A Comparative Study of Serum 25-Hydroxy Vitamin D Levels in Children with Seizures Receiving Monotherapy and Polytherapy

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Abstract

The association between serum 25-hydroxy vitamin D (25(OH)D) antiepileptic drugs (AEDs) and bone health in individuals with epilepsy has been recognized for more than 30 years. Several studies indicate an increased risk for bone loss in patients on antiepileptic medication as well as low levels of serum 25(OH)D. Patients on polytherapy AED are at a higher risk of adverse drug effects compared with those on monotherapy. The present study assessed serum 25(OH)D levels in children receiving AED and compares those children receiving monotherapy versus polytherapy. This is a prospective cross-sectional study conducted in a tertiary care hospital setting on children with seizures receiving AEDs for period of more than 6 months. Participants were enrolled in three groups: 25 children on monotherapy, 25 children on polytherapy, and 25 healthy controls. Serum 25(OH)D level was performed for all children and analyzed. Serum 25(OH)D levels were normal in 52%, insufficient levels in 43.3%, and deficient in 6.7% of children. Vitamin D level was insufficient in 40% of children receiving monotherapy and 52% receiving polytherapy AED. Vitamin D deficiency was present in 4% in monotherapy group and 16% in polytherapy group which was statistically significant (*p*-value 0.047). Vitamin D deficiency was higher in children receiving AED compared with normal controls. Vitamin D deficiency and insufficiency were higher in children on polytherapy. Our study emphasized the importance of monitoring vitamin D levels in children receiving AED to detect abnormalities in vitamin D levels.

Keywords
- antiepileptic drugs
- polytherapy
- seizures
- 25(OH)D

Introduction

The goal of treating a child with seizure is primarily to achieve good seizure control while minimizing the adverse effects of antiepileptic drugs (AEDs). Seizures are often controlled with a single AED, while children who have poorly controlled seizures require polytherapy. AEDs are well known to cause adverse effects which may lead to noncompliance of AED. Some of the adverse effects following use of AED are fatigue, drowsiness, poor concentration, and weight gain. Patients on polytherapy AED are at a higher risk of adverse drug effects compared with those on monotherapy due to associated drug–drug interactions.[1]

Vitamin D plays a key role in maintaining calcium homeostasis as well as bone mineral metabolism.[2] The association

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between vitamin D, AEDs, and bone health in individuals with epilepsy has been recognized for more than 30 years.[3] Several studies indicate an increased risk for bone loss in patients on antiepileptic medication as well as low levels of serum 25-hydroxy vitamin D (25(OH)D) which is the major circulating form of vitamin D3.[4] There are studies addressing the effect of vitamin D supplementation on seizures in patients with pharmacoresistant epilepsy.[5] Although few comparable research data are available for children, adults with epilepsy are known to be at significantly increased risk for vitamin D deficiency compared with the general population.[6] Seizures pose a risk for injury including fractures especially in children who suffer from seizures with motor manifestations as well as those with impaired motor function and coordination.[7] The Indian Council of Medical Research recommends that vitamin D supplementation 400 IU/day should be provided in populations with minimal sun exposure, while there are no recommendations for individuals at higher risk of vitamin D deficiency.[8] There are few studies on assessment of vitamin D levels in children receiving AEDs. Very few studies have been published comparing vitamin D levels in children receiving monotherapy versus polytherapy AED. In India, it is not a routine practice to supplement calcium or vitamin D to children on AEDs; even in the United Kingdom, only 3% of pediatric neurologists were reported to be using prophylactic calcium and vitamin D therapy for children on anticonvulsants.[9] The present study assesses serum 25(OH)D levels in children receiving AED and compares those children receiving monotherapy versus polytherapy.

Materials and Methods

Study Design

A cross-sectional prospective study was done after obtaining approval from ethical committee under the ethical code SMC/IEC/2018/11/216 where patients were recruited by consecutive, enumerative, and convenient sampling of children in three groups.

