Effects of sodium valproate and levetiracetam monotherapy on vitamin D status in epileptic children: A study from Eastern India

Jyotirmoy Sen[1], Sumana Kanjilal Datta[1], Hasibur Rahaman Molla[1], Priyanka Gupta[1], *Suprit Basu[1], Sumit Sarkar[1]

Sri Lanka Journal of Child Health, 2022; **51**(3): 364-368
DOI: http://dx.doi.org/10.4038/sljch.v51i3.10224

Abstract-

Objectives: To compare serum vitamin D levels of paediatric epilepsy patients treated with valproic acid or levetiracetam monotherapy with those of age and sex matched controls.

Method: An analytical, cross-sectional study was carried out in a tertiary care hospital in eastern India. Sixty children aged 2-12 years with idiopathic epilepsy, on either sodium valproate or levetiracetam monotherapy for 6 months or more were included in this study and 30 age and sex matched healthy children were taken as controls. Children having calcium or vitamin D supplementation, children on two or more antiepileptic drugs and children on any chronic medication which can affect bone metabolism were excluded from this study. Serum 25-hydroxy vitamin D concentrations of >20 ng/ml was taken as vitamin D sufficiency, from 12-20 ng/ml as vitamin D insufficiency and <12 ng/ml as vitamin D deficiency.

Results: Of the 60 patients included in the study 42 (70%) were males and 18 (30%) were females. Among the 30 control 8 (60%) were males and 12 (40%) were females. Patients receiving sodium valproate and levetiracetam therapy had mean serum 25-hydroxy vitamin D levels of 15.54±10.05 ng/ml and 14.54±8.68 ng/ml respectively. Among controls, mean serum 25-hydroxy vitamin D level was 21.09±4.79 ng/ml. Sodium valproate group ($p < 0.001$) and levetiracetam group ($p=0.003$) had significantly lower serum 25-hydroxy vitamin D levels than the control group.

Conclusion: Sodium valproate and levetiracetam monotherapy were significantly associated with hypovitaminosis D. Duration of valproate therapy had a negative correlation with the serum vitamin D level.

(Key words: Sodium valproate, Levetiracetam, Epilepsy, Vitamin D, Paediatrics)

Introduction

Epilepsy is a common neurological disorder in children requiring long-term anticonvulsant therapy[1]. Long-term anticonvulsant therapy is associated with an increased incidence of vitamin D deficiency (VDD)[2,3]. Initial studies reported association of VDD with mainly enzyme inducing antiepileptic drugs (EIAEDs)[4,5]. However, recent studies have found no difference between EIAEDs and non-EIAEDs in their action on 25-hydroxy vitamin D status[6]. Now the preferred choice is levetiracetam or valproic acid[7]. Recently studies have been done to find the relationship between valproic acid therapy and serum vitamin D in the adult population[8,9]. Very few studies have investigated the effects of levetiracetam on serum vitamin D. There is paucity of data regarding hypovitaminosis D in children on valproate or levetiracetam monotherapy in Eastern India.

Objectives

To compare serum vitamin D levels of paediatric epilepsy patients treated with valproic acid or levetiracetam monotherapy with those of age and sex matched controls.

Method

An analytical, cross-sectional study was carried out from 1st May 2019 to 30th April 2020 in a tertiary care super speciality East Indian hospital.

Sixty children aged 2-12 years with idiopathic epilepsy, 30 on sodium valproate monotherapy and 30 on levetiracetam monotherapy for 6 months or more were included in the study and 30 age and sex matched healthy children attending the outpatient department due to any other illness were taken as controls.

Children getting calcium or vitamin D supplementation, children on 2 or more antiepileptic

[1]*Institute of Postgraduate Medical Education and Research, Kolkata, India*
**Correspondence:* supritbasu94@gmail.com
https//orcid.org/0000-0003-2016-3272

(Received on 02 November 2021: Accepted after revision on 17 December 2021)
The authors declare that there are no conflicts of interest
Personal funding was used for the project.

drugs, children on chronic medication that could affect bone metabolism and children having any chronic disease or having clinical evidence of rickets were excluded from the study.

Consecutive sampling was used. Sample size was calculated bases on the formula:

$$\text{Sample size} = \frac{\{z^2 \times p\,(1-p)\}/d^2}{1 + [\{z^2 \times p\,(1-p)\}/d^2]-1}{N}$$

Now putting z (value of standard normal distribution) = 1.96
P (proportion in infinity population) = 0.80
d (absolute precision) =0.04
N (Average number of seizure patient admitted in our hospital per year) = 100
We got sample size of 80 (approx.)

