A study of vitamin D status in Egyptian pediatric epileptic patients on monotherapy antiepileptic drugs: a hospital-based study

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Received 27 August 2020
Revised 02 September 2020
Accepted 07 September 2020
Published 21 July 2021

The Egyptian Journal of Laboratory Medicine 2020, 1:21–5

Introduction and aim

Epilepsy is a chronic condition with an incidence of 4–10/1000 worldwide. Antiepileptic drugs (AEDs) remain the mainstay of treatment for epilepsy. AEDs in common use are carbamazepine (CBZ), phenytoin, phenobarbitone, and sodium valproate. Long-term therapy by AEDs is associated with bone disorders, affected by both duration and dose of these drugs. The effect of antiepileptic on serum vitamin D levels is controversial and uncertain, so further clinical studies to ascertain the effect of old and newer AEDs on serum levels of vitamin D level in epileptic patients are needed, thus accomplishing a suitable usage of vitamin supplementation. The aim of this study is to assess the longitudinal effect of AEDs on serum 25-hydroxyvitamin D [25(OH) D] levels and bone mineral metabolism markers among Egyptian pediatric epileptic patients on monotherapy AEDs.

Participants and methods

The study was carried out on 62 epileptic patients attending the Neuropediatric Outpatient Clinic, Children's Hospital Cairo University, with history of seizures (age ranges from 1 year up to 12 years), and 64 children not on AEDs as a control group. Daily dietary intake of calories, calcium, and phosphorus was characterized by dietary recall method. Patients on valproate were 37.1% of patients, whereas 32.3% were on levetiracetam and 30.6% were on CBZ. Valproate dose ranged between 10 and 40 mg/kg/day, with a mean dose of 30.4 ± 8.1 mg/kg/day, whereas levetiracetam dose ranged between 20 and 50 mg/kg/day, with a mean dose of 26 ± 8.8 mg/kg/day, and CBZ dose ranged between 15 and 40 mg/kg/day, with a mean dose of 31.8 ± 8.9 mg/kg/day. All patients on AED and control group were evaluated for vitamin D level. Serum calcium, phosphorus, Mg, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, creatinine, and urea were measured for both patient and control groups.

Results

Marked vitamin D deficiency was detected in 31 epileptic patients (50%) (mean ± SD: 13.4 ± 7.6 ng/ml) compared with the control group (6.2%) (mean ± SD: 60.4 ± 17.9 ng/ml) ($P = 0.000$), whereas mild deficiency was remarkable in 19 patients with epilepsy (30.6%) compared with five (7.8%) controls. Overall, 54.8% of the severely deficient patients in vitamin D were on CBZ, whereas 41.9% were on valproate, and 3.2% were on levetiracetam, with statistical significance on comparing vitamin D level with the type of AEDs ($P < 0.0005$). Laboratory data showed that there was a statistically significant difference in calcium, phosphorus, Mg, and alkaline phosphatase (ALP) levels comparing epileptic patients with the control group ($P < 0.000$, 0.000, 0.048, and 0.000, respectively).

Keywords:
antiepileptic drugs, bone disorders, osteomalacia, vitamin D deficiency

The Egyptian Journal of Laboratory Medicine 1:21–5

Introduction

Epilepsy is a chronic disease of the nervous system with chronic recurrent attacks of seizures which occur in the absence of any metabolic-toxic disease [1]. It is one of the world's most prevalent non-communicable diseases [1]. The antiepileptic drugs (AEDs) in common use for prevention of recurrence of seizures are carbamazepine (CBZ), phenytoin, phenobarbitone, and sodium valproate [2], but they have been associated with reduced bone mineral density and fracture risk through their effect on vitamin D metabolism depending on the duration, dose, and type of therapy [3].

Regulation of vitamin D3 metabolism depends mainly on the enzymes involved in its synthesis (CYP27B1) or catabolism (CYP24A1) [4]. Low serum calcium activates the secretion of parathyroid hormone that acts on the kidney to induce 25-hydroxyvitamin D [25(OH)D]-1α-hydroxylase [5]. Reductions in

serum phosphorus are associated with increased 1,25(OH) 2D synthesis with the same mechanism [6].