Period of Study

One year (December 2018–December 2019).

Study Area

Department of Pediatrics, Saveetha Medical College and Hospital, Chennai.

Aim and Objectives

The aim of the study was to compare the serum 25(OH)D levels in children with seizure disorder on AEDs receiving monotherapy and polytherapy for a period of more than 6 months.

Study Sample

Study participants were children aged 1 to 18 years, who presented in outpatient department for seizure follow-up and were receiving AEDs for more than 6 months. Children with generalized, focal, epileptic syndromes, atypical febrile seizures, and unclassified seizures were included in the study. Total 75 children were enrolled in the following three groups.

1. Group 1: 25 children on monotherapy with AEDs for more than 6 months
2. Group 2: 25 children on polytherapy with AEDs for more than 6 months
3. Group 3: 25 normal controls.

Inclusion Criteria

Children of age between 1 and 18 years presenting with all types of seizures including atypical febrile seizure, who are taking AED treatment for more than 6 months duration and not taking vitamin D supplementation.

Exclusion Criteria

Children diagnosed with chronic kidney disease, malabsorption syndrome, chronic liver disease, and simple febrile convulsions.

Procedure

The informed written consent was obtained after explaining the study in detail to the parents or guardians. Detailed history, general examination, anthropometry, and neurological examination were performed. Classification of seizure was done after obtaining semiology details such as type of seizure and electroencephalogram (EEG) abnormality. Details of AEDs received by the child for duration of therapy, dose, and compliance were obtained. In monotherapy group, out of 25 patients, 20 received sodium valproate, 4 received phenytoin, and 1 received oxcarbamazepine. In polytherapy group, out of 25 patients, 9 received two-drug combination, out of them, 7 received sodium valproate, 4 received levetiracetam, 3 received phenytoin, and 1 received either clobazam, carbamazepine, or clonazepam. Sixteen patients received three-drug combination in which 16 of them received sodium valproate, 9 received levetiracetam, and 5 received clobazam as shown in ►**Figs. 1** and **2**.

Investigations such as complete blood count, renal function test, liver function test, EEG, computed tomography (CT), or magnetic resonance imaging (MRI) of the brain were done. All children underwent blood sampling to estimate 25(OH)D levels. About 3 mL of venous blood sample was withdrawn

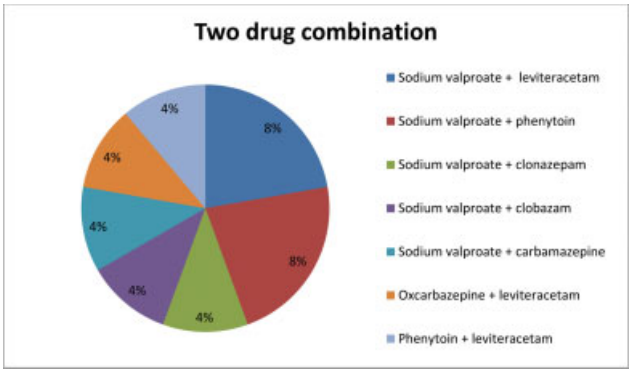

Fig. 1 Two-drug combination of antiepileptic drugs.

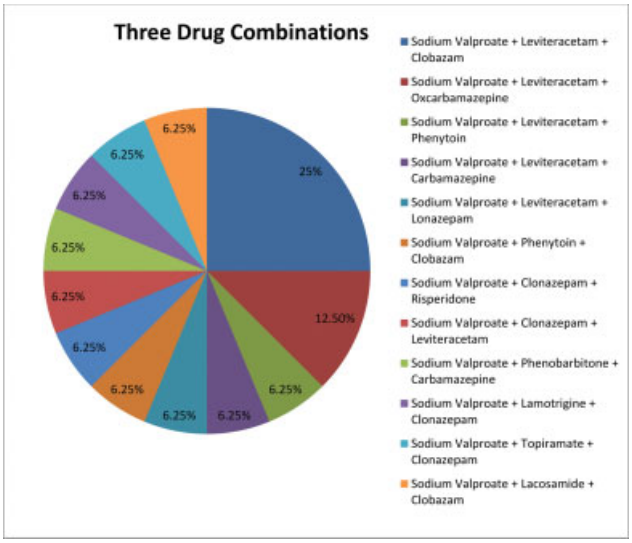

Fig. 2 Three-drug combination of antiepileptic drugs.

