ORIGINAL RESEARCH

Alteration in serum vitamin D among the ambulatory children on sodium valproate as an antiepileptic medication

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ABSTRACT

Aim: To assess the correlation of Sodium Valproate on serum Vitamin D3 levels in ambulated epileptic children on sodium valproate monotherapy. **Material & Method**: Study was conducted from January 2020 to Dec 2021 at a tertiary care centre in North India. Ambulatory children with epilepsy aged one to 18 years receiving Sodium Valproate monotherapy for more than six months are included. Children on valproate were cases and healthy children as controls. Children on more than one drug and those who didnot consent were excluded. **Result**: 130 children were included in the present study. Vitamin D levels were significantly lower in children on valproate therapy compared to the controls. Mean levels in cases and controls were 14.98+ 2.19 ng/ml cf. 25.90+ 3.14ng/ml respectively ($p<0.001$).Additionally, there was a strong negative correlation of serum valproate and vitamin D levels. (Pearson's correlation value of < .0001).A strong negative correlation of duration of AED and vitamin Dlevels among the cases was also observed (Pearson's correlation value of < .0001). Further, it was noted that after vitamin D3 supplements of 60000 IU weekly for six weeks, 10% children did not achieve levels of 20 ng/ml (defined at the cut off for deficiency). The study concluded that all children on valproic acid medication be given vitamin D supplementation, regularly monitored with vitamin D3 levels in blood. Vitamin D3 levels should be reviewedafter supplementation as not all children may become sufficient. **Conclusion**: There is a significant risk of vitamin D deficiency in ambulant children with drug treated epilepsy. Blood vitamin D levels should be monitored on a regular basis throughout anticonvulsant therapy.

Keywords: Sodium Valproate, Vitamin D3, Children, Epilepsy

INTRODUCTION

Childhood is one of the most important ages of bone mineralization. Apart from genetic factors, bone growth is affected by the mode of life, hormones, exercise, age body characteristics and nourishment. The understanding of the importance of vitamin D in different health functions has grown exponentially in recent years. Beyond its well-known role in bone health, vitamin D is involved in numerous functions such as cardiovascular health, tumor prevention, immunological functioning, and glucose metabolism.

Vitamin D levels vary substantially in different subsets of population as well as among populations from different geographical regions. Many factors affect the vitamin D levels in blood including antiepileptic drugs. Epilepsy is one of the common illness of the childhood. It is estimated in various studies that the overall prevalence of epilepsy in India is 5.59-10 per1000.[1-3] As a treatment, these children receive antiepileptic drugs [AEDs], on long term basis often for several years. These drugs trigger off many adverse or undesirable effects including influence over bone mineralization due to effects on vitamin D metabolism. However, less focus has been paid to interaction between epilepsy and vitamin D which is a member of broadfamily of steroid hormone signalling via nuclear and membrane-associated receptors. Notmany Indian studies are available on this subject.[4] Studies of vitamin D therapy in children with epilepsy have been limited by lack of stratification with regard to confounding factors. Due to lack of awareness, it is not common practice to supplement calcium or vitamin D in children with antiepileptic drugs — United Kingdom had only 3% of pediatric neurologists using prophylactic calcium and vitamin D medication for anticonvulsantinfants.[5,6] In India, it is even less.[5] There is a need for more studies particularly from patients with rural background,

malnutrition and more likely to suffer the vitamin D deficiency. Hence, we conducted this study to assess the prevalence of vitamin D deficiency among the children who are on sodium valproate medication and also to find any correlation between the sodium valproate and the serum vitamin D3 in ambulatory children. Present study aimed to assess serum Vitamin D3 levels in ambulatory children on Sodium Valproate for control of seizures.

MATERIAL & METHOD

This cross sectional study was conducted at department of Paediatrics, Subharti MedicalCollege, Meerut both IPD and OPD for the duration of September 2019 to March 2021.Ambulatory children with seizures aged one-year to 18 years on monotherapy on Sodium Valproate for more than 6 months are included in the present study. children who are on chronic medication like steroids, thiazides, bisphosphonates, anticancer drugs, anti-hypertensive drugs, history of malabsorption, renal disease and parents refusing to be part of study were excluded from the study.