Inhibitory factors for vitamin D synthesis include 1,25(OH)2D suppressing [25(OH)D]-1α-hydroxylase enzyme, decreasing its own synthesis [6], and the fibroblast growth factor-23, which is a protein mostly expressed in bones and cartilage and regulate phosphate metabolism inhibits the 1α-hydroxylase enzyme [7].

The commonest theory for the lowering effect of AEDs on vitamin D levels is the induction of the cytochrome P450 enzymes in the liver with increased conversion of vitamin D to inactive metabolites there, and the inactive vitamin D results in decreased absorption of calcium in the intestines, leading to hypocalcemia and increase in parathyroid hormone in circulation and increase bone turnover [8].

This in turn causes mineral resorption from bone to keep calcium within normal range for vital functions [9]. Serum biochemical changes that may predispose the individuals to the risk of rickets and osteomalacia usually appear within a period of three months of AED intake [10].

Mandatory guidelines whether to supplement calcium and vitamin D in a patient with epilepsy from day of initiation of AED therapy or whether baseline data of markers of bone formation, resorption, and vitamin D levels are not available based on studies and recommendations [11].

Participants and methods

This comparative study was carried out in the Pediatric Department, Faculty of Medicine, Cairo University Children's Hospital during the period from September 2018 to March 2019.

The study included two groups: group A (cases) represented children with uncomplicated idiopathic epilepsy who were on standard recommended doses of AEDs for more than 6 months. Group B was taken as a control group, which included apparently healthy children not on AEDs and matched for age and sex with cases.

Children having kidney disease, hyperparathyroidism, liver insufficiency, diabetes mellitus, and those on drugs like corticosteroids, and taking vitamin D derivatives were excluded from the study.

Age, sex, type of epilepsy, and type and duration of antiepileptics used were recorded. Anthropometric measurements using the 2006 WHO international growth charts were plotted. Overall, 5-ml venous blood was drawn. Vitamin D levels were measured using enzyme-linked immunosorbent assay based on competitive binding using the DRY-HYBRID-XL 25-OH Vitamin D kits (DRG Germany www.drg-diagnostics.de, DRG GmbH, R&D and Production-Marburg, Germany), whereas serum Ca, Mg, phosphorus, alkaline phosphatase, urea, creatinine, and transaminases were measured on Beckman Coulter (5350 Lakeview Pkwy S Drive Indianapolis, Indiana 46268 USA) AU 680 autoanalyzer in Clinical and Chemical Pathology Department, Pediatric Hospital, Cairo University.

The results were recorded and documented on predesigned preformat. Analysis of data was done using SPSS-17. For the categorical (qualitative) variables, frequency and percentage were calculated. Mean and SD were calculated for numerical (quantitative) variables. χ^2 test was used to compare vitamin D levels among patient and control groups, and among the monotherapy used in the patient group, and P less than 0.001 was taken as significant.

Results

In group A (patient group), mean age of the patients was 6.8 ± 3.1 years, whereas in group B, it was 6.9 ± 3.2 years. Frequency and percentage of male and female in group A was 36 (58.1%) and 26 (41.9%), respectively, whereas in group B (control group) was 33 (51.6%) and 31 (48.4%), respectively (Table 1).

The current study illustrated that marked vitamin D deficiency was a remarkable finding in 50% of epileptic patients (mean: 13.4 ± 7.6 ng/ml) compared with control grou (6.2%) (mean: 60.4 ± 17.9 ng/ml ($P < 0.0005$) (Table 2).

Vitamin D levels among patients with generalized tonic/clonic seizures were statistically significantly higher than its level among patients with partial seizures and complex partial seizures ($P < 0.0005$), whereas there was no statistical significance on comparing vitamin D level neither to age of onset of seizures nor to its frequency (Table 3).