which was collected in red capped tubes. The city is situated at coastal area near the Bay of Bengal in South India, there is tropical climate throughout the year, patients were coming from in and around Chennai, there is no seasonal variation, and the blood sample was taken throughout the year to measure vitamin D level. Blood samples were centrifuged within 3 hours of collection and serum separation. Analysis for serum vitamin D was done by chemiluminescent immunoassay method. 25(OH)D level was classified according to the World Health Organization as deficiency $<$ 20 ng/mL, insufficiency 21 to 29 ng/mL, and normal $>$ 30 ng/mL.

Statistical Methods

The collected data were analyzed with IBM SPSS statistics software 23.0 version. To describe about the data, descriptive statistics frequency analysis and percentage analysis were used for categorical variables, and the mean and standard deviation were used for continuous variables. To find the significant difference between the bivariate samples in independent groups, the unpaired sample *t*-test was used. To find the significance in categorical data, chi-square test was used. In both the above-mentioned statistical tools, the probability value $>$0.05 is considered as significant level. Serum 25(OH) D levels in the three groups were compared for statistical significance. The associations of various factors with vitamin D levels such as patient age, gender, EEG, MRI or CT abnormality, patient age at seizure onset, and duration of AEDs were also compared for statistical significance.

Results

Total number of participants who were initially enrolled was 80, out of which 3 children were excluded based on the eligibility criteria and 2 refused to give consent. Analysis was done in the three groups which comprised 25 children in Group 1 receiving monotherapy, 25 children in Group 2 receiving polytherapy, and 25 healthy controls in Group 3. All 75 children underwent blood sampling for 25(OH)D levels.

Out of 75 children, 41.3% were between 1 and 5 years, 36% were between 6 and 10 years, and 22.7% were older than 10 years (►**Table 1**). Percentage of boys was 65.3% as compared with girls 34.7%.

Generalized tonic-clonic seizure was the most common type of seizure (86%), whereas 8% of children had myoclonic seizures. Comparison between type of seizure with groups showed no significant association (*p*-value 0.259) (►**Table 2**).

Eighty-four percent of study participants had abnormal EEG finding in the polytherapy group, while 52% in the

Table 1 Age distribution

Age in y	Frequency	Percentage
1–5	31	41.3
6–10	27	36.0
$>$10	17	22.7
Total	75	100.0

Table 2 Comparison between types of seizure with groups

			Groups		Total	*p*-Value
			Monotherapy	Polytherapy		
Types of seizure	Tonic	Count	0	1	1	0.259#
		%	0.0	4.0	2.0	
	Tonic-clonic	Count	22	21	43	
		%	88.0	84.0	86.0	
	Myoclonic	Count	1	3	4	
		%	4.0	12.0	8.0	
	Atypical	Count	2	0	2	
		%	8.0	0.0	4.0	
Total		Count	25	25	50	
		%	100.0	100.0	100.0	

monotherapy group had EEG abnormalities. Comparison between EEG abnormality and groups showed statistical significance with *p*-value of 0.016. Children underwent either CT of the brain or MRI of the brain which revealed MRI abnormalities in 32% and CT abnormalities in 12% of children. Serum 25(OH)D levels among the study participants was normal in 52%, insufficient in 43.3%, and deficient in 6.7% of children (►**Table 3**).

