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Original Research Article

Serum vitamin D status in children with epilepsy on antiepileptic drugs and its relation to the frequency of breakthrough seizures

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ABSTRACT

Background: Epilepsy is the most common neurological disorder in children requiring long term drug therapy which are associated with vitamin D deficiency. Antiepileptic actions of vitamin D deficiency have been extensively studied in animal models but human data, particularly in children is lacking. Objectives were to study the levels of serum vitamin D in children with epilepsy on antiepileptic drugs and to study the correlation between levels of vitamin D and frequency of breakthrough seizures.
Methods: hospital-based cross-sectional study. Participants: A total of 94 children with epilepsy were included in the study. Intervention: The patients were on a minimum of 6 months of antiepileptic drug therapy. Anthropometric measurements were taken and blood samples were analysed for vitamin D, serum calcium, phosphate, complete blood counts and renal profile.
Results: The present study showed a statistically significant relationship between serum vitamin D deficiency and antiepileptic drugs (p value <0.001), the number of AEDs with patients on polytherapy ≥2 AEDs having lower vitamin D levels (p value <0.001) and the duration of antiepileptic drugs (p value of 0.016). Linear regression analysis also showed a statistically significant relationship between serum vitamin D deficiency and seizure frequency (p value of <0.001, 95% confidence interval: -3.465, -2.275).
Conclusions: Case studies and epidemiological data also support the evidence of connection between levels of serum vitamin D and epilepsy and the use of vitamin D3 as a potential therapy for human epilepsy. This study is conducted with an aim to highlight the role of vitamin D in children with epilepsy in seizure control.

Keywords: Epilepsy, Vitamin D, Antiepileptic drugs, Breakthrough seizures

INTRODUCTION

Human rabies continues to be endemic in India.[1] Annual A seizure is a transient event resulting from abnormal excessive or synchronous neuronal activity in the brain.[1] Of all the neurological disorders in children, epilepsy is the most common.[2] A study conducted in India reported a prevalence of 1.1 patients per 1000 population.[3] Although in children, the prognosis of epilepsy is favourable, approximately 30% of the children with epilepsy are still to be on treatment in a 5 year period as reported by long term population based outcome studies.[4]

Antiepileptic drugs (AEDs) used in the long term treatment of epilepsy induces hepatic P450 enzymes, which accelerates metabolism of vitamin D leading to increased breakdown of vitamin D to inactive products and thus causing abnormal bone metabolism. Comorbid conditions such as cerebral palsy is frequently present in children with epilepsy which further limits their mobility

and combined with a low dietary intake and lack of sunlight exposure often results in severe hypovitaminosis D. Valproate, which is a widely used AED in pediatric patients, is an inhibitor of cytochrome p450 system but bone loss has also been reported in children receiving Valproate.[5,6]

The mechanism by which vitamin D exerts its antiepileptic activity is still under study. Growing evidences suggest that vitamin D has multiple functions in the developing and adult brain, including maintenance of calcium balance and signalling, regulation of neurotropic factors, providing neuroprotection, contributing to synaptic plasticity and modulating neurotransmission. All the three major metabolites of vitamin D turnover, 25-hydroxyvitamin D_3 ($25(OH)D_3$), 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) and 24,25-dihydroxyvitamin D_3 ($24,25(OH)_2D_3$) have been identified in the cerebrospinal fluid of humans.[7] These metabolites cross the blood brain barrier in a similar fashion to other steroid hormones and small ligands that bind to nuclear receptors.[8] Although the enzyme catalysing conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$, CYP27B1, is mainly expressed in the kidney but several studies using immunohistochemical techniques have demonstrated the distribution of this enzyme in non-renal human tissues such as in the cerebellar Purkinje cells and as well as within neuronal cells of cerebral cortex.[9,10]