Correlation of vitamin D level with the type of monotherapy among patients showed a statistically significant difference, with marked vitamin D deficiency in patients on CBZ therapy than in patients receiving sodium valproate therapy and levetiracetam (Table 4).

The study also demonstrated that the longer the duration of AED intake, the more implicated vitamin D deficiency, with statistically significant

Table 1 Comparison of personal data among epileptic cases and control group

	Groups [*n* (%)]	
	Epilepsy cases (*n*=62)	Control (*n*=64)
Age (years)		
Range	1.5-12	2-12
Mean±SD	6.8±3.1	6.9±3.2
Sex		
Male	36 (58.1)	33 (51.6)
Female	26 (41.9)	31 (48.4)
Residence		
Urban	38 (61.3)	39 (60.9)
Rural	24 (38.7)	25 (39.1)

Table 2 Comparison of 25-hydroxyvitamin D level among epilepsy cases and control group

	Groups		*P*
	Epilepsy cases (*n*=62)	Control (*n*=64)	
25-OHD (ng/ml)			
Range	3.5-39	9.5-80	
Mean±SD	13.4±7.6	60.4±17.9	<0.0005
25-OHD (ng/ml) [*n* (%)]			
Severely deficient (<10 ng/ml)	31 (50)	4 (6.2)	

Table 3 Comparison of 25-hydroxyvitamin D values regarding the seizure characterization among epilepsy cases

	25-OHD (ng/ml)		*P*
	Range	Mean±SD	
Type of seizures			
Generalized tonic/clonic	6-39	16.5±7	0.000
Simple partial	4.5-13.5	6.3±2.3	
Complex partial	3.5-12.5	7.2±3.9	
Frequency of attacks			
No history of seizures in the previous 3-6 months	4.5-39	14.2±8.1	0.360
Once in the previous month	3.5-25	13.2±6.1	
Once in the previous week	6-6	6±2.1.	

Table 4 Comparison of 25-hydroxyvitamin D values regarding the type of antiepileptic drug among epilepsy cases

Type of AED	25-OHD (ng/ml)		*P*
	Range	Mean±SD	
Valproate	9-16.5	12.2±2.4	
Levetiracetam	6-39	21.5±7.3	
Carbamazepine	3.5-13.5	6.5±2.6	0.001

AED, antiepileptic drug.

difference for the duration of therapy for more than 2 years of therapy (9.9 ± 5.2 ng/ml) than less than 2 years (15.5 ± 8 ng/ml) ($P < 0.001$).

ECG is very crucial for diagnosis and follow-up of epilepsy. In this study, vitamin D deficiency in patients with epileptogenic activity in their EEG (96.8%) was remarkable than the patients with normal EEG (3.2%) ($P = 0.008$).

Statistical significant correlation was found between calcium (8 ± 0.6 mg/dl) ($P < 0.0005$), magnesium (1.7 ± 0.2 mg/dl) ($P = 0.002$), and AL (248.5 ± 88.1 U/l) ($P = 0.000$) and vitamin D level, whereas there was no statistically significant correlation between vitamin D level and urea, creatinine, alanine transaminase, and aspartate transaminase enzymes activity.

Discussion

Epilepsy is estimated to affect more than 50 million people globally, and with the rapid rise in using AEDs for prevention of seizures, the bone disease and the incidence of bone fracture are emerging as severe health risk for millions of people, particularly in childhood, which is the most critical period of bone growth [12].

This study supported the evidence that long-term therapy with the anticonvulsant drugs, CBZ, levetiracetam, and sodium valproate can result in serum biochemical abnormalities consistent with hypovitaminosis D in children, not related to movement disorders or dietary deficiencies.

The two mechanisms suggestive for inactivation of vitamin D by AEDs are hepatic enzyme induction and activation of pregnane X receptor and steroid xenobiotic receptors. Increased 25(OH) D insufficiency promotes the physiological adaptive mechanisms of consequent secondary hyperparathyroidism. Hypovitaminosis D results in decreased calcium absorption from the intestine [3].