While comparing serum 25(OH)D levels in the three groups, 68% of children in control group, 56% in monotherapy group, and 32% in polytherapy group had serum 25(OH)D levels >30 ng/mL. Serum 25(OH)D levels were insufficient in 32% in control group, 40% in monotherapy group, and 52% in polytherapy group. It was seen that vitamin D deficiency was present in 16% of children receiving polytherapy group, 4% in monotherapy group, and none in the control group. This was statistically significant with *p*-value of 0.047 (►**Table 4**).

The mean serum 25(OH)D levels in the monotherapy (30.5 ng/mL) and the control (32.33 ng/mL) groups were in the normal range, whereas in the polytherapy group, the mean serum 25(OH)D levels were 25.96 ng/mL, which was in the insufficient range. Comparison between serum 25(OH)D levels with groups by one-way analysis of variance (►**Table 5**), *F*-value of 8.258, and *p*-value of 0.001 shows statistical significant association.

The relative risk of vitamin insufficiency in polytherapy group as compared with control group is 2.12 (95% confidence interval [CI]: 1.13–3.99, Z = 2.33) and vitamin D deficiency in monotherapy group as compared with control group is 9 (95% CI: 0.50–158.85, Z = 1.50). The relative risk of vitamin insufficiency in monotherapy group as compared

Table 3 Serum 25(OH)D levels among study participants

Vitamin D levels (ng/mL)	Frequency	Percentage
Normal >30	39	52.0
Insufficiency 21–29	31	41.3
Deficiency <20	5	6.7
Total	75	100.0

Abbreviation: 25(OH)D, 25-hydroxy vitamin D.

Table 4 Comparison between serum 25(OH)D levels with groups

			Groups			Total	Chi-square value	*p*-Value
			Monotherapy	Polytherapy	Controls			
Levels, ng/mL	Normal >30	Count	14	8	17	39	3.252	0.047[a]
		%	56.0	32.0	68.0	52.0		
	Insufficiency 21–29	Count	10	13	8	31		
		%	40.0	52.0	32.0	41.3		
	Deficiency <20	Count	1	4	0	5		
		%	4.0	16.0	0.0	6.7		
Total		Count	25	25	25	75		
		%	100.0	100.0	100.0	100.0		

Abbreviation: 25(OH)D, 25-hydroxy vitamin D.
[a]Statistical significant at $p < 0.05$ level.

Table 5 Comparison of serum 25(OH)D with groups by one-way ANOVA

	N	Mean	SD	*F*-value	*p*-Value	
Monotherapy	25	30.50	6.24	8.258	0.001[a]	
Polytherapy	25	25.96	6.13			
Controls	25	32.33	4.58			
Post hoc tests—multiple comparisons—Tukey's HSD						
(I) Groups		Mean difference (I–J)	Standard error	*p*-Value	95% CI	
					Lower bound	Upper bound
Monotherapy	Polytherapy	4.536[b]	1.613	0.017[b]	0.68	8.39
	Controls	−1.828	1.613	0.497	−5.69	2.03
Polytherapy	Controls	−6.364[b]	1.613	0.001[c]	−10.22	−2.51

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; HSD, honestly significant difference; SD, standard deviation; 25(OH)D, 25-hydroxy vitamin D.
[a]Highly significant at $p < 0.01$ level.
[b]Statistical significant at $p < 0.05$.
[c]Highly significant at $p < 0.01$.

with control group is 1.3 (95% CI: 0.66–2.83, Z = 0.864) and vitamin D deficiency in monotherapy group as compared with control group is 3 (95% CI: 0.12–70, Z = 0.68). This shows that the relative risk of vitamin D insufficiency is high in polytherapy as compared with monotherapy and control groups.

In monotherapy group, 80% of children received sodium valproate and 40% had vitamin D insufficiency, while 4% had deficiency. Other than sodium valproate, 16% of patients received oxcarbamazepine and 4% received levitriacetam in monotherapy group.

