ORIGINAL ARTICLE

How Antiepileptics May Change the Serum Level of Vitamin D, Calcium, and Phosphorus in Children with Epilepsy

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Abstract

Objective

Studies have shown vitamin (Vit) D deficiency and bone disease in long-term use of antiepileptics, especially in young individuals. This study aimed to determine the relationship between antiepileptic drugs and the level of Vit D, calcium (Ca), and phosphorus (P) in children with epilepsy at the Shohada Hospital from 2016 to 2017.

Materials & Methods

In this case-control study, 60 consecutive children with epilepsy at the Shohada Hospital from 2016 to 2017 under treatment with anti-convulsions for more than six months were enrolled as the case group. The level of Vit D, Ca, and P was determined in the case group and compared with 60 children without seizure as the control group.

Results

The mean Ca and P were alike across the groups ($P > 0.05$). The mean Vit D3 level was 31.3 and 40 in the case and control groups, respectively, with significant difference ($P=0.0001$). The mean Ca and P were alike across the types of drug in the case group ($P > 0.05$); however, the mean Vit D3 level was lower in the case versus control group with significant difference ($P=0.040$).

Conclusion

Totally, according to the obtained results, it may be concluded that treatment with antiepileptic drugs, especially stimulant type, is related to the lower Vit D3 level, but not to the Ca and P levels.

Keywords: Epilepsy; Antiepileptic; Vitamin Ddeficiency; Long-Term; Children

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Introduction

Convulsion is a common medical condition which results in epilepsy in 0.5-0.8% of cases worldwide. Studies showed that medications could keep 70% of patients away from epilepsy, even with mono-therapy. Since epileptic disorders are more common among children, relevant medications are also much more frequently used in them. Some of antiepileptic drugs such as phenytoin, phenobarbital, and carbamazepine are strong stimulants for hepatic microsomal enzymes (1), resulting in changes in the metabolism of exogenous or endogenous substances (2). These drugs usually decrease serum level of Ca and vitamin (Vit) D toward osteomalacia (3). In children, antiepileptics, immobility, multidrug or long-term treatments, and inappropriate nutrition are known as aggregating factors in this regard (4). Although Vit D supplements are prescribed for children in their first two years of life, due to multiple issues related to nutrition and life style in our country, rickets, hypocalcemia, and other relevant medical conditions like immune disorders are still common in children (5).

Epilepsy has different types including partial, generalized, absence, tonic, clonic, tonic - clonic, atonic, and myoclonic, but their details and causes are not the main focus of the present report. Each category of epilepsy has its choice medication; however, phenytoin, phenobarbital, carbamazepine, sodium valproate, levetiracetam, and lamotrigine are the most commonly used medications. Previously, dosages of medications were determined through trial and error, lasting for months or even more. Recently, the optimal dose of anti-seizure drugs has been determined based on serum level measurements. Previous studies through biochemical and radiological assessment confirmed side effects of the metabolism of Vit D, calcium (Ca), and phosphorus (P), resulting in rickets (5-10). Although Yildiz et al. (2017) found no correlation between the serum level of Vit D and long-term treatment with phenobarbital, carbamazepine, sodium valproate, and levetiracetam (11), Fong et al. (2014) reported 22% and 41% Vit D deficiency and insufficiency, respectively (12). The rates were even more in Lee's report in 2015, i.e. 79% Vit D deficiency after only 1 year of treatment. The reason was probably combined therapy or treatments for more than 2 years, tube feeding, and overweight condition (13). Considering the common use of antiepileptics in childhood, it is worth assessing their effects on Vit D, Ca, and P to know the mechanism of these effects so that rickets and hypocalcemia could be prevented. To this end, the current study attempted to measure the named parameters among children taking antiepileptics and compare them with others.

Materials & Methods

Through a case-control study, children with epilepsy who were prescribed antiepileptic medications for at least 6 months were selected. The aim was to compare the serum level of Vit D3, Ca, and P. Finally, 120 referrals from 2016 to 2017 participated in the study by census. There was no randomization to select the patients. Children with medical conditions affecting bone metabolism (hepatic, renal, metabolic, or endocrine diseases), chronic diseases (cancer, diabetes mellitus, GI tract problems), and moving disorders as well as those using other medications

such as Vit D/Ca supplements or corticosteroids causing neuromuscular diseases were excluded from the study. The participants were divided into two groups including case (60 participants) and control (60 participants). Cases were epileptic children using antiepileptic medications at least for 6 months, and controls were selected from referrals to general clinics at the Shohada Hospital, Tehran, Iran. The groups were matched for age and sex before enrollment, and demographics, types of epilepsy, duration of treatment and names of drugs were recorded from the charts. A single laboratory measured the studied items. Vit D deficiency and insufficiency were defined as 25-hydroxy Vit D<20 ng/ml and 20≤VitD≤29, respectively. The epileptic medications were categorized as enzyme stimulants and non-stimulants, with the former including phenytoin, carbamazepine, phenobarbital, and primidone. The enzyme non-stimulants were lamotrigine, levetiracetam, topiramate, clobazam, sodium valproate, and ethosuximide.

