

Evaluation of Serum Vitamin D level in Epileptic Children on Anticonvulsant Drug Therapy

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Abstract

Introduction: Epilepsy is widely regarded as the most common neurologic disorder of childhood. There are two main groups of antiepileptic drugs: hepatic enzyme inducers that induce hepatic P450 system and non-inducers. Nevertheless, non-enzyme-inducing AEDs can also be correlated with hypovitaminosis D; the mechanism for this needs to be investigated. Vitamin D deficiency, and thus impaired bone health, is known to be associated with hepatic CYP450 enzyme-inducing antiepileptic drugs therapy and polytherapy, especially when used for extended periods of time.

Aim of the study: Evaluation of vitamin D in serum of epileptic children on anticonvulsant.

Subjects and Methods: A cross-sectional case control research was performed on 90 children. It involved 45 cases with epilepsy on AEDs and 45 healthy control subjects. They were subjected to full medical history, general and neurological examination, electroencephalography, vitamin D level, serum calcium and phosphorus level.

Results: Twenty four patients represented about(53.3%) of all our cases which were on antiepileptic drugs for greater than six month had vitamin D deficiency, compared to one healthy child represented about (2.2%) who had vitamin D deficiency. Decreasing of serum vitamin D level more in patient who took AEDs for > 1 year than those who were treated for duration of 6 months to 1 year (57.1% vs. 40.0%).

Conclusions: Our data support that antiepileptic drugs which are used by children with epilepsy lead to decrease in serum vitamin D which is important for the homeostasis of calcium, phosphate & magnesium. Its importance is most essential in bone metabolism. Deficiency was more in patient who took polytherapy for long time.

Keywords: Epilepsy, antiepileptic drugs and vitamin D.

1. Introduction

Epilepsy is the most prevalent chronic neurologic disorder in children. It impacts among 0.5% and 1% of children (1). Epilepsy is distinguished by the recurrence of unprovoked seizures. (2). Epilepsy prognostic factors include the genesis of the condition, EEG abnormalities, the type of seizures encountered, the number of seizures that were present before therapy began, and inadequate initial responses to medication (3). Vitamin D is a fat-soluble vitamin that plays an essential part in the metabolic processes that involve calcium and phosphorus (4). Within the central nervous system, vitamin D plays a crucial role in the regulation of cell proliferation and differentiation, as well as neurotransmission and immunological response (5). Hypovitaminosis D is a disease that affects people all over the world. Hypovitaminosis D has been associated with factors such as gender, pubertal stage, skin pigmentation, the time of year that serum is collected, urban residence, geographical conditions (degree of latitude, etc.), obesity, chronic diseases (skin disease, malabsorption, cholestasis, renal insufficiency), and chronic medications (antiepileptic drugs and glucocorticoids) (6). There are primarily two categories of medications used to treat epilepsy: those that stimulate the production of hepatic enzymes, such as carbamazepine, phenytoin, and topiramate; and those that do not stimulate the production of hepatic enzymes, such as clonazepam, levetiracetam, valproate, and zonisamide. When contrasted with non-inducers, enzyme inducers have the potential to have a more detrimental effect on bone mineral density (BMD) (7). Vitamin D shortage is linked to the elevated hepatic metabolism of vitamin D, which in turn reduces intestinal calcium absorption, and this is especially true of long-term antiepileptic medication therapy and polytherapy (8). Further research is needed to identify the mechanism linking non-enzyme-inducing AEDs to hypovitaminosis D. Children with epilepsy who use valproate have been shown to have reduced levels of 25-hydroxyvitamin D (25-OHD) and bone mineral density (9).

Subjects and methods

1.1. Subjects

Inclusion criteria

- 1- Age of children was from 2-12 years old.
- 2- Children with epilepsy under (AED) mono or polytherapy for 6 months or more.

Exclusion criteria

- 1- cases with hepatic disorder.
- 2- cases with renal disorder.
- 3-cases on vitamin D supplement less than 6 months before sampling.

- 4- Patients with any endocrinal disorders.

- 5- Patients with metabolic disorders including (cystic fibrosis and crohn)

1.2. Study design

This is a cross-sectional case-control research that aims to determine whether antiepileptic drugs effect on serum vitamin D or not. This work was conducted from October 2020 to September 2021.