In polytherapy group, 76% was on sodium valproate combined with other AEDs and 52% had insufficiency, while 16% had deficiency. In polytherapy group, the most common two-drug combination was sodium valproate with levitiracitam (8%), sodium valproate with phenytoin (8%), sodium valproate with clonazepam (4%), sodium valproate with clobazam (4%), and sodium valproate with carbamazepine (4%), oxcarbamazepine with levetiracetam (4%), and phenytoin with levetiracetam (4%) as seen in ►**Fig. 1**. In polytherapy group, the most common three-drug combination was sodium valproate, levetiracetam, and clobazam (25%) followed by sodium valproate, levetiracetam, and oxcarbamazepine (12.5%), as shown in ►**Fig. 2**. Among patients taking two-drug combination, vitamin D deficiencies were 55% as compared with 75% who were taking three-drug combination therapy.

We divided the patients in three groups: patients taking AEDs

- Group 1: From 6 months to 1 year,
- Group 2: 1 to 2 years
- Group 3: > 2 years.

Fourteen children received monotherapy and 3 received polytherapy in Group 1, 9 children received monotherapy and 20 children polytherapy in Group 2, and 2 patients received monotherapy and 2 polytherapy in Group 3. As the duration of AEDs was varying between the monotherapy and polytherapy groups, a statistical difference between these periods could not be assessed.

Discussion

Vitamin D is an essential nutrient that maintains homeostasis of calcium and phosphorous in the body. Studies indicate that vitamin D deficiency is present worldwide in more than 1 billion people.[10] Research has shown that adult epilepsy patients on AEDs can exhibit deficiency of vitamin D. Our study was performed to estimate serum 25(OH)D levels in children receiving AEDs and compare the levels between monotherapy and polytherapy groups.

In the present study, 41% of children were between 1 and 5 years and 36% were between 5 and 10 years, and number of boys was 63.5%. In a prospective hospital-based study conducted in children with seizure, it was observed that seizure was more common in boys (61%) as compared with girls (39%).[11] In a prospective study conducted on 202 children with seizure, 17.3% had generalized seizure, 22.8% had focal, and 51.5% had specific epilepsy syndrome.[12] However, in our study, generalized tonic-clonic seizure was the commonest type of seizure seen in 86% of children. It was seen that EEG abnormalities were higher in polytherapy group (84%) than the monotherapy group (54%) in our study. In a pilot study conducted on 100 children younger than 18 years confirmed as epilepsy, it was observed that 51% had generalized tonic-clonic seizures, while 30% had febrile seizures and 40% participants had abnormal EEG findings.[13]

In our study, the overall serum 25(OH)D levels was normal in 52% of children, 41.3% had insufficient levels, and 6.7% were deficient. Insufficient levels of vitamin D was present in 40% of children in monotherapy group and 52% in polytherapy group, while deficiency was present in 4 and 16% in monotherapy and polytherapy groups, respectively, which was statistically significant (p-value 0.047). Vitamin D deficiency and insufficiency were higher in children who received two or more AEDs than children on monotherapy. However, it was also noticed that 32% healthy controls had vitamin D insufficiency, although no child in control group had vitamin D deficiency. Similar findings were observed in another cross-sectional observational study done to compare serum 25(OH)D levels in 38 children on AED with 44 controls which showed that 75% of patients were vitamin D deficient (<20 ng/mL), while 21% were insufficient and significantly lower value of vitamin D (p-value 0.038) were found in polytherapy group.[14]

A study comparing 363 epileptic children with 159 healthy controls showed significant decrease in serum 25 (OH)D levels in epileptic group.[15] In a study by Akman et al performed in Ankara, Turkey, in children between the ages of 1 and 16 years, values were observed to be 8 and 25.5% for vitamin D deficiency and insufficiency, respectively. This problem may be related to spending more time indoor, air pollution, insufficient access to playgrounds, and decreased sun exposure.[16]

In our study, the mean serum 25(OH)D levels was normal in control group (32.33 ng/mL) and monotherapy group (30.5 ng/mL), while it was insufficient in polytherapy group (25.96 ng/mL) which was statistically significant.