Suggesting local production of vitamin D within the human brain. In one of the earliest study conducted by Chiristiansen et al in 1974 in patients with pharmacoresistant epilepsy and low serum $25(OH)D_3$ levels concluded that 40% reduction in seizure frequencies can be achieved by vitamin D supplementation.[11] Four decades later another study concluded that high doses of vitamin D in patients with poorly controlled epilepsy can result in a significant reduction in seizure frequency and contrary to the authors' hypothesis, the seizure control was independent of serum calcium and magnesium levels.[12] Low serum vitamin D levels have been implicated in a number of disorders including multiple sclerosis, schizophrenia, Parkinson disease, autism among others. However, the role of vitamin D in seizure control, particularly in children needs more attention. The study is conducted with the following objectives: To study the levels of serum vitamin D in children with epilepsy on Antiepileptic drugs. To study the correlation between levels of vitamin D in the serum and the frequency of breakthrough seizures.

METHODS

The present study is a hospital based cross sectional study conducted in the department of paediatrics, Gauhati Medical College and Hospital over a period of one year from 1 of July 2020 to 30 of June 2021. A total of 115 patients with epilepsy presented during this period out of which 94 children were included in the study. Prior clearance from Institute Ethics Committee was obtained.

Inclusion criteria

All children with epilepsy who were on antiepileptic drug therapy for more than 6 months were included.

Exclusion criteria

Exclusion criteria were; Children with poor drug compliance, Children with pre-existing Vitamin D metabolism disorders as VDDR, malabsorption syndromes, kidney disease, liver disease or children on medications that might affect vitamin D metabolism such as glucocorticoids, Children with nutritional deficiency states, Children on vitamin D supplementation and Refusal to consent.

Procedure

Of the 115 children presenting with epilepsy, 7 had poor drug compliance, 5 had nutritional deficiency, 8 cases were on vitamin D supplementation and 1 case refuse to consent. All the children were on a minimum of 6 months of antiepileptic drug therapy. Informed written consent was obtained from all the parents of children included in the study. The classification of epilepsy was done according to the ILAE classification of epilepsy. The patients' epilepsy was classified up to epilepsy type.[7]

A detailed history was taken in all the children included in the study about the age, type of epilepsy, duration of antiepileptic drug therapy, dose of antiepileptic drug, compliance, presence or absence of delayed development milestones (DDM) and the number of seizure episodes in past 6 months. A detailed anthropometric assessment was performed in all patients according to WHO definitions and children having nutritional deficiency were excluded from the study. Blood samples were taken to analyse serum vitamin D along with serum calcium, phosphate, complete blood count and renal function. Serum Vitamin (total 25-hydroxy vitamin D3) quantification was done by using VITROS 5600 Immunodiagnostic method. Recent literatures have defined vitamin D deficiency as vitamin D <20 ng/ml.[5] In our study, we have interpreted the serum vitamin D levels as follows: < 20 ng/ml: Deficiency 20-29 ng/ml: Insufficiency 30- 70 ng/ml: Sufficiency 70- 150 ng/ml: Non-toxic overdose.

Data analysis

The data thus collected was tabulated and analysed using Statistical product and Service Solutions (SPSS) version 21. The discrete data are expressed in percentage. Results on continuous measurements are presented as mean ± standard deviation and are analysed using Chi square test. Pearson's correlation coefficient (r) and multiple linear regression analysis were used to measure the associations among continuous variables. For analysis, statistical significance was fixed at 5% level (p value <0.05).

RESULTS

In our study we have enrolled 94 cases (71 males and 23 females) of a total of 115 cases of children presenting with epilepsy we did not find a statistically significant distribution of serum vitamin D deficiency with sex (p value: 0.187).

Table 1: Distribution of Serum Vitamin D levels according to Gender.

Sex	Serum vitamin D Levels (ng/ml), N (%)				Total	Chi value	P value
	<20	20-30	30-70	70-150			
Females	7 (30.4)	2 (8.7)	12 (52.2)	2 (8.7)	23 (100)	4.802	0.187
Males	11 (15.5)	13 (18.3)	45 (63.4)	2 (2.8)	71 (100)		
Total	18 (19.1)	15 (16)	57 (60.6)	4 (4.3)	94 (100)		

Table 2: Relation of Serum Vitamin D status and Duration of AEDs.