Serum was separated by centrifuging at room temperature. Serum was stored at –20°C until vitamin D estimation was performed. Vitamin D level and sodium valproate level were analysed by using chemiluminescence method. Cases with vitamin D deficiency, they were prescribed with vitamin D supplementation of vitamin D3 oral preparation 60,000 IU for the6weeks of course and re-assessed for the improvement in the level of vitamin D. In this group, vitamin D3 levels were estimated after four weeks of the last dose of vitamin D.

STATISTICAL ANALYSIS

All the data were entered in excel sheet and the analysis was performed using SPSS v21 operating on windows 10. The demographic details of the patients are represented as frequency and percentage, the continuous variables using mean and standard deviation. The mean difference between the two continuous variables was analysed using the unpaired student t-test. a p-value of <0.05 was considered statistically significant.

RESULT

A total of 143 individuals were enrolled in the present study. Of these, 73 were cases and 65were controls. However, of the 73 cases, there were 8 cases who dropped out and were not included in the study. Thus, a total of 65 cases and 65 controls were finally included in the study and their results analysed. The mean age of cases was 13.11±1.8yrs and a control was12.89±1.7yrs of age. (p>0.05) The mean weight of children was found to be 39.12±7.3kg incases and 40.86±5.96kg in controls (p>0.05). Among all, 47.7% were female children and52.3% were male children, with marginal male predominance. In children who were taken as controls, we did not find any deficiency of vitamin D levels which was taken as <20ng/ml. Inour study mean levels were 25.9+3.14 ng/ml. We had only one child with 19.8 ng/ ml level of vitamin D. Most cases were in insufficiency range of 20-29 ng/ml (80%). Less than 20% (12cases) had levels above 30ng/ ml to be counted as sufficient. In present study found significantly lower vitamin D levels in children on sodium valproate as compared to the children in control group (p<0.001).The mean level of serum valproate among the cases was found to be 119.02±7.63. The mean duration of AED was found to be 19.02±3.54 months.

There is a strong negative correlation of serum valproate and vitamin D levels among thecases (p<0.001). There is a strong negative correlation of duration of AED and vitamin D levels among the cases (p<0.001).In the present study, there was significant number of children among the cases under valproatetreatment who had the deficiency of vitamin D. Mean levels were 14.98ng/ml (10.5-18.80).We did not have even a single child who was not deficient in vitamin D.

Table 1: Demographic details of the patients included

	Group	Mean	SD
Age (years)	Case	13.11	1.83
	Control	12.89	1.72
Weight (kg)	Case	39.12	7.37
	Control	40.86	5.96
Gender	Female		
	Male		
Serum valproate level (µg/ml)	Case	119.02	7.63
Duration of AED (months)	Case	19.02	3.54

Table 2: Comparison of serum vitamin D level among cases and controls

	Group	Mean	SD	p-value
Vitamin D 3 level (ng/ml)	Case	14.98	2.19	0.001**
	Control	25.90	3.14	

Table 3: Pearson correlation of serum vitamin D level with the serum valproate level and duration of AED

		Serum valproate level	Duration of AED in months
Vitamin D 3 level	r	-.841**	-.627**
	Sig	.000	.000
**. Correlation is significant at the 0.01 level (2-tailed).			