1.3. Statistical Methods

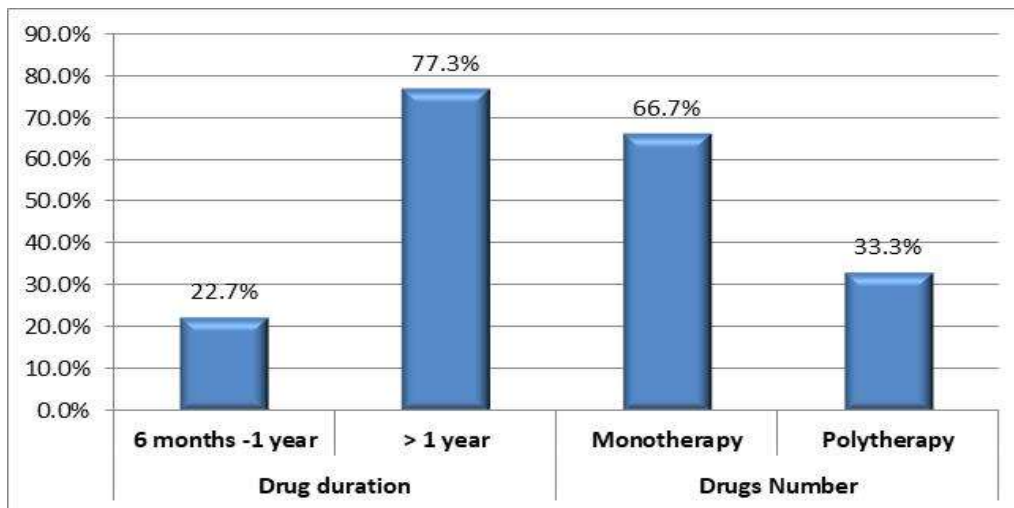
The study was approved by ethical committee of fayoum faculty of medicine. An informed written consent was obtained from all parents of the cases included in our research. The

researcher briefed the parents on the objectives, examination, and investigation procedures of the study.

2. Results

In this study, 90 patients were included group I it included 45 patient with epilepsy and on anticonvulsants for more than 6 month. Group II (control group): It included 45 healthy children. Frequency of vitamin D deficiency was higher in patients was treated for > 1 year than those was treated for duration 6 months to 1 year (57.1% vs. 40.0%), The results showed no significant variation, p=0.197.

Figure (1): Characteristics of antiepileptic (duration and number):



According figure (1): about 66.7% of cases on monotherapy, 33.3% on polytherapy .77.3% of cases on antiepileptic for more than one year, 22.7% of cases on antiepileptic for aduration of 6 month to a year.

Figure (2): Vitamin D status in all participate children (N=90).