Vitamin D level	N	Mean Duration of AEDs	SD	P value
<20 ng/ml (Deficiency)	18	36.50	27.97	0.016
20-30 ng/ml (Insufficiency)	15	17.93	9.84	
30-70 ng/ml (Sufficiency)	57	20.75	20.49	
70-150 ng/ml (Non-toxic overdose)	4	10.25	5.32	
Total	94	22.87	21.47	

Table 3: Vitamin D deficiency and frequency of breakthrough seizures.

Vitamin D level	N	Mean BTS in last 6 months	SD	P value
<20 ng/ml (Deficiency)	18	9.89	3.88	<0.001
20-30 ng/ml (Insufficiency0	15	5.00	4.47	
30-70 ng/ml (Sufficiency)	57	0.49	0.83	
70-150 ng/ml (Non-toxic overdose)	4	0.50	0.58	
Total	94	3.01	4.49	

Table 4: Linear regression analysis of Patients' epilepsy characteristics.

Parameters	β	Std. Error	T value	95.0% CI		P value	R value
				Lower Bound	Upper Bound		
Age	-0.840	0.577	-1.455	-1.987	0.307	0.149	-0.15
Duration of AEDs	-0.256	0.084	-3.034	-0.424	-0.088	0.003	-0.302
BTS in last 6 months	-2.870	0.300	-9.578	-3.465	-2.275	<0.001	-0.707
Calcium	3.563	3.393	1.050	-3.176	10.303	0.296	0.109
Phosphate	1.903	3.418	0.557	-4.886	8.691	0.579	0.058

Among these children, 5 (5.3%) were less than 1 year of age, 48 (51.1%) were between 1-3 years of age, 8 (8.5%) were between 4-6 years, 15 (16%) were between 7-9 years of age and 18 (19.1%) were of age 10 or more years. We did not find a statistically significant relation between age of the patients and serum vitamin D deficiency (p value: 0.065) (Table 1, Figure 1). In the study population, 18 patients (19.1%) had serum vitamin D levels <20 ng/ml, 15 patients (16%) had 20-30 ng/ml and 57 patients had normal levels which accounted for 60.6% cases. The serum vitamin D levels ranged between 7.8 ng/mL and 100 ng/mL, with a mean of 39.16 ng/ml and standard deviation of 18.23 ng/ml (Figure 2). Among the AEDs Valproate was the most common drug used in the study population with 62.8% children on Valproate monotherapy, 13.8% on Valproate and Levetiracetam combination therapy and 2.2% in Valproate and Phenytoin combination therapy. 14.9% and 6.4% children were on Phenytoin and Levetiracetam monotherapy respectively. Distribution of Vitamin D levels showed that among the children with Vitamin D deficiency 61.1% were on Valproate monotherapy, 27.7% were on combination therapy with Valproate and Levetiracetam and 11.2% were on Valproate and Phenytoin combination therapy (Figure 3). There was also a significant relationship between the number of AEDs with patients on polytherapy (≥2 AEDs) having lower vitamin D levels (p value <0.001) and duration (p value: 0.016). However, it is important to note that the patients on polytherapy were on a longer duration of AEDs with a mean of 37.4 months as compared to monotherapy (mean=20.11 months) (Figure 4, Table 2). Out of the 94 cases included in the study 18 cases that had

Vitamin D deficiency had a mean breakthrough seizure of 9.89±3.88 episodes in a 6 months period, 15 cases with insufficient levels had a mean 5±4.47 episodes, 57 cases with normal levels of Vitamin d had 0.49±0.83 episodes. The p value is <0.001 and r value is -0.707 (Figure 5, Table 3). Multiple linear regression analysis including the age distribution, duration of AEDs, frequency of breakthrough seizures in last 6 months, mono vs. poly drug therapy, serum calcium and phosphate levels with Vitamin D levels shows a statistically significant association with serum Vitamin D deficiency and breakthrough seizures (Table 4).