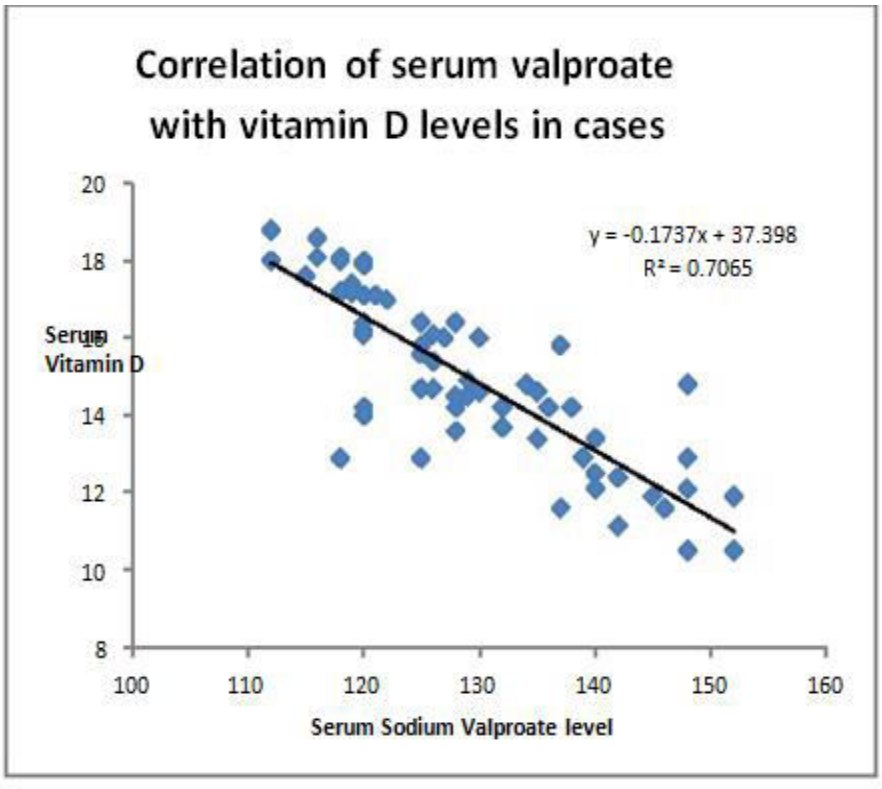

Figure 1: Correlation of serum valproate with vitamin D levels in cases

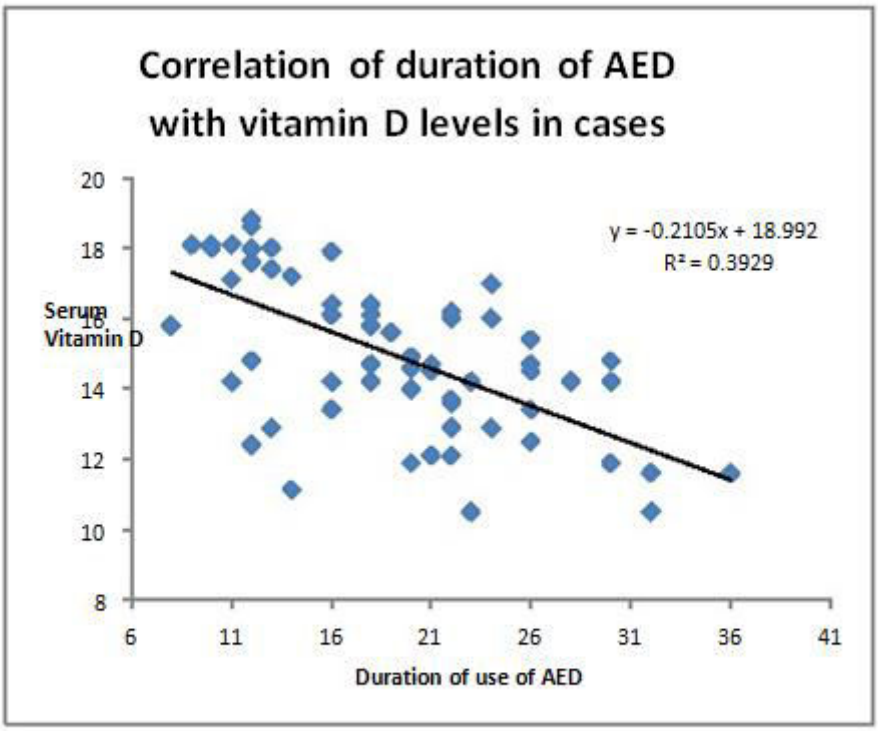

Figure 2: Correlation of duration of AED with vitamin D levels in cases

Table 4: Comparison of the vitamin D deficiency among the cases and control

	Vitamin D Deficiency (≤20ng/ml)		Sufficient Vitamin D (> 20ng/ml)		Chi-square (p-value)
	Nos.	%	Nos.	%	
Case	63	96.9%	2	3.1%	97.06(0.00)**
Control	7	10.7%	58	89.3%	

