loss of bone density resulting from the use of antiepileptics may be due to Vitamin D deficiency indirectly caused by antiepileptics, as well as the direct increase of bone turnover by antiepileptics [14]. The cross-sectional study by Ferhat et al. found low Vitamin D levels in 50% of patients using antiepileptics but did not find any correlation with bone mineral density measurements [15]. Lamotrigine is an antiepileptic that does not alter the cytochrome P450 system [16] and it seems that its relationship with Vitamin D is not due to the liver, but relate to its pharmacological effects. Lamotrigine blocks sodium and calcium channels [17] similar to Vitamin D. Hence, it is reasonable that lamotrigine may potentiate its effect while Vitamin D supplementation may be an effective strategy in controlling seizures in patients using lamotrigine. Several animal studies have revealed that Vitamin D increases the effect of many antiepileptics, in addition to its own anticonvulsant effect. For instance, several studies have shown that Vitamin D potentiates the effects of traditional drugs such as phenytoin, valproate, carbamazepine, as well as second-generation antiepileptics such as lamotrigine and oxcarbazepine. A study using an experimental epilepsy model in rats showed that Vitamin D supplementation increased the effect of lamotrigine on seizure control and cognition [19]. In our study, all patients using lamotrigine had Vitamin D levels below 20 ng/dl, and calcium levels were normal. Valproic acid (sodium valproate) is an antiepileptic frequently preferred in the first-line treatment of both partial and generalized epilepsy, acting by blocking voltage-dependent sodium channels without inducing enzymes in the liver. Long-term use of valproic acid has been shown to result in loss of bone mineral densitometry in both children and adults; however, there are conflicting results in the literature regarding its effect on calcium and Vitamin D metabolism [2,20]. A study suggested that the effect of valproic acid on bone metabolism was due to increased urinary calcium and phosphorus excretion, leading to renal tubular dysfunction [19]. In addition to the use of antiepileptics, there are also other factors that might affect Vitamin D levels, such as geographical features, exposure to sunlight, gender, nutrition in Vitamin D deficiency. Based on this, we created a control group living in the same geographical region, having similar ages and gender ratios in our study. Participants consisted of individuals living in the same geographical region and the same climate. In the literature, it is emphasized that use of multiple antiepileptics and long-term antiepileptic therapy are important risk factors for the development of Vitamin D deficiency. In our study, almost all patients who used the same drug for at least 1 year and received monotherapy. Current literature is scarce of the possible effects of deficient levels of Vitamin D on epilepsy pathogenesis regardless of the use of antiepileptics. Hence it is still unclear whether Vitamin D has a direct epileptogenic effect or

show the reverse pattern. Experimental studies investigating the role of Vitamin D in epilepsy has shown that intrahippocampal and intravenous Vitamin D supplementation increases the seizure threshold especially in mice. In support of this view, another study showed an increased susceptibility to seizures with the elimination of the Vitamin D receptor in transgenic mice [9]. In a pilot study in patients with Vitamin D deficiency and drug-resistant epilepsy, Christian et al. showed that Vitamin D supplementation resulted in significantly reduced number of seizures [20]. Although our current results support the hypothesis that epilepsy itself may cause Vitamin D deficiency rather than antiepileptics, a definitive conclusion can only be made with the data of the epileptic patient population who do not use antiepileptics. However, since this population is difficult to find and its planning will cause ethical problems, it seems difficult to reach a definite conclusion. Considering all of these evidences, our results draw attention to the primary role of epilepsy at the hypothetical level despite our data of low calcium levels in carbamazepine treated groups.

Limitations: The limitation of our study is the low sample size among the drug groups in antiepileptic users. Furthermore, the fact that the participants' exposure to sunlight during the day was not questioned can also be considered as a minor weakness of our studyalthough this effect will be minimal since patients in the same season and in the same geographical region were selected. Additionally, small sample size in evaluating the effect in the population that does not use antiepileptics should be considered as a relative limitation due to ethical concerns. We believe that future longitudinal antiepileptic studies, in which vitamin D levels are measured before and after treatment, will shed some light on this limitation.

Conclusion

Our study shows that decreased levels of Vitamin D and calcium levels can be found in antiepileptic users; however, except for the low calcium in the carbamazepine group, this alterationsdoes not make a significant difference compared to the control group and it is too early to come to a definitive conclusion without replicating the same results in larger treatment cohort.

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