

# Association of long term sodium valproate monotherapy and vitamin D3 levels in epileptic children

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## Author's Contribution

<sup>1</sup> Conception of study

<sup>1,4</sup> Experimentation/Study conduction

<sup>1,2</sup> Analysis/Interpretation/Discussion

<sup>2,3,5</sup> Manuscript Writing

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## Abstract

**Objective:** To determine the association of long term sodium valproate monotherapy and vitamin D3 levels in epileptic children

**Materials and Methods:** This cross-sectional study was conducted in the Department of Paediatrics, Children Hospital, Pakistan Institute of Medical Sciences, Islamabad for six months from 15<sup>th</sup> February 2019 to 14<sup>th</sup> August 2019. A total of one hundred and thirty (n=130) children and adolescents of either gender between age 3-18 years who had a history of two seizures at least 24 hours apart in their life and were on sodium valproate monotherapy for more than one year were enrolled in this study through non-probability, consecutive sampling. Serum vitamin D3 (25-hydroxy vitamin D) levels were measured in all the patients at the time of enrolment into the study. All the demographic data and laboratory investigations were entered on the predesigned proforma and analyzed through SPSS version 17.

**Results:** Vitamin D3 deficiency was found in 47 (36.2%) children which were significantly higher among patients with older age and longer duration of treatment (P<0.05) while gender and BMI of the patients did not show any significant difference (P>0.05).

**Conclusion:** Significant percentage of epileptic children on sodium valproate monotherapy was found to have vitamin D3 deficiency. Therefore we recommend routine screening of vitamin D3 deficiency in all the epileptic children on long-term sodium valproate therapy followed by vitamin D supplementation in deficient patients.

**Keywords:** Epilepsy, sodium valproate, vitamin D3 deficiency.

## Introduction

Epilepsy is the most common neurological disease affecting 50 million people of all ages throughout the world.<sup>1</sup> Out of these, 85% live in developing countries.<sup>1</sup> In the United States and Europe the prevalence of epilepsy is 6.8 and 5.5 per 1000 population respectively.<sup>2</sup>

The prevalence of epilepsy in urban and rural areas of Pakistan is 7.4 and 14.8 per 1000 respectively with an overall average prevalence of 9.99 per 1000 population.<sup>3</sup> Prevalence of childhood and adolescent epilepsy under 16 years of age in Pakistan is 7 per 1000 population with equal distribution in urban and rural areas.<sup>4</sup> Almost 50% of patients develop epilepsy in their childhood.<sup>5</sup> In Pakistan, only 34% patients of with epilepsy are managed properly by qualified doctors with anti-epileptic drugs (AEDs). The rest of the patients are treated by paramedics and faith healers.<sup>4</sup> Sodium valproate is one of the commonly used AEDs in the world. The majority of AEDs are inducers of hepatic cytochrome P450 isoenzymes which decrease the level of vitamin D<sub>3</sub> (25-hydroxy vitamin D) in the body due to its rapid metabolism in the liver.<sup>6</sup> But sodium valproate is not an inducer of hepatic cytochrome P450 isoenzymes but still results in a low level of vitamin D<sub>3</sub> in the body due to inhibition of 25-hydroxylation of vitamin D in liver mitochondria.<sup>7</sup>

Childhood is the most commonly affected age group in epilepsy which is the most critical period for growth and development. A low level of vitamin D<sub>3</sub> in the body at this age results in short stature due to its effect of reduced bone mineral density. Reduced bone mineral density is also one of the factors responsible for increased frequency of fractures in epileptic patients.<sup>8</sup> Low levels of vitamin D<sub>3</sub> in the body result in aggravation of seizures as it down-regulates cytokine IL-6, which is a proconvulsant.<sup>9</sup> Consequently many treating physicians increase the dose of AEDs to control the seizures which further aggravates deficiency of vitamin D<sub>3</sub> in the body and this vicious circle continues.

In epileptic patients, vitamin D<sub>3</sub> deficiency and reduced bone mineral density also result from other factors like malnutrition, decrease physical activity and reduce sunshine exposure which confuses the actual association of sodium valproate and vitamin D<sub>3</sub> deficiency. This led the scientists to investigate this matter in different geographical areas of the world with varying sunshine exposure and dietary habits of patients which shows different results.<sup>6,10</sup>

Literature research revealed only one study from Pakistan which was done on 26 epileptic children to look for the effect of sodium valproate monotherapy for at least 3 months on vitamin D<sub>3</sub> levels.<sup>11</sup> No such study in Pakistan done so far on epileptic children taking sodium valproate monotherapy for more than one year. Therefore, this study was conducted on a large sample size to determine the association of long-term sodium valproate monotherapy and vitamin D<sub>3</sub> levels in epileptic children.