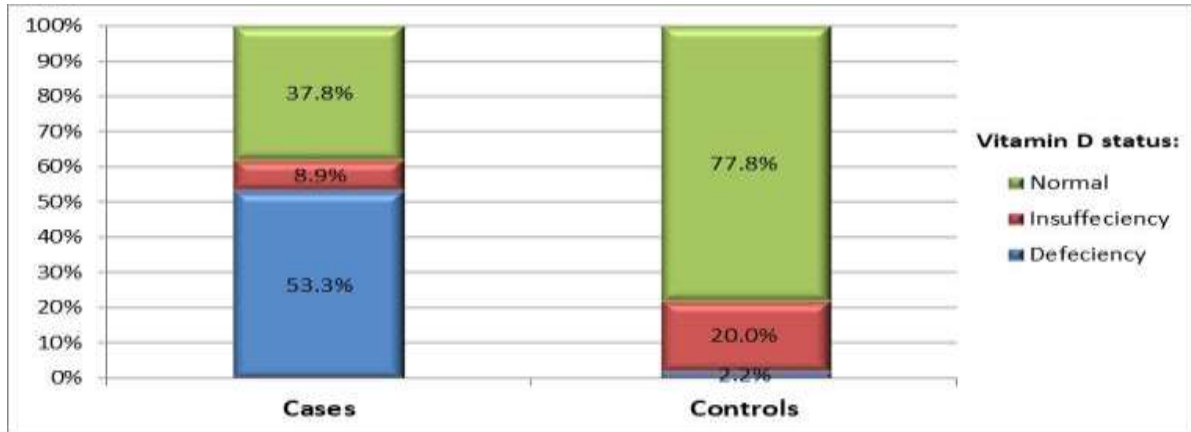


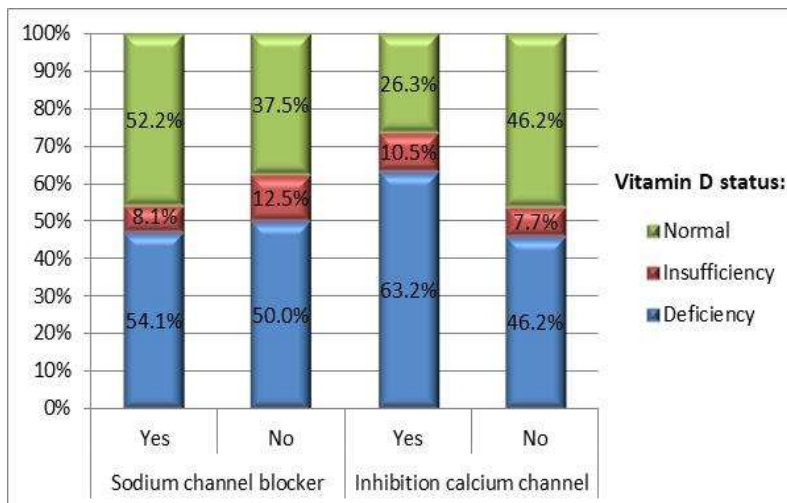
Figure (2) show 53.3% of cases have deficiency of vitamin D compared to 2.2% of controls, 37.8% of cases have normal vitamin D level on compared to 77.8% of controls and 8.9% of cases have insufficiency vitamin D compared to 20% of controls.

Table (1): Relation among vitamin D status & drugs number in cases (N=45)

	Deficiency (N=24)		Insufficiency (N=4)		Normal (N=17)		P-value
	N	%	N	%	N	%	
Drugs Number							
Monotherapy	13	43.3%	3	10.0%	14	46.7%	0.158 (NS)
Polytherapy	11	73.3%	1	6.7%	3	20.0%	

Table (1): Although frequency of vit D deficiency was higher in participants treated with polytherapy than those treated with monotherapy (73.3% vs. 43.3%), it was not statistically significant, p=0.158.

Figure (3): Relation amongst vitamin D status and drugs type.



In figure (3) There was no significant relation amongst vitamin D status & taking sodium channel blocker or inhibition calcium blocker, $p=0.922$ and 0.399 , respectively.

Table (2): Relation among vitamin D status and drugs duration in case group (N=45).

	Deficiency (N=24)		Insufficiency (N=4)		Normal (N=17)		P-value
	N	%	N	%	N	%	
Drug duration							
6 months -1 year	4	40.0%	0	0.0%	6	60.0%	0.197 (NS)
> 1 year	20	57.1%	4	11.4%	11	31.4%	

While occurrence of vitamin D deficiency was higher in patients was treated for > 1 year than those was treated for duration 6 months to 1 year (57.1% vs. 40.0%), this variance was not significant, $p=0.197$, this was described above in table (2).

Discussion

In children, epilepsy is the most common form of chronic neurological disease, affecting among 0.5 – 1.0% worldwide (1)

Children are disproportionately affected by epilepsy. To maintain seventy percent of patients free from epilepsy, AEDs should be initiated as monotherapy (10).

Some fat-soluble compounds, including vitamin D, are called secosteroids. Parathyroid hormone [PTH] plays a crucial role in bone metabolism by regulating blood calcium levels through intestinal absorption of calcium and phosphate, an increase in osteoclast number, and encouragement of appropriate PTH function (11).

Epileptic children have a higher chance of having weak bones and are also more likely to have other risk factors for vitamin D insufficiency (12).

Because of the numerous negative consequences that may be resulting from children's continued use of AEDs, it is now recommended that their blood levels be monitored on a regular basis and that they take vitamin D supplements. This is due to the fact that children's continued use of these medications can create these problems (13).

Children treated with AEDs had known to have problems with bone metabolism and two to three times and the fracture risk of healthy controls (14).

The American Academy of Pediatrics had recommended 400 IU to 1000 IU of vitamin D for children who had treated recently for vitamin-D deficiency (11).

Our research is one of the scarce reports to record the changes occurring in the levels of serum vitamin D in epileptic children throughout treatment with antiepileptic drugs. According to the findings of this study, 53.3 percent of epileptic children who were being treated with anti-epileptic medications had inadequate levels of vitamin D in their serum, whereas 2.2 percent of healthy people were found to have inadequate levels of vitamin D in their serum. Mridula et al. (2017) found results that were comparable to these ones (15). Bhat et al. (2019)(16) is another study of epileptic patients on antiepileptic drugs which showed about 43.3% of cases with decreased vitamin D levels compare to 13.3% of healthy controls.