Although the calculated sample size of cases was 80, this could not be achieved due to the COVID-19 pandemic.

Demographic data including age, gender, weight, height, body mass index (BMI), antiepileptic drugs, duration of epilepsy, seizure frequency and duration of antiepileptic therapy were collected. Serum protein, serum calcium and serum alkaline phosphatase (ALP) were assessed in addition to serum 25-hydroxy vitamin D levels as hypovitaminosis D can impact levels of serum calcium and ALP and malnourished children might have low serum proteins which can be a confounder of this study. Data were collected by filling the pre-structured, pre-validated questionnaire. Serum 25-hydroxy vitamin D was measured by the nephelometric method. Serum 25-hydroxy vitamin D concentration >20 ng/ml was taken as vitamin D sufficiency, from 12-20 ng/ml as vitamin D insufficiency and <12 ng/ml as VDD[10].

Ethical issues: Approval for the study was obtained from the Ethical Review Committee of the Institute of Postgraduate Medical Education and Research, Kolkata, India (No. IPGME&R/IEC/2019/074 dated 04.02.2019). Informed written consent was obtained from the parents of the participating children and assent from the children aged more than 7 years, prior to commencement of the study.

Statistical analysis: Data were collected and recorded on Microsoft Excel data sheets. Categorical variables were expressed as frequencies and percentages and compared across groups using Pearson's Chi Square test and Fisher's Exact Test. Continuous variables were expressed as mean, median and standard deviation and compared across groups using Mann-Whitney U test. Statistical software SPSS version 20 was used for the analysis. $p< 0.05$ was considered significant.

Results

Table 1 shows the demographic and laboratory features of cases and controls.

Table 2 is a comparative study of serum 25-hydroxy vitamin D level with anticonvulsants.

Table 1: ***Demographic and laboratory features of cases and controls***

Variable	Cases *(n=60)*	Controls *(n=30)*	p-value
Age (months) - n (%)			
24-35	12 (20.0)	03 (10.0)	
36-47	09 (15.0)	05 (16.6)	0.686
48-59	08 (13.3)	05 (16.6)	
60 and over	31 (51.7)	17 (56.6)	
Sex - n (%)			
Male	42 (70.0)	18 (60.0)	0.343
Female	18 (30.0)	12 (40.0)	
Socio-economic status (modified Kuppuswamy scale)			
Upper-Lower	22 (37.0)	08 (27.0)	0.342
Lower	38 (63.0)	22 (73.0)	
Serum albumin (g/dL) Mean ± SD	3.73±0.61	3.67±0.69	0.648
Serum protein (g/dL) Mean ± SD	6.39±0.62	6.20±0.67	0.143
Serum calcium (mg/dL) Mean ± SD	7.95±1.55	8.64±0.70	0.086
Serum alkaline phosphatase (IU/L) Mean ± SD	165.51±91.88	171.73±71.50	0.473
Serum 25-hydroxy vitamin D3 - *n (%)*			
Sufficient	15 (25.0)	15 (50.0)	0.0004
Insufficient	23 (38.3)	15 (50%)	
Deficient	22 (36.7)	0 (0)	

Table 2: ***Comparative study of serum 25-hydroxy vitamin D level with anticonvulsants***

Serum 25-Hydroxy vitamin D level (ng/mL)		
Sodium valproate group (n=27)	**Mean ± SD**	**Median**
	15.54 ± 10.45	15.90
Control group (n=30)	21.09 ± 4.79	20.10
p-value	<0.001	
Serum 25-Hydroxy vitamin D level (ng/mL)		
Levetiracetam group (n=33)	**Mean ± SD**	**Median**
	14.54 ± 8.68	14.16
Control group (n=30)	21.09 ± 4.79	20.10
p-value	0.003	

Average doses of sodium valproate and levetiracetam used in this study were 26.67±8.44 mg/kg/day and 37.73±15.62 mg/kg/day respectively. Mean duration of sodium valproate therapy was 18.48 months and mean duration of levetiracetam therapy was 20.70 months.

Table 3 shows the correlation between duration of sodium valproate and levetiracetam therapy with serum 25-hydroxy vitamin D level. Significant negative correlation was found between duration of sodium valproate use and serum 25-hydroxy vitamin D level with a p value of 0.002, but no significant correlation was found between duration of levetiracetam therapy and serum 25-hydroxy vitamin D level.

