

**Vitamin D Deficiency in Ambulant Children on Carbamazepine or Sodium Valproate
Monotherapy**

**MINI SREEDHARAN¹, KALPANA DEVADATHAN¹, KUNJU PA MOHAMMED¹, BINDUSHA
SASIDHARAN², JAYAKUMAR PARAMESWARAN PILLAI³, MINIKUMARI AMMA VASUMATHY AMMA³
AND SABOORABEEGUM MUTHUBEEVI³**

*From Departments of ¹Pediatric Neurology, ²Pediatrics and ³Biochemistry; Government Medical
College, Thiruvananthapuram, India.*

*Correspondence to: Dr Kalpana Devadathan, Additional Professor, Department of Pediatric
Neurology, Government Medical College, Thiruvananthapuram, Kerala, India.
vijaykalpana10@gmail.com*

Received: May 17, 2017; **Initial review:** July 03, 2017; **Accepted:** January 03, 2018.

PII: S097475591600117

***Note:** This early-online version of the article is an unedited manuscript that has been accepted for
publication. It has been posted to the website for making it available to readers, ahead of its
publication in print. This version will undergo copy-editing, typesetting, and proofreading, before
final publication; and the text may undergo minor changes in the final version.*

ABSTRACT

Objective: To assess the effect of monotherapy with Carbamazepine (CBZ) and Sodium valproate (VPA) on serum 25-OH Vitamin D levels in children with epilepsy compared to controls.

Design: Cross-sectional study.

Setting: Outpatient department of a tertiary-care Pediatric Neurology centre, and a nearby day-care centre and school.

Study period: June 2012 to May 2013

Participants: Children with epilepsy aged 2 to 13 years on monotherapy with CBZ ($n=28$) or VPA ($n=28$) for at least 6 months; 109 age-matched controls from a nearby day-care centre and school.

Results: The median (IQR) values of 25 (OH) vitamin D was 18.0 ng/mL (13.7-27.3), 21.35 ng/mL (16.4 -25.2) and 30.5 ng/mL (19.1-43.7) in CBZ, VPA and control group, respectively ($P= 0.008$). 60.7% of patients in CBZ group and 35.7 % in VPA group had low 25 (OH) D levels (<20 ng/mL) compared to 27.8% in controls ($P=0.001$).The serum alkaline phosphatase level was higher in children on carbamazepine therapy ($P=0.001$) than controls.

Conclusion: This study identifies significant risk of vitamin D deficiency in ambulant children with epilepsy on monotherapy with Carbamazepine or Sodium Valproate. Children on antiepileptic drugs require regular monitoring of Vitamin D levels.

Biochemical abnormalities of bone mineral metabolism in children receiving antiepileptic-drugs, first identified in 1979 [1], is still a poorly studied topic from this region. In India, it is not a routine practice to supplement calcium or vitamin D in children on antiepileptic drugs; even in the UK, only 3% of Pediatric Neurologists were reported to be using prophylactic calcium and vitamin D therapy for children on anticonvulsants [2]. Available evidence indicates that vitamin D levels in the Indian population is below the optimal levels recommended by the US Institute of Medicine or US Endocrinology Society [3]. Majority of previous studies included children on polytherapy, institutionalized children or those with cerebral palsy who were indoors most of the time and from geographic areas with less sunshine, all of which are independent risk factors for low Vitamin D levels. We planned this study to assess the effect of monotherapy with two most commonly used AEDs, CBZ and VPA, on bone mineral metabolism in ambulatory children with epilepsy, with normal physical and mental development.

METHODS

Kerala is a state located at the southern tip of India and receives adequate sunshine throughout the year. Consecutive ambulant children (aged 2-13 years) with epilepsy and having apparently normal physical and mental development, and attending the Pediatric Neurology outpatient department of a tertiary referral Hospital in Kerala between June 2012 and May 2013, on either CBZ or VPA monotherapy for at least six months were included in the study after taking informed consent. The study protocol was approved by the Institutional Research Board and ethical clearance was granted by the Institutional Ethical Committee. Children who received Vitamin D or calcium supplementation, those on polytherapy with antiepileptic drugs (AEDs) or any chronic medications likely to affect bone metabolism like vitamin A, anabolic steroids, bisphosphonates, glucocorticoids, thiazides, calcitonin etc. and children with history of malabsorption, hypothyroidism, hepatic or renal diseases were excluded from the study. Control group included age-matched children attending a nearby day-care centre and a school, who were not on any continuous medications during the same period of study.

Demographic data including age, weight, height, BMI, average duration of exposure to sunlight per day, type of epilepsy, drugs used for treatment of epilepsy, duration of epilepsy, frequency of seizures per month, type of epilepsy, and duration of antiepileptic therapy were collected. Serum calcium, phosphorus, alkaline phosphatase, proteins, urea, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), fasting lipid profile and 25 –hydroxy Vitamin D [25 (OH) D] levels were assessed. Serum was separated by centrifuging at room temperature and then stored at -20⁰ C until vitamin D analysis was performed.