In a study conducted on 13 adults with pharmacoresistant epilepsy, serum 25(OH)D levels was measured before and after administration of vitamin D. Patients were followed up for seizure recurrence for 90 days and seizure recurrence was significantly reduced by 40% (p-value 0.04) showing that serum 25(OH)D levels has an anticonvulsant effect.[5]

Enzyme-inducing AED such as phenytoin sodium, phenobarbitone, and carbamazepine are known to interfere with the vitamin D metabolism and cause low vitamin D levels.[17,18] A study on 100 epileptic children observed that 31.1% on sodium valproate and 37.7% on carbamazepine had deficiency of vitamin D.[17] Enzyme inducers such as carbamazepine cause inactivation of vitamin D by induction of hepatic enzymes and activation of steroid and xenobiotic receptor. However, sodium valproate may cause vitamin D deficiency by inhibition of different hepatic enzymes.[18] Eighty percent of children in monotherapy group received sodium valproate and 40% had vitamin D insufficiency, while

4% had deficiency. In polytherapy group, 76% was on sodium valproate combined with other AEDs and 52% had insufficiency, while 16% had deficiency. The commonest prescribed AED in treatment group was sodium valproate in 78% of participants.

Other risk factors for vitamin D deficiency are nutritional deficiency, lack of exposure to sunlight, chronic kidney disease, chronic liver diseases, and malabsorption syndromes.[19] It has been recommended by the Endocrine Society Clinical Practice Guidelines that the patients who are at risk for vitamin D deficiency including patients on AEDs must undergo evaluation of vitamin D status by performing serum 25(OH)D levels.[20]

Increased attention to vitamin D status among children with epilepsy is warranted, as vitamin D has a vast impact on bone health of children and also other issues such as reducing the frequency of seizures and increasing immunity. Dietary advice regarding increased intake of vitamin D–rich foods should be given in children receiving AED therapy. It is important to check vitamin D levels in children receiving polytherapy AED. The impact of AEDs on vitamin D levels should be kept in mind by pediatrician and pediatric neurologist while prescribing long-term AED therapy.

Limitations

Major limitations of the present study are the small sample size. Dietary history of the child to determine intake of vitamin D–rich foods, body weight, as well as history of exposure to sunlight was not taken into the study. Vitamin D levels were not done before starting AED. This may have helped identify preexisting vitamin D deficiency.

In conclusion, the present study shows that the presence of vitamin D deficiency is statistically significant in children with epilepsy receiving AEDs, compared with normal controls. Vitamin D deficiency and insufficiency were higher in children who received polytherapy. Our study emphasizes the importance of monitoring the serum 25(OH)D levels periodically in children receiving antiepileptic therapy, especially in children receiving polytherapy to detect vitamin D insufficiency and deficiency.

Conclusion

The present study showed that the presence of vitamin D deficiency is statistically significant in children with epilepsy receiving AEDs, compared with normal controls. Vitamin D deficiency and insufficiency were higher in children who received polytherapy. Our study emphasizes the importance of monitoring the vitamin D levels periodically in children receiving antiepileptic therapy, especially in children receiving polytherapy to detect vitamin D insufficiency and deficiency. "Practical recommendation is that we should monitor vitamin D levels periodically along with supplementation of vitamin D who are having insufficiency or deficiency specially children on monotherapy and polytherapy AEDs. In clinics where serum vitamin D level estimation facilities are not available, an empirical vitamin supplementation in patient on AEDs will be useful. Further studies can be done to analyze the cost–benefit ratio of serum vitamin D levels estimation versus routine supplementation."

Conflict of Interest
None declared.

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