Table 3: ***Correlation between duration of sodium valproate and levetiracetam therapy with serum 25-hydroxy vitamin D level***

Drug used				**Serum hydroxy vitamin D (ng/ml)**
Sodium valproate	Spearman's rho coefficient	Duration of drug therapy	Correlation coefficient	-0.569
			p Value	0.002
Levetiracetam	Spearman's rho coefficient	Duration of drug therapy	Correlation coefficient	-0.310
			p Value	0.079

Table 4 shows the correlation between serum 25-hydroxy vitamin D level and dose of anticonvulsants used. No correlation was found between dose of anticonvulsant used and the serum 25-hydroxy vitamin D level.

Table 4: ***Correlation between serum 25-hydroxy vitamin D level and dose of anticonvulsants used***

Drugs used				**Serum hydroxy vitamin D (ng/ml)**
Sodium valproate	Spearman's rho coefficient	dose of drug (mg/kg)	Correlation coefficient	-0.339
			p Value	0.083
Levetiracetam	Spearman's rho coefficient	dose of drug (mg/kg)	Correlation coefficient	-0.156
			p Value	0.386

Also, no statistically significant correlation was found between serum calcium and serum alkaline phosphatase level in relation to serum 25-hydroxy vitamin D level (Table 5).

Table 5: ***Correlation between serum Ca and serum ALP levels in relation to serum 25-OH vitamin D level***

Serum 25-hydroxy vitamin D3 (ng/mL)		**Alkaline phosphatase (IU/L)**	**Serum calcium (mg/dL)**
Deficient	Q1	115.0	7.90
	Median	133.0	8.30
	Q3	178.3	9.45
Insufficient	Q1	105.0	6.70
	Median	167.0	8.30
	Q3	242.0	9.30
Sufficient	Q1	128.0	6.50
	Median	147.0	7.80
	Q3	151.0	8.90
p-value		0.463	0.310

Ca: Calcium, ALP: Alkaline phosphatase, Q1: first quartile, Q3: third quartile, OH: hydroxy

Discussion-

In our study a significantly high number of children on antiepileptic drugs (AEDs) had hypovitaminosis D in comparison to controls. All children had idiopathic epilepsy and were receiving either valproate or levetiracetam monotherapy. We tried to ensure that both the AED group and the control group were similar to avoid confounding factors. In this study among the total 60 cases, 75% had low levels of serum 25-hydroxy vitamin D, 36.7% having deficient levels and 38.3% having insufficient levels, whereas among the total 30 controls 50% had insufficient levels of serum 25-hydroxy vitamin D. Studies by Sreedharan M, *et al*[11] and Abdullah AT *et al*[12] in paediatric patients showed similar results.

Our study also showed that patients receiving sodium valproate and levetiracetam had significantly lower mean serum 25-hydroxy vitamin D levels as compared to controls ($p<0.001$ and $p<0.003$ respectively). The exact mechanism by which sodium valproate/levetiracetam causes vitamin D deficiency is not clear but it may be mediated by a different (other than cytochrome P450) hepatic enzyme inhibition. It is proposed that valproate inhibits the 25-hydroxylase activity on vitamin D in liver mitochondria without inhibiting the components of cytochrome P450- linked mono-oxygenase systems. Some authors speculated that genetic variations related to vitamin D receptor polymorphism may influence vitamin D status in patients with epilepsy on non-enzyme inducing AED treatment. Abdullah AT *et al*[12] and Sreedharan M, *et al*[11] also had found similar results with use of sodium valproate in the paediatric population.

Currently, there is scanty data regarding vitamin D status using levetiracetam, especially in East Indian children. We found no significant correlation between the dose of anticonvulsants used and vitamin D level, which is supported by Duygu A, *et al*[13] in the adult population. Our study showed that there is a significant negative correlation between the duration of sodium valproate used and serum 25-hydroxy vitamin D level, similar to findings by Chaudhuri IR, *et al*[14]. However, there was no significant correlation between duration of levetiracetam therapy and serum 25-hydroxy vitamin D level ($p = 0.079$). This is supported by Duygu A, *et al*[13] which was done in the adult population. After thorough literature review no such study was found showing this relationship in the paediatric population. Our primary objective of this study was to establish relationship between serum vitamin D level and levetiracetam or valproate monotherapy for at least 6 months. This result came as secondary finding of our study.

Strengths of our study were strict selection criteria, exclusion of bedridden children and exclusion of children on more than one AED so that changes in various parameters could be attributed to the drugs themselves. Limitations in the study included non-measurement of vitamin D levels prior to starting sodium valproate / levetiracetam therapy so that we cannot definitely attribute the levels to antiepileptic drugs alone, the small sample size and the short minimum duration (6 months) for which anticonvulsants were taken.