25 (OH) D level was analysed using ELISA 96T kit, Diametra, Italy (supplied by Tricore Medical Systems) within two weeks of sample collection. The lowest detectable concentration of 25 OH vitamin D is 0.3 ng/mL at 95% confidence limit. The intra assay variability was less than 6.4% and inter-assay variability was less than 6.95% (precision values as per the manufacturer). Children with serum level of 25 (OH) D level of more than 20 ng/mL (50 nmol/L) was considered sufficient, levels between 12-20 ng/mL (30-50 nmol/L) were considered insufficient, and below 12 ng/mL (<30 nmol/L) were considered deficient [4].

Sample size: A priori power calculation based on a previous study [5] indicated that a sample size of 30 children in each group would provide 80% power to detect a 10% difference in 25(OH) D concentration, using a two-tailed t-test, while controlling type I error rate to 5%.

Statistical analysis: Comparison of quantitative data between two groups were analyzed by independent sample t test or Mann Whitney U test according to the nature of the data. Comparison of quantitative data among more than two groups were analyzed by independent sample t test or Mann

Whitney U test according to the nature of the data. Comparison of quantitative data among more than two groups were analysed by ANOVA with post hoc analysis or Kruskal Wallis test. Association between qualitative data were analyzed by Chi-square test. A *P* value of <0.05 was taken as statistically significant. Data analysis was performed using SPSS version 22.0.

RESULTS

56 children with epilepsy (28 each receiving CBZ and VPA monotherapy) and 109 controls were enrolled in the study. None of the cases or controls had fractures, bone pain, muscle pain or muscle weakness. Clinical features of rickets were absent in both cases and controls (**Table I**). Serum Albumin and protein levels were in the normal range for all the three groups.

The median values of 25 (OH) vitamin D were 18.0 ng/mL (IQR 13.7-27.3), 21.35 ng/mL (IQR 16.4-25.2) and 30.1.5 ng/mL (IQR 19.1-43.7) in the CBZ, VPA and control group, respectively (*P*=0.008). Comparison between CBZ and Controls (*P*=0.01) and VPA and Controls (*P*=0.02) also showed significant differences (**Fig. 1**). The proportion of participants with subnormal vitamin D levels (<20 ng/mL) were significantly different between the groups (**Table II**). Alkaline phosphatase levels were significantly higher among children on CBZ compared to controls (*P*=0.001) (**Table III**).

DISCUSSION

This hospital-based cross-sectional study found a significantly high proportion of children receiving AEDs to have hypovitaminosis D, as compared to controls.

The strengths of our study include the strict selection criteria, exclusion of bed-ridden subjects and children on polytherapy with AEDs, and a large number of healthy control children. Lack of exposure to natural sunlight and osteoporosis following inactivity are two well-known contributors of osteoporosis. Some of the previous studies included significant percentage of children with cerebral palsy and on polytherapy [6]. Borusiak, *et al.* [7] found significant hypocalcemia and low levels of Vitamin D among 128 ambulant children on multiple antiepileptic drugs. As all the children in our study were on monotherapy, the alteration in various parameters can be attributed to the drug itself. The one important limitation of our study is the cross-sectional design; a longitudinal follow up of these children might have been a more accurate reflection of bone health in these children. Lee, *et al.* [8] longitudinally followed up children with epilepsy on antiepileptic drugs and found that a high proportion of children had hypovitaminosis D before the start of treatment and a significant decrease was noted between the initial and the follow up after 6 months [8], suggesting epilepsy as a risk factor for vitamin D deficiency which will be augmented by antiepileptic drugs. We did not attempt the bone mineral density estimation by DEXA scan which accurately reflects the bone health, because of

financial constraints and the risk of exposure to X-ray irradiation. Other parameters like osteocalcin levels, serum parathormone levels and calcitonin levels were also not assayed.

Fong, *et al.* [9] found that Indian ethnicity, immobility and polytherapy with AEDs were significant risk factors for low Vitamin D levels in children with epilepsy. Seth *et al.* found that 83% of non-ambulant children with cerebral palsy on antiepileptic drugs were vitamin D deficient [10]. Other authors have also reported low vitamin D levels in adults and children [11, 12]. However, Turan, *et al.* [13] noted that CBZ, VPA and phenobarbitone therapy did not show any effect on serum Vitamin D levels, as reported with VPA in another study [14]. Hepatic induction of the cytochrome P450 enzyme system leading to increased catabolism of vitamin D is the principal mechanism reported in case of enzyme inducing drugs like Carbamazepine [15]. Valproate inhibits the 25-hydroxylase activity on vitamin D in liver mitochondria without inhibiting the components of cytochrome P450-linked mono-oxygenase systems [16]. It is proposed that genetic variations like polymorphisms in Vitamin D receptor (VDR) gene may predispose one to Vitamin D deficiency [17]. The significant increase in serum alkaline phosphatase in children on carbamazepine may be attributed to changes in bone mineral metabolism due to its enzyme inducing property [18]. Mikati, *et al.* [19] studied the effect of low dose vs high dose vitamin D in ambulatory adults and children on antiepileptic drugs and found that high-dose vitamin D therapy substantially increased bone mineral density at several skeletal sites in adults. In children, both doses resulted in comparable increases in bone mass.