The other proposed mechanisms include inducers of cytochrome P450 enzyme system, resulting in decreased intestinal calcium absorption, impaired response to parathyroid hormone, and secondary hyperparathyroidism [9].

This study was undertaken to assess the prevalence of 25(OH) D deficiency, which is the most accurate marker for vitamin D status, among Egyptian pediatric epileptic patients.

There is a lack of Egyptian population-based studies, which hinders the estimation of the prevalence of vitamin D deficiency among Egyptian children generally and in patients with epilepsy especially on regular AEDs therapy. The available studies were either international or were done in other Arabic or African countries and estimated that 1 billion people worldwide are vitamin D deficient or insufficient [5].

The results of this study showed significant decrease in vitamin D among the patient group (80.6%) (mean ± SD: 13.4 ± 7.6 ng/ml) than the control group (14.3%) (mean ± SD: 60.4 ± 17.9 ng/ml)

P = 0.000). These results are supported by an Indian study, which identified a significant risk of vitamin D deficiency in children with epilepsy on monotherapy with CBZ or valproate (VPA). Almost 60.7% of patients in CBZ group and 35.7% in VPA group had low 25(OH) D levels compared with 27.8% in controls (P = 0.001) [13].

In this study, 37.1% of patient group were on valproate, 32.3% were on levetiracetam, and 30.6% were on CBZ AEDs. The results established that severe [25(OH) D] deficiency was significantly associated with CBZ (54.8%), whereas 41.9% were on valproate and 3.2% were on levetiracetam (P = 0.001).

Similar studies have advocated the current study findings such as Yaghini *et al.* [14], which illustrated vitamin D deficiency in 37.7% of patients on CBZ therapy, whereas in another study, the prevalence of vitamin D was significant among those on valproate (31.1%) therapy. The difference in these results can be explained by racial and sample size variations.

The results of this study demonstrated a significant effect of the duration of receiving AEDs on the severity of vitamin D, with mean 25(OH) D level of 15.5 ± 8 ng/ml for duration of drugs intake less than 2 years and 9.9 ± 5.2 ng/ml for more than 2 years of therapy. These results had been confirmed by Chaudhuri and colleagues, who found that patients with epilepsy on long-term therapy (mean duration of treatment 40.4 ± 12.8 in months) had significant vitamin D deficiency compared with those on shorter duration with normal 25(OH) D (25.2 ± 10.5 months).

This study reported a significant correlation between the severity of vitamin D deficiency and the dose of AEDs. The mean doses of AED were of valproate (30.4 ± 8.1 mg/kg/day), levetiracetam (26 ± 8.8 mg/kg/day), and CBZ (31.8 ± 8.9 mg/kg/day), with P values of 0.002, 0.044, and 0.042, respectively, although Hamed *et al.*[5] in their study found that there was no significant relation between vitamin D level and dose of AED.

In this study, calcium level among the epileptic patients (8 ± 0.9 mg/dl) was significantly lower than the control group (9.9 ± 0.7 mg/dl), with P less than 0.0005. This observation was supported by Chaudhuri *et al.* [13], who reported lower mean calcium levels in epileptic patients (7.7 ± 1.4) compared with controls (8.7 ± 1.4) (P = 0.01).

Strengths of our study lie in recruitment of cases and controls from the same hospital, thus reducing the differences based on ethnicity, social customs, and socioeconomic status. Moreover, to the best of our knowledge, our study was the first study done in Egypt to assess the prevalence of [25(OH)D] deficiency among Egyptian pediatric epileptic patients.

Conclusions and recommendations

AEDs affect the bone mineral metabolism adversely, as manifested by decreased vitamin D levels in serum of patients taking AEDs, especially on long-term therapy. Vitamin D and calcium supplementation should be started with AED therapy. Further large sample size studies should be done, where baseline vitamin D level before initiation of AED therapy should be measured and combined with the assessment of bone mineral density by DEXA scan.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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