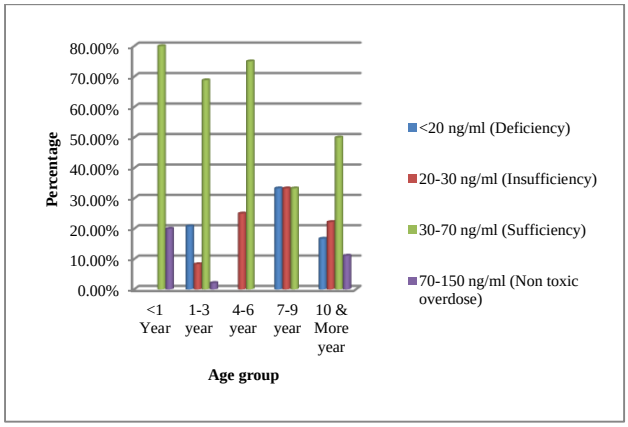

Figure 1: Distribution of Serum Vitamin D Levels with age.

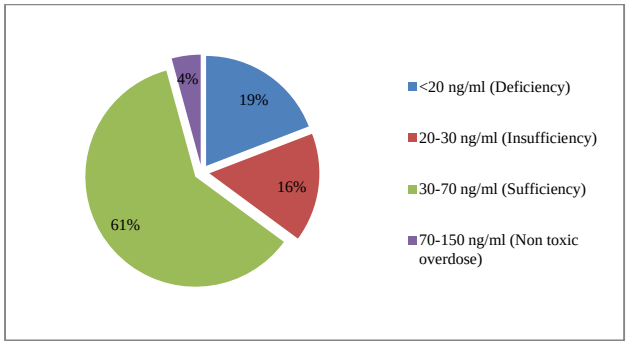

Figure 2: Distribution of Serum Vitamin D levels in the study group.

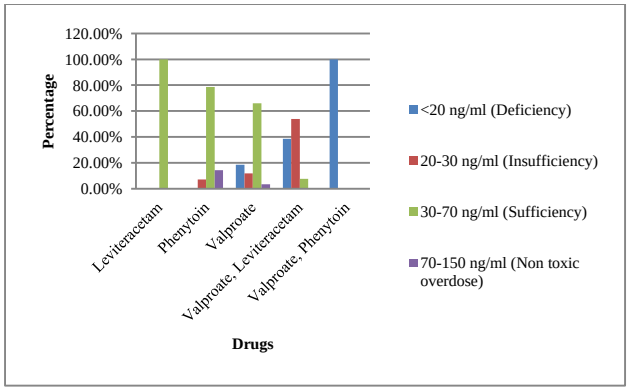

Figure 3: Distribution of Serum Vitamin D Levels in Children taking Different AEDs.

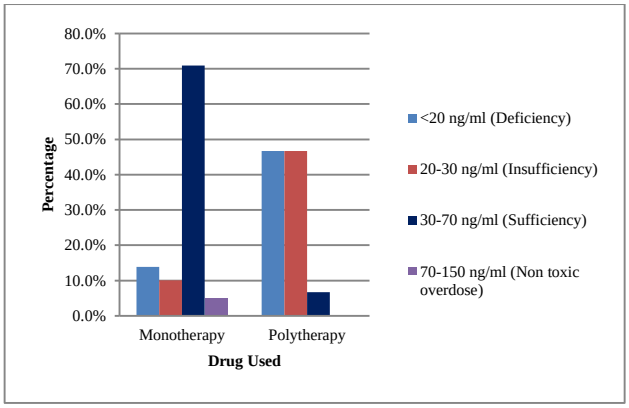

Figure 4: Relation of Serum Vitamin D levels and mono vs. poly drug therapy.