## Materials and Methods

After seeking permission from the research and ethics committee of Pakistan Institute of Medical Sciences (PIMS), Islamabad, this cross-sectional study was conducted in the Paediatric department of, Children Hospital, Pakistan Institute of Medical Sciences, Islamabad. Patients from 3 to 18 years of age of either gender with a history of two seizures at least 24 hours apart in their life and who were on sodium valproate monotherapy for more than one year were included in this study. Patients receiving vitamin D supplements, taking two or more AEDs, having any other systemic disease or neurological deficit were excluded from this study.

Total 130 patients were taken as a sample size by using the WHO sample size calculator with the following values of calculations; 95% confidence level, anticipated population proportion=31.1%<sup>5</sup>, and absolute precision required=8%.

All the patients who fulfilled the inclusion criteria were recruited through non-probability, consecutive sampling & written informed consent was obtained from parents/guardians before enrollment in the study. Vitamin D<sub>3</sub> levels (25-hydroxy vitamin D) were measured through the radioimmunoassay technique with the Diasorin SR kit by LIASON in all the patients from the hospital's laboratory free of cost. Patients were considered vitamin D<sub>3</sub> deficient if its level is < 20 ng/ml. All the demographic data, height, weight, BMI, and laboratory investigations were entered on the predesigned proforma.

The data was then entered and analyzed using SPSS version 17. Mean  $\pm$  SD was calculated for quantitative variables like age, body mass index (BMI), and serum vitamin D<sub>3</sub> levels. Frequencies and percentages were calculated for qualitative variables like gender and vitamin D<sub>3</sub> deficiency. Effect modifiers like age, gender, BMI, and duration of treatment before checking vitamin D levels were stratified. Post-

stratification chi-square test was applied and  $P$ -value  $\leq 0.05$  was considered significant.

## Results

In this study, a total of 130 children was enrolled out of which 47 (36.2%) were found to have vitamin D<sub>3</sub> deficiency. Characteristics of patients are shown in Table 1.

The deficiency of vitamin D<sub>3</sub> was significantly higher among patients with older age and longer duration of treatment ( $P < 0.05$ ) while gender and BMI did not show any significant difference ( $P > 0.05$ ) as shown in Table 2.

**Table 1: Characteristics of patients**

Characteristics	Mean $\pm$ SD
Age (years)	8.4 $\pm$ 4.2
BMI (Kg/m <sup>2</sup> )	17.7 $\pm$ 2.7
Duration of treatment (years)	4.9 $\pm$ 2.6
Vitamin D <sub>3</sub> levels (ng/ml)	27.2 $\pm$ 12.9
<b>Variables</b>	<b>n (%)</b>
<b>Gender</b>	
Male	58 (44.6%)
Female	72 (55.4%)
<b>Vitamin D<sub>3</sub> Deficiency</b>	
Present	47 (36.2%)
Absent	83 (63.8%)

**Table 2: Comparison of vitamin D<sub>3</sub> deficiency with patient's age, gender, duration of treatment, and BMI**

Variables	Vitamin D <sub>3</sub> Deficiency		Total	P-Value Chi-Square
	Present (%)	Absent (%)		
Age	3-10 years	22 (26)	63 (74)	0.001
	>10-18 years	25 (55.6)	20 (44.4)	
Gender	Males	22 (38)	36 (62)	0.705
	Females	25 (35)	47 (65)	
Duration of treatment	< 5 Years	13 (17)	64 (83)	0.001
	> 5 Years	34 (64)	19 (36)	
BMI	Normal	35 (37)	60 (63)	0.788
	Over weight	12 (34)	23 (66)	

## Discussion

In recent years, the importance of vitamin D<sub>3</sub> has increased due to its role in increasing immunity and prevention of allergies and cancers. Therefore its deficiency in epileptic children has become even more important as seizures worsen during infections. Our study shows that 36.2% (n=47/130) of patients taking sodium valproate monotherapy have vitamin D<sub>3</sub> deficiency. This deficiency was found in higher percentages among older age children with a longer duration of treatment ( $P < 0.05$  in both cases) while gender and BMI of patients have no significant effect on vitamin D<sub>3</sub> deficiency.