In our study the mean level of vitamin D among cases was 48.9 and 70 among controls. But in a study by Al-Taeae et al. (2021) (17) there was significantly high level of vitamin D₃ in cases with epilepsy. The rate of Vit D deficiency in our study was 53.3% of cases and rate of vitamin D insufficiency was 8.9% of cases whereas, Saket et al. (2021) (10) reported about 10% of cases had vitamin D deficiency and 38.3% had vitamin D insufficiency. Our study percentage was higher than Fong et al. (2014) (18) reported 22% of cases had vitamin D deficiency and 41% of cases had vitamin D insufficiency. In our work, vit D deficiency was noted especially among cases who took sodium channel blocker antiepileptics like valproic acid. In Mridula et al. (2017)(15) study, vitamin D deficiency was most noted in patient who received carbamazepine as mono-therapy.

There are difference in prevalence of vitamin D deficiency from 4 to 75 percent in pediatric cases with epilepsy on AEDs which had been reported in different studies (19).

There was significant correlation among the length of time spent on antiepileptic medication and a drop in the 25(OH) D level in the blood (13).

Final vitamin D levels were lower for individuals treated with antiepileptic medicines for more than a year in comparison to individuals administered with antiepileptic drugs for durations of 6 months to less than a year. This result is similar to a research by Kamili et al. (2020) (20). However this variance was not statistically significant. In Saleh et al. (2020)(11) study, There was a substantial decrease in vitamin D levels among antiepileptic drug patients, and their follow-up revealed that prolonged duration of antiepileptic usage was connected with a significant reduction in vitamin D levels.

In our study, prevalence of serum vitamin D deficiency was higher in cases treated with polytherapy than those treated with monotherapy (73.3% vs. 43.3%). This result is similar to Tosun et al. (2017) (21). In Saleh et al. (2020) (11), The occurrence of vitamin D deficiency among pediatric epilepsy individuals taking antiepileptic medications was high, particularly in the polytherapy group.

Seizures, whether focal or generalized, had no effect on serum vitamin D level in our cases, and this study's findings support the notion that seizure type has no effect on serum vitamin D level.

In Australia and Malaysia, cross-sectional studies of adolescents with epilepsy produced comparable results (22).

Our observation was supported by Mridula et al. (2017) (15), who discovered that epileptic patients had substantially lower mean calcium levels than controls ($P= 0.016$).

Another longitudinal cohort study showed that patients with hypocalcemia had higher prevalence of developing vitamin D deficiency as contrasted with those with normal and high calcium levels (23). In the research of Indian epileptic children, Chaudhuri et al. (2017) (24), found low Ca serum levels. There was a significant connection among serum calcium & vitamin D; active calcium absorption decreases when serum vitamin D concentration decreases (20).

Hyperphosphatemia was observed in our study with high significant mean level in epileptic patient in contrast to controls ($p<0.0001$), that was opposite to Saket et al. (2021) (10) which showed hypophosphatemia in 25.4% of cases and hypocalcemia in 24.4% of cases. While there was no significant variance amongst cases and controls as regard serum Ca and Ph in Osman et al. (2017) (25) study.

We also found prevalence of serum vitamin D level deficiency was high in patient was treated with antiepileptic drugs for long time but this deficiency was not statistically significant, similar result in Toopchizadeh et al. (2018) (26) study.

In this study 71.1% of cases had generalized epilepsy and 17.8% had focal. In Saket et al. (2021) (10) study type of convulsion types, 60% of all the cases were generalized tonic-clonic followed by partial (23.3%).

2.2% of patient in our study had normal EEG and 97.8% had abnormal EEG in the form of subcortical epileptic activity (40%), focal focus (17.8%), brain insult (15.6%) and focal with secondary generalized (2.4%).

Normal EEG does not exclude epilepsy, in our study around 2.2% of patients with normal EEG but they had epilepsy. But (Abd El Naby & Naguib., 2018) (27) study showed abnormal EEG in the epilepsy group represent (52%).

Conclusion Our data support that antiepileptic drugs which are utilized by children with epilepsy lead to decrease in serum vitamin D which is important for the

homeostasis of calcium, phosphate and magnesium. Its importance is most essential in bone metabolism. Deficiency was more in patient who took polytherapy for long time.

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