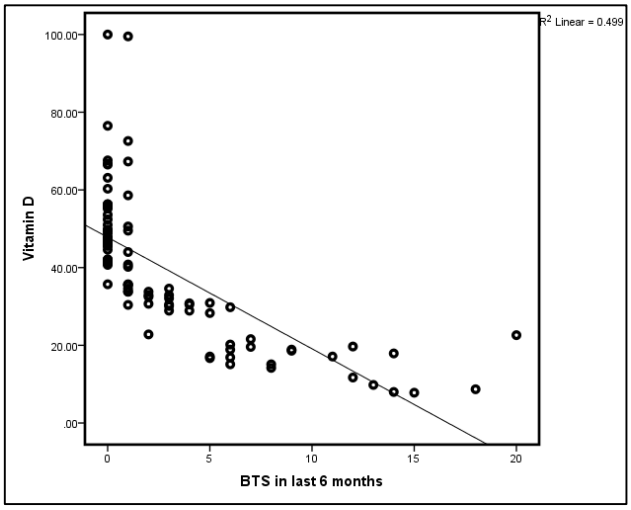

Figure 5: Scatter plot showing Serum vitamin D Levels and frequency of breakthrough seizures.

DISCUSSION

In the present study we have enrolled 94 cases of a total of 115 cases of children presenting with epilepsy. A similar study conducted by Patil et al included 70 children aged 2-16 years over a period of 1 year, in a tertiary care hospital in Maharashtra, India.[13] In a study conducted by Fong et al 111 children with epilepsy were evaluated for the presence of vitamin D deficiency in South Queensland.[5] In a similar study, Sonmez et al conducted a study on vitamin D deficiency in children with idiopathic epilepsy in a cohort of 60 children in Turkey in 2015.[8] Nagarjunakonda et al conducted a case control study on 98 subjects (43 epileptic and 55 non epileptic) on vitamin D deficiency in epileptic patients on AED polytherapy and drug resistant epilepsy in Andhra Pradesh, India in 2016.[14] The Male: Female ratio of the sample group is 3:1. The present study did not find a statistically significant distribution of serum vitamin D deficiency according to the sex distribution with a p value of 0.187. Other studies also report the same.[5,8] However, in a study conducted by Fong in epileptic children in Malaysia, revealed a significant risk of vitamin

D deficiency in female children as compared to males (p=0.005).[15]

Table 5: Patients' epilepsy characteristics associated with vitamin D status as compared to other studies.

Factors	Present study (P value)	Fong et al (P value)	Fong et al (P value)
Age	0.065	0.855	0.002
Gender	0.187	0.696	0.005
Duration of AEDs	0.016	0.152	0.047
Polytherapy	<0.001	0.001	0.023
Calcium	0.051	-	-
Phosphate	0.165	-	-
Frequency of breakthrough seizures	**<0.001**		0.084

In our study we found a negative correlation between age and serum vitamin D deficiency but it is not statistically significant (Pearson correlation r:-0.15, p=0.149). Fong et al in their study in Malaysian children revealed a significant increase in risk of vitamin D deficiency with increase in age (p=0.002).[15] Other studies did not find a significant relation between vitamin D deficiency and age.[5,8,13]

In the present study serum vitamin D levels ranged between 7.8 ng/mL and100 ng/ml, with a mean of 39.16 ng/ml and standard deviation of 18.23 ng/ml. 19.1% cases had vitamin D deficiency and 16% cases had insufficiency. Fong et al in Malaysian children with Epilepsy, mean serum vitamin D ranged between 7.5 ng/ml and 140.9 ng/ml, with a mean value of 53.9 ng/ml.[15] 22.5% cases were identified with vitamin D deficiency and 19.7% had insufficiency. Studies on vitamin D status in children with epilepsy report a deficiency rate ranging from 4% to 75%.[5,9,16] Akman et al observed vitamin D deficiency in 8% and insufficiency in 25.5% children aged 1-16 years in Turkey.[17]