Table 5: Comparison of the serum vitamin D level post supplementation of vitamin D to cases

	Group	Mean	SD	p-value
Vitamin D 3 level (ng/ml)	Case	14.98 (10.50 – 18.80)	2.19	0.001**
	After supplementation with Vitamin D	27.34 (19.36 – 35.21)	4.26	

DISCUSSION

While Vitamin D3 levels are supposed to be laboratory specific, most of the studies have taken 20ng/ml as cut-off for deficiency. A total of 130 individuals included in present study after obtaining the informed consent from the parents of the children. Among them, 65were the cases and 65 as controls. The mean age of cases was 13.11±1.8yrs and a control was12.89±1.7yrs of age. (p>0.05) The mean weight of children was found to be 39.12±7.3kg in cases and 40.86±5.96kg in controls (p>0.05). Among all, 47.7% were female children and 52.3% were male children, with marginal male predominance. However, it is difficult to interpret it as such; because, it is possible that male children had a better access to health care facilities due to gender bias in the society at large.We

analysed children in three categories. First was, serum vitamin D levels in children who received valproate as antiepileptic drug for at least six months, 2nd group was levels of vitamin D levels in healthy children and then 3rd category was vitamin D levels in cases on valproate therapy who were supplemented with vitamin D in this group, vitamin D3 levels were estimated after four weeks of the last dose of vitamin D.

In children who were taken as controls, we did not find any deficiency of vitamin D levels which was taken as <20ng/ml. In our study mean levels were 25.9+3.14 ng/ml. We had only one child with 19.8 ng/ ml level of vitamin D. Most cases were in insufficiency range of20-29 ng/ml (80%). Less than 20% (12 cases) had levels above 30ng/ ml to be counted a sufficient. The community-based Indian studies of the past decade done on apparently healthy controls reported a prevalence ranging from 50% to 94%[7,8]and hospital based studies have reported an overall vitamin D deficiency to be 40-93%.[9] But, majority of studies have been in pregnant or lactating women, old people above 60 years of age as also on cord blood depicting maternal status.[10] Two hospital based studies from Kolkata and Chandigarh for children 1-16years age group reported deficiency in 40-50% cases. A study by Kadam from Pune in school going under-privileged girls reported deficiency of 34%,[11] while Kapil from Kangra Himachal Pradesh reported 80% children in school going age to suffer from vitamin D deficiency.[12] Thus, except for study from Himachal, deficiency of vitamin D in school going children has been reported to be 34-50%. Choudhary from Delhi reported two groups as deficient vs. not deficient and found 34.5% children to be deficient.[13]Basu from Kolkata reported median levels to be 19ng/ml, 52% children were deficient, 24 % insufficient and 22% having levels above 30ng/ml.[14]Angurana from Chandigarh reported 40% deficiency, 26% having insufficient and34% children in 3mo to 12 years group having sufficient vitamin D levels.[15]

It is difficult to explain why we had <2% vitamin D deficiency, but if we take adequacy of vitamin levels to be in <20% children, findings are similar to those by others. One probable reason for marginally better vitamin D levels could be that most cases in our study were rural children who probably got better exposure to sun light and lesser of air pollution as compared to those in cities. These findings are similar to those of kadam et. al from Pune.[11]

Second group we analysed was of children who were on sodium valproate monotherapy for seizure disorder for minimum of six months. A time interval of six months from the initiation of therapy was taken so that the body stores which might have been adequate prior to treatment would not affect the results. In the present study, there was significant number of children among the cases under valproate treatment who had the deficiency of vitamin D. Mean levels were 14.98ng/ml (10.5-18.80). We did not have even a single child who was not deficient in vitamin D. This is somewhat comparable with findings from other studies.[4,16]