Conclusions

Sodium valproate and levetiracetam monotherapy were significantly associated with hypovitaminosis D. Duration of valproate therapy had a negative correlation with the vitamin D level.

.

References

1. Petty SJ, O'Brien TJ, Wark JD. Anti-epileptic medication and bone health. *Osteoporosis International* 2007; **18**(2): 129-42. https://doi.org/10.1007/s00198-006-0185-z PMid: 17091219

2. Drezner MK. Treatment of anticonvulsant drug-induced bone disease. *Epilepsy and Behaviour* 2004; **5**(Suppl. 2): S41-47. https://doi.org/10.1016/j.yebeh.2003.11.028 PMid: 15123011

3. Cansu A, Yesilkaya E, Serdaroglu A, Hirfanoglu T, Camurdan O, Gaijlbahar O, *et al*. Evaluation of bone turnover in epileptic children using oxcarbazepine. *Pediatric Neurology* 2008; **39**: 266-71. https://doi.org/10.1016/j.pediatrneurol.2008.07.001 PMid: 18805365

4. Nakken KO, Tauboll E. Bone loss associated with use of antiepileptic drugs. *Expert Opinion on Drug Safety* 2010; **9**: 561-71. https://doi.org/10.1517/14740331003636475 PMid: 20201711

5. Lee RH, Lyles KW, Colon-Emeric C. A review of the effect of anticonvulsant medications on bone mineral density and fracture risk. *American Journal of Geriatric Pharmacotherapy* 2010; **8**: 34-46.

https://doi.org/10.1016/j.amjopharm.2010.02.003
PMid: 20226391 PMCid: PMC3570810

6. Teagarden DL, Meador KJ, Loring DW. Low vitamin D levels are common in patients with epilepsy. *Epilepsy Research* 2014; **108**: 1352-6. https://doi.org/10.1016/j.eplepsyres.2014.06.008
PMid: 25060996 PMCid: PMC4149948

7. Paris P. Avner ED, Treatment of seizures and epilepsy. In: Kliegman RM, Blum NJ, Shah SS, St Geme III, Tasker, Wilson, Behrman RE. Nelson Textbook of Pediatrics, 21st ed. Philadelphia: Elsevier; 2019. p. 3100-11.

8. Koo DL, Joo EY, Kim D, Hong SB. Effects of levetiracetam as a monotherapy on bone mineral density and biochemical markers of bone metabolism in patients with epilepsy. *Epilepsy Research* 2013; **104**: 134-9. https://doi.org/10.1016/j.eplepsyres.2012.09.002
PMid: 23032070

9. Lee R, Lyles K, Sloane R, Colón-Emeric C. The association of newer anticonvulsant medications and bone mineral density. *Endocrine Practice* 2012; **14**: 1-22. https://doi.org/10.4158/EP12119.OR
PMid: 22982796 PMCid: PMC3769485

10. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, *et al*. Global consensus recommendations on prevention and management of nutritional rickets. *Journal of Clinical Endocrinology and Metabolism* 2016; **101**: 394-415. https://doi.org/10.1210/jc.2015-2175
PMid: 26745253 PMCid: PMC4880117

11. Sreedeharan M, Deadathan K, Kunju PAM, Sasidharan B, Pillai JP, Amma MAV, *et al.* Vitamin D deficiency in ambulant children on carbamazepine or sodium valproate monotherapy. *Indian Pediatrics* 2018; **55**: 307-10. https://doi.org/10.1007/s13312-018-1273-9

12. Abdullah AT, Mousheer ZT. Vitamin D status in epileptic children on valproic acid; a case-control study. *Archives of Academic Emergency Medicine* 2020; **8**(1): e13.

13. Duygu A, Betül TG, Pelin DA, Hüseyin S, Dilek A, Baki A . Effects of oxcarbazepine and levetiracetam on calcium, ionized calcium and 25-OH vitamin-D3 levels in patients with epilepsy. *Clinical Psychopharmacology and Neuroscience* 2016; **14**(1): 74-8. https://doi.org/10.9758/cpn.2016.14.1.74
PMid: 26792043 PMCid: PMC4730931

14. Chaudhuri IR, Mridula KR, Rathnakishore CH, Balaraju B, Bandaru VCS. Association of 25-hydroxy vitamin D deficiency in paediatric epileptic patients. *Iranian Journal of Child Neurology* 2017; **11**(2): 48-56.