The present study showed a statistically significant relationship between serum vitamin D deficiency and antiepileptic drugs with a p value of <0.001. Valproate was most commonly associated with serum vitamin D deficiency. Nicolaidou et al reported hypovitaminosis in 49% of the children on Carbamazepine or Valproate therapy.[16] Chaudhuri et al reported that risk of vitamin D deficiency in children with epilepsy was highest with Valproate (odds:4.0; 95% confidence interval: 1.4-11.6).[18]

In our study we found a significant relationship between the number of AEDs and vitamin D deficiency with patients on polytherapy ≥2 AEDs having lower vitamin D levels (p value <0.001). Similarly Fong et al also reported an increased risk of serum vitamin D deficiency with polytherapy (p=0.002; adjusted odds ratio: 5.74; (95% confidence interval: 1.87, 17.65).[5] Bergqvist et al also reported a negative impact of AED polytherapy on serum vitamin D and Bone mineral density (BMD).[9] Again Fong et al in a study on vitamin D status in Malaysian children with epilepsy re-emphasised the role of polytherapy on vitamin status.[15] Children on >1 antiepileptic drugs were at more risk of developing vitamin D deficiency (p=0.023, odds ratio: 2.16; 95% confidence interval: 1.07, 4.36). Chandrika et al however did not report any significant difference in serum vitamin D levels in children on monotherapy or polytherapy.[20] In the study 54% children on monotherapy had vitamin D deficiency while in the polytherapy group, 51.5% children had vitamin D deficiency (p=0.79). Our study found a statistically significant relationship between serum vitamin D deficiency and the duration of antiepileptic drugs with a p value of 0.016. Children with serum vitamin D levels <20 ng/mL were on a mean duration of 36.5±27.97 months, while children with insufficient levels were on a mean duration of 17.93±9.84 months.[15] Fong et al also reported a potential association of duration of AEDs with vitamin D deficiency but it was not statistically significant (p=0.152).[15] Again Fong et al in their study on Malaysian children with epilepsy reported a significant association between duration of antiepileptic therapy (>5 years) and vitamin D deficiency (p=0.047).[15] Similar results were also observed by Patil et al (p=0.013) and Seung et al (r=-0.283, p=0.033) in their studies.[13,21] Our study found a statistically significant relationship between serum vitamin D deficiency and seizure frequency with a p value of <0.001, 95% confidence interval: -3.465, -2.275. In one of the earliest studies, Christiansen et al[11] showed that vitamin D therapy has resulted in 30% reduction in seizure frequency, independent of serum calcium and magnesium levels. Hollo et al also achieved decreased seizure frequency (40%) with vitamin D supplementation (p=0.04).[12] They also found a non-significant tendency for patients with larger proportional increase in serum vitamin D levels exhibiting a larger proportional reduction in seizure frequency (p=0.13, Spearman rank order correlation). Fong et al in their study on Malaysian children with epilepsy found a potential association with serum vitamin D deficiency with seizure frequency but it was not statistically significant (p=0.084).[15] Siegel et al conducted a study on rat models that concluded that stereotactic injection of 50 or 100 µg of 1,25 vitamin D into the hippocampus of rats significantly elevated the seizure threshold.[22] Kalueff et al in their study on mouse models of seizures found that subcutaneous injection of 33 µg of 125 vitamin D incurred an anticonvulsant effect in chemically induced model of seizures.[23] The acute efficacy of the antiepileptic action suggests non genomic action of vitamin D. Also, the differences in calcium levels in the control and experimental models were not significant, hence the anticonvulsant action vitamin D were independent of its role in calcium metabolism.

CONCLUSION

The study was conducted with an aim to highlight the role of Vitamin D in children with epilepsy. The study found a

significant risk of increased seizure episodes in children with Vitamin D deficiency. Several studies have confirmed that antiepileptic drugs used in the management of epilepsy results in low Vitamin D levels. As concerns, low levels of Vitamin D predisposing the children to frequent seizure episodes needs to be further evaluated as also the potential for Vitamin D as an antiepileptic drug in conjunction with the existing AEDs in pharmacoresistant epilepsy. Risks of Vitamin D deficiency with newer AEDs in children also needs to be studied.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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