In study by Ramya S et al., 65 children (75.5%) had vitamin D levels <20 ng/ml (deficiency), 15 (17.4%) children had vitamin D levels between 21-29ng/ml (insufficiency) and 6 (7.1%) children had vitamin D levels >30ng/ml (sufficiency).[17] Sreedharan[4] from Kerala however reported that the 60.7% of patients who were receiving carbamazepine as antiepileptic and 35.7 % of children on valproate as antiepileptic had low 25 (OH)HCC levels (<20 ng/mL). They found 27.8%children in controls group to be deficient in vitamin D levels. On this basis they suggested that children on antiepileptic drugs should have regular monitoring of Vitamin D levels, and/ or supplementation with calcium and vitamin D even in children with normal growth anddevelopment.[4]

Consistent with the present study, Chaudhuri IR et al., documented 25-hydroxyvitamin D (≤20 ng/mL) deficiency was significantly higher among epileptics (44%) compared to control subjects (20%).[18] Abdullah AT et al. from Iraq categorised the vitamin D levels as severe vitamin D3 deficiency was defined as a level less than <5 ng/ml; deficiency was defined as the level between (5-15 ng/ml); insufficiency was defined as the level between (15-20 ng/ml);and between (20-30 ng/ml)vitamin D was deemed sufficient. They found none of the children in control had the severe vitamin D deficiency compared to the cases on antiepilepticmedications.[19] In study by Bhat AM et al., who took the deficiency of vitamin D <20ng/ml found that out of 30 cases, 13(43.3%) had decreased vitamin D levels to <20ng/dl where as in controls out of 30 only 4(13.3%) had decreased vitamin D level to < 20ng/dl.[20]

In present study found significantly lower vitamin D levels in children on sodium valproate as compared to the children in control group (p<0.001).The mean level of serum valproate among the cases was found to be 119.02±7.63. The mean duration of AED was found to be 19.02±3.54 months. Similar to present study, Chaudhuri IR et al., found a significant lower vitamin D level in cases compared to controls. The mean Vitamin D in cases was found to be 18.3±6.2 and in controls with 27.7±3.9).[18]Similarly in study by Bhat A et al., also documented the lower levels of serum vitamin D among the cases compared to healthy control children.[20] Ramya S et al, documented a higher prevalence of vitamin D insufficiency among the children with epilepsy compared to the control.[17]

In study by Sreedharan et al., found that patients with monotherapy of the anti- epileptics showed a significant higher risk of vitamin D deficiency in them compared to the control group.[4]

Almost all studies are unanimous that there is a potential risk of vitamin D deficiency in children on anti-epileptic drugs including valproic acid. The frequency and levels may be different in different

studies depending the inherent vitamin D level status of the children included in the study and criteria for deficiency defined. However ours is the only study who has done the simultaneous serum valproate levels as well to document that therapeutic levels of serum valproate are associated with significant risk of subclinical vitamin D deficiency in children and adolescents.

The main pathogenetic mechanism appears to be based on decreased active levels of vitamin D, which could be induced by AEDs inducing hepatic cytochrome P450 enzymes, resulting in its conversion to inactive metabolites in the liver microsomes. Hypocalcemia can be caused by decreased absorption from the stomach as a result of hypovitaminosis D. This could result in an increase in circulating parathyroid hormone. Secondary hyperparathyroidism causes accelerated bone turnover, which raises serum alkaline phosphatase levels. There is a strong negative correlation of serum valproate and vitamin D levels among the cases.($p<0.001$)There is a strong negative correlation of duration of AED and vitamin D levels among the cases.($p<0.001$) In similar to present study, various studies have documented the severity of vitamin D deficiency with the duration of long term use of AED.[18] The exact duration of AEDs that cause vitamin D insufficiency is unknown. Vitamin D levels were shown to be considerably lower after 18 months of taking AEDs in a study by Cansu et al.[21]