Statistics: The current study was approved by the ethics committee of the Shahid Beheshti University of Medical Sciences under the code "IR.SBMU. MSP.REC.1396.668". The central measures including means and standard deviations (SD) along with frequencies were reported using SPSS software. The confidence interval of 95%, the type-one error of 0.05, and the significance level of 0.05 were considered. An independent t-test and Chi-square tests were used for quantitative and qualitative variables, respectively.

Ethics: No subject was enrolled in the study without written consent by the parents, and no extra charge or test was forced. All the laboratory data were safely kept by the principal investigators, and the families were informed by the feedback.

Results

A total number of 120 individuals participated in the current study, including 60 cases and 60 controls. Males made up 46.7% of the cases and 51.7% of the controls with no significant differences (P-value=0.715). Age was not different between the groups with the similar mean and SD of 5.72±2.9 years in the cases and 5.64±2.9 years in the controls. There was neither different height nor different weight comparing the groups.

In terms of convulsion types, 60% of all the cases were generalized tonic-clonic followed by partial (23.3%), clonic (10%), absence (5%), and tonic (1.7%). Table 1 shows drugs used by the participants, of which 35% were stimulant drugs including phenytoin, carbamazepine, phenobarbital, and primidone and 65% were non-stimulants drugs such as sodium valproate, levetiracetam, topiramate, and ethosuximide. The mean duration of drug use was 8.6 months in the case group; while the control group took no drugs or placebos.

The average levels of Ca, P, and Vit D are reported in Table 2 in the both groups with similar values in Ca and P but a different value in Vit D (P value<0.001). There were three serum level ranges for each parameter to measure in this study. The elements Ca and P showed no difference between the groups at low, normal and high levels. However, Vit D significantly differed in the studied groups at the three levels (P-value=0.015) and Vit D insufficiency was obviously observed more in the cases. Similar findings were also obtained regarding the mean of the studied parameters, with Vit D as the only significantly different item after comparing the stimulant and non-stimulant drug users among the cases (P-value=0.04). Ca and P had very close levels between the cases using

the both groups of drugs (Table 1). Low, normal, and high levels of the elements and Vit D were compared between the stimulant and non-stimulant drug users to detect statistically similar results for all the three levels, as shown in Table 1. Table 3 summarizes different ranges of Ca, P, and Vit D in the case group in terms of duration of drug use to present similar frequencies. With no statistically meaningful changes, Table 4 shows the gender mean of the participants.

Table 1. The use rates of the prescribed medications based on their metabolic mechanism in the case group and their effects on the serum level of the studied elements

Non-Stimulant				Stimulant				Medications		
Ethosuximide	Topiramate	Levetiracetam	Na Valproate	Primidone	Phenobarbital	Carbamazepine	Phenytoin			
1(1.7)	5(8.3)	14(23.3)	19(31.7)	11(18.33)	2(3.33)	3(5)	5(8.33)	n (%) Serum level		
9.84±1.51				9.83±0.69				<8.5 n (%)		Calcium
5(12.8)				1(4.8)				8.5-10.5 n (%) n(%)		
23(59)				17(81)				>10.5 n (%)		
11(28.2)				3(14.3)				Sig		
0.222								Serum level		
5.14±1.05				5.19±0.96				<3.5 n (%)		Phosphorus
2(5.1)				1(4.8)				3.5-5.5 n (%)		
27(69.2)				11(52.4)				>5.5 n (%)		
10(25.6)				9(42.9)				Sig		
0.388								Serum level		
33.53±11.26				27.19±10.82				Yes n (%)	Deficiency	Vitamin D3
15(38.5)				14(66.7)				No n (%)		
24(61.5)				7(33.3)				Sig		
0.070										

Table 2. Means and level classification of calcium, phosphorus, and vitamin D in the both groups

Element	Category	Case	Control	Sig
Ca	Total(Mean±SD)	9.83±1.28	9.99±0.99	0.449
	<8.5 n (%)	6(10)	2(3.3)	
	8.5-10.5 n (%)	40(66.7)	44(73.3)	
	>10.5 n (%)	14(23.3)	14(23.3)	
P	Total(Mean±SD)	5.15±1.01	5.43±0.96	0.131
	<3.5 n (%)	3(5)	4(6.7)	
	3.5-5.5 n (%)	38(63.3)	30(50)	
	>5.5 n (%)	19(31.7)	26(43.3)	
Vit D	Total(Mean±SD)	31.31±11.43	40±14.68	<0.001
	<20 n (%)	6(10)	4(6.7)	
	20-30 n (%)	23(38.3)	10(16.7)	
	>30 n (%)	31(51.7)	46(76.7)	