Taha Abdullah et al carried out a study in Iraq on 50 epileptic patients and 50 healthy children as control. Epileptic patients were 2 to 15 years old taking valproic acid for 6 months or more as monotherapy. They found a low level of vitamin D<sub>3</sub> in 70% of patients as compared to 30% of healthy children. This study revealed almost 2 times more deficiency of

vitamin D<sub>3</sub> in epileptic children as compared to our study.<sup>6</sup>

Sreedharan et al did their study in Kerala, India on 56 epileptic patients, 2 to 13 years old, and 109 controls. Out of 56 patients, 28 were on sodium valproate monotherapy for at least 6 months and the other 28 were on carbamazepine monotherapy. They found vitamin D<sub>3</sub> deficiency in 36% (n=10/28) patients on sodium valproate monotherapy as compare to 28% (n=30/109) children in the control group which is exactly similar to the result of our study.<sup>12</sup>

Chaudhuri et al conducted their study in Hyderabad India on 100 epileptic patients below 18 years of age and 50 controls. Out of 100 patients, 21 patients were on sodium valproate monotherapy for 12 months or more. They found vitamin D<sub>3</sub> deficiency in 31.1% of patients taking sodium valproate monotherapy as compare to 24% in the control group which is slightly lower than that of our study.<sup>5</sup>

Rafiq et al carried out a study in Rawalpindi, Pakistan on 34 epileptic children and 34 healthy controls. Out of 34 patients, 26 were on sodium valproate

monotherapy and 8 were on carbamazepine monotherapy for more than 3 months. They found vitamin D<sub>3</sub> deficiency in 32.4% of all patients (n=11/34) as compared to 5.9% (n=2/31) in the control group. This cannot be compared to the results of our study as a separate percentage of vitamin D<sub>3</sub> deficient patients taking sodium valproate monotherapy is not mentioned.<sup>11</sup>

Ginige et al conducted a retrospective study on 119 epileptic children of Sri Lanka taking AEDs and 86 healthy controls. Out of 119 epileptic patients, 27 were on sodium valproate monotherapy. Their results showed that 60.7% (n=17/27) of children taking sodium monotherapy were vitamin D<sub>3</sub> deficient as compared to 45.3% of children in the control group. These results are 2 times higher than those of our study.<sup>13</sup>

Razazizan et al conducted their study in Iran on 48 ambulatory epileptic children, 2-14 years old, on AED monotherapy for at least 6 months and 48 healthy controls. Out of these 48 patients, only 9 patients were on sodium valproate monotherapy. They found a low level of vitamin D<sub>3</sub> in 17% of all patients (n=8/48) as compare to 31% (n=15/48) controls. In this study, AEDs did not cause vitamin D<sub>3</sub> deficiency which is contrary to all the above studies. We cannot compare our results with this study as well because the author did not mention a separate percentage of patients with vitamin D<sub>3</sub> deficiency who were taking sodium valproate monotherapy.<sup>10</sup>

Shellhaas et al found in their study that girls and children with high BMI are more at risk of vitamin D<sub>3</sub> deficiency which is different from the results of our study.<sup>14</sup>

Kumar et al in their study show that the prevalence of vitamin D<sub>3</sub> increases with the increase in the age of children which is consistent with our study.<sup>15</sup> This may be due to the fact that older children spend more time indoors due to their educational commitments.<sup>16</sup>

Some studies also found that vitamin D<sub>3</sub> deficiency and low bone mineral density are significantly more common in patients with a long duration of treatment with sodium valproate.<sup>5,17</sup> This finding is similar to that of our study.

Our study has some limitations. We didn't include patient's diet, activities, and sunshine exposure in our study which can affect their vitamin D<sub>3</sub> levels. We did not check vitamin D<sub>3</sub> levels in healthy control children. We also did not check the patient's serum calcium levels and bone mineral densities due to financial constraints.

In summary, the results of the majority of the above-cited studies indicate that vitamin D<sub>3</sub> deficiency was found in a significant percentage of epileptic children on sodium valproate monotherapy which can result in a variety of health issues in them. We, therefore, recommend routine screening of vitamin D<sub>3</sub> deficiency in all epileptic children taking sodium valproate therapy. Further studies should be done to determine the minimum dose of vitamin D supplementation which can prevent its deficiency caused by sodium valproate.

## Conclusion

Our study shows that a significant percentage of epileptic children on sodium valproate monotherapy have vitamin D<sub>3</sub> deficiency which is higher among older age children with a longer duration of treatment. Therefore we recommend routine screening of vitamin D<sub>3</sub> deficiency in all epileptic children on long-term sodium valproate therapy followed by vitamin D supplementation in deficient patients.

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