Study by Ramya S et al., documented a linear relation between the vitamin D level and the duration of anticonvulsant use with decrease in the levels of vitamin D with prolonged use of anticonvulsant.[17] In study by Chaudhuri IR et al., cohort of epileptics with normal vitamin D had a mean exposure length of 25.2 months, which was significantly greater than prior data; this could be due to Indians' increased exposure to sunlight. India is a tropical country, and the study was conducted in South India in a city with daytime temperatures ranging from 20 to 30degrees Celsius, with only a 10 degree Celsius difference between winter and summer.[18]

This study reinforces the deleterious effects of AEDs on bone mineral metabolism and is consistent with current global literature. Supplementing with vitamin D may aid in the prevention of these problems. Several randomized controlled trials have demonstrated that vitamin D therapy combined with AEDs has a favourable effect in children; however, information on the length of therapy, the significance of diet/exercise, and the role of monitoring vitamin D levels is still insufficient. Studies also noted that among epileptics, elevated alkaline phosphatase and low serum calcium were significantly associated with deficiency of 25-hydroxyvitamin D ($P=0.0001$).[18]

Basu et al., in his study conducted around the metropolitan city of Kolkata showed that a large section of children and adolescents are nutritionally deficient of vitamin D and they required supplementation to replenish the body stores and correct the circulating levels to optimum level. The median vitamin D concentration in the preschool and school going children was found to be 23 and 17 ng/ml, respectively and deficiency was seen in 42 and 61 % subjects. Similar statistics have been seen in reports in children living in the northern, western and southern states of the country.[14]Angurana K et al., stated that the possible determinants of low vitamin D status in our children could be due to the lack of vitamin D supplementation, inadequate sun exposure, less time spent on outdoor physical activity and greater indulgence in indoor activities like watching television, computer gaming, and other recreational activities.[15]

Abdullah et al., recommended in his study that to prevent vitamin D3 insufficiency in epileptic children on continuous valproate medication, vitamin D levels should be monitored on a regular basis. To optimize seizure control, all epileptic children should be provided vitamin D3 supplementation, even before the commencement of antiepileptic medicines, and these kids should follow a well-balanced diet and healthy lifestyle.[19] Bhat A et al., stated that blood vitamin D levels and bone mineral density should be monitored on a regular basis throughout anticonvulsant therapy, and therapeutic vitamin D and calcium supplementation should begin as soon as possible.[20]

There is a scarcity of experimental data to support worldwide screening and targeted therapies for epileptic children with vitamin D deficiency. To date, the majority of studies have been inconsistent and of poor quality. Larger studies with clinically important outcomes, such as fractures, are required, as are populations at risk, such as those with symptomatic generalized epilepsy, reduced mobility, and anticonvulsant poly therapy. Despite the fact that vitamin D hypervitaminosis is uncommon in children, continuous administration of vitamin D supplements, optimization of vitamin D levels, and administration of greater doses may increase vitamin D toxicity. Vitamin D excess is uncommon and usually asymptomatic in epileptic children. Sreedharan et al., stated that influence of anti epilepticmedicines on bone health should be addressed by all pediatricians, since early detection of vitamin D deficiency and providing the calcium and vitamin D supplementation can aid the majority of children on long-term anticonvulsants.[4] Supplementing with vitamin D may aid in the prevention of these problems. Several randomized controlled trials have demonstrated that vitamin D therapy combined with AEDs has a favorable effect in children; however, information on the length of therapy, the significance of diet/exercise, and the role of monitoring vitamin D levels is still insufficient.

LIMITATION

The study is bound with some limitations being; it is a single centric study, and COVID-19 pandemic lockdown affecting the children mobility outdoor.

Pre-treatment vitamin D levels were not analysed among the included participants.

CONCLUSION

This study identifies a significant risk of vitamin D deficiency in ambulant children with drug-treated epilepsy. Antiepileptic medications have a negative impact on bone mineral metabolism, as evidenced by lower vitamin D levels in antiepileptic drug patients' serum. As a result, blood vitamin D levels and bone mineral density should be monitored on a regular basis throughout anticonvulsant therapy, and therapeutic vitamin D and calcium supplementation should begin as soon as possible.

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