Table 3. Means and level classification of calcium, phosphorus, and vitamin D in the case group based on the duration of antiepileptic treatment

Element	Category	Mean±SD	min	max	Sig
Ca	Low	7.17±1.17	6	9	0.133
	Normal	8.48±2.52	6	18	
	High	9.64±3.15	6	17	
	Total	8.62±2.64	6	18	
P	Low	8±1	7	9	0.158
	Normal	8.18±2.37	6	17	
	High	9.58±3.13	6	18	
	Total	8.62±2.64	6	18	
Vit D	Low	8.67±1.86	7	12	0.993
	Inadequate	8.57±2.48	6	18	
	Normal	8.65±2.94	6	17	
	Total	8.62±2.64	6	18	

Table 4. Distribution of the serum level of calcium, phosphorus, and vitamin D in the both groups based on the participants' sex

Element	Sex	Mean	SD	Sig
Ca	Female	9.83	1.26	0.403
	Male	10	1	
P	Female	5.37	0.94	0.380
	Male	5.21	1.04	
Vit D	Female	35.85	16.13	0.875
	Male	35.45	11.05	

Discussion

The current study showed lower serum Vit D in the antiepileptic drug users, especially among children who took stimulant antiepileptics, although the serum level of Ca and P was not statistically different. The rates of Vit D deficiency and insufficiency were 10% and 38.3%, which were slightly lower than what Fong et al. (2014) reported (12). Borusiak et al. (2013) showed 13.3% Vit D reduction due to antiepileptics among 128 children who were healthy regardless of their epilepsy (9). This rate of reduction is less than what we claimed; however, hypocalcemia and hypophosphatemia were detected to be 24.4% and 25.4% in their study but only 10% and 5% in our study, respectively. Durá-Travé et al. considered valproic acid and levetiracetam as the main medications to treat Vit D deficiency through mono-therapy and reduce Ca (14). High alkaline phosphatase and low Ca serum levels were shown in a study on Indian epileptic children by Chaudhuri et al. who associated Vit D deficiency to carbamazepine mono-therapy followed by sodium valproate (15). They obtained an odds ratio of 4.0 in this regard, showing a 4-fold Vit D deficiency risk by valproic acid in children. Albaghdadi et al. concluded that the above mentioned medication caused low bone mineral density and hypovitaminosis D resulting from valproic acid in adults known as epileptic cases. This could raise the significance of monitoring epileptic patients for bone structure and osteoporosis during their childhood (16). On the contrary, Serin et al. and Paticheep et al. reported no bone mineral loss and Vit D deficiency in pediatric patients taking long-term antiepileptic drugs (17, 18). They also showed no difference between levetiracetam, as a bone-protective antiepileptic drug, and other medications usually prescribed for this purpose. Toopchizadeh et al. claimed that although Vit D deficiency and bone mineral density reduction were more prevalent in CP children compared with healthy ones, antiepileptic medications may need to be further investigated before being recognized as the main cause of these problems (19).

Many studies investigating the effects of antiepileptic drugs on minerals and electrolytes in the body believed that the most frequent effects of these medications were on Ca, P, and Vit D. Among these studies is the one by Ashrafi who compared 119 patients under antiepileptics with 119 controls to show the effects of the aforementioned medications on bone minerals, especially PTH (20). Increased inactive forms of Vit D are mainly due to hepatic microsomal enzyme cytochrome

P450, which is chiefly directed by carbamazepine, phenytoin, phenobarbital, and primidone. On the other hand, phenytoin and phenobarbital could reduce Ca intestinal absorption. Moreover, these medications as well as carbamazepine and sodium valproate increase the bone metabolism rate, and the last two also inhibit the effect of parathormone on bone metabolism. Moreover, phenytoin inhibits activation of osteocalcin. It is not deniable that renal tubular metabolic disorders are among other causes of rickets through the increased urinary loss of Ca and P (21-24). We attempted to exclude all conditions affecting the serum level of Ca, P, Vit D to limit their alterations only to antiepileptics.

In Conclusion

Antiepileptics were associated with the low serum level of Vit D in the treated children, especially those receiving stimulants, although these medications did not statistically affect the serum level of Ca and P in the current study. However, the authors recommend to conduct more multidisciplinary studies with bigger sample sizes, and also, to provide or revise clinical guidelines to select the best epilepsy treatment in children, especially in those at the risk of losing Ca, P, and Vit D due to any other condition.

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Authors Contribution

SS designed and supervised all the processes, and NV collected the data and prepared the primary manuscript, AAHA and HSF reviewed the he primary manuscript. All authors have seen and approved the content of the final manuscript that is currently being submitted and have contributed significantly to the work.

Conflict of interest

The authors declare no conflict of interest.

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