This study shows that serum 25 OH Vitamin D levels are significantly low in children on carbamazepine or valproate monotherapy. 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 and development, no limitation of physical activity and adequate exposure to sunshine. The impact of antiepileptic drugs on bone health is to be addressed by all Pediatricians, as early identification of vitamin D deficiency and supplementation of calcium and vitamin D can help majority of children on long term anticonvulsants.

Contributors: MS,KD: conceptualised the idea, design, collection of data, analysis, preparation of manuscript, review of literature; PAMK: supervised the study and edited the manuscript; BA: collection and analysis of data of the control population; JP: statistical analysis and preparation of tables and figures; MV: biochemical analysis and interpretation of data; SB: supervised the biochemical analysis

Funding: A research grant of Rs 50000/- from SAT Hospital endowment fund; *Competing interest:* None stated.

WHAT IS ALREADY KNOWN?

- Vitamin D deficiency is common in children with developmental delay on multiple antiepileptic drugs.

WHAT THIS STUDY ADDS?

- Vitamin D deficiency is also seen in normal children on monotherapy with Carbamazepine or Sodium Valproate alone.

REFERENCES

1. Offermann G, Pinto V, Kruse R. Antiepileptic drugs and vitamin D supplementation. *Epilepsia* 1979; 20:3-15.
2. Fong CY, Mallick AA, Buren CP, Patel JS. Evaluation and management of bone health in children with epilepsy on long-term antiepileptic drugs: United Kingdom survey of paediatric neurologists. *Eur J Paediatr Neurol*. 2011; 15:417-23.
3. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al*; Endocrine Society. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2011; 96:1911-30.
4. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, *et al*. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. *Horm Res Paediatr*. 2016; 85:83-106.
5. Ramelli V, Ramelli GP, Lava SA, Siegenthaler GM, Cantù M, Bianchetti MG, *et al*. Vitamin D status among children and adolescents on anticonvulsant drugs in southern Switzerland. *Swiss Med Wkly*. 2014; 13:w13996.
6. Coppola G, Fortunato D, Auricchio G, Mainolfi C, Operto FF, Pascotto A, *et al*. Bone mineral density in children, adolescents, and young adults with epilepsy. *Epilepsia*. 2009; 50:2140-6.
7. Borusiak P, Langer T, Heruth M, Karenfort M, Bettendorf U, Jenke AC. Antiepileptic drugs and bone metabolism in children: Data from 128 patients. *J Child Neurol*. 2013; 28:176-83.
8. Lee YJ, Park KM, Kim YM, Yeon GM, Nam SO. Longitudinal change of vitamin D status in children with epilepsy on antiepileptic drugs: prevalence and risk factors. *Pediatr Neurol*. 2015; 52:153-9.
9. Fong CY, Kong AN, Poh BK, Mohamed AR, Khoo TB, Ng RL, *et al*. Vitamin D deficiency and its risk factors in Malaysian children with epilepsy. *Epilepsia*. 2016; 57:1271-9.

10. Seth A, Aneja S, Singh R, Majumdar R, Sharma N, Gopinath M. Effect of impaired ambulation and anti-epileptic drug intake on vitamin D status of children with cerebral palsy. *Paediatr Int Child Health*. 2017; 37:193-8.
11. Misra A, Aggarwal A, Singh O, Sharma S. Effect of carbamazepine therapy on vitamin D and parathormone in epileptic children. *Pediatr Neurol* 2010; 43:320-4.
12. Menon B, Harinarayan CV. The effect of anti-epileptic drug therapy on serum 25-hydroxyvitamin D and parameters of calcium and bone metabolism—A longitudinal study. *Seizure*. 2010; 19:153-8.
13. Turan MI, Cayir A, Ozden O, Tan H. An examination of the mutual effects of valproic acid, carbamazepine, and phenobarbital on 25-hydroxyvitamin D levels and thyroid function tests. *Neuropediatrics*. 2014; 45:16-21.
14. Rauchenzauner M, Griesmacher A, Tataarczyk T, Haberlandt E, Strasak A, Zimmerhackl LB, *et al.* Chronic antiepileptic monotherapy, bone metabolism, and body composition in non-institutionalized children. *Dev Med Child Neurol*. 2010; 52:283-8.
15. Pack AM, Morrell MJ. Adverse effects of antiepileptic drugs on bone structure: epidemiology, mechanisms and therapeutic implications. *CNS Drugs*. 2001; 15:633-42.
16. Tomita S, Ohnishi J, Nakano M, Ichikawa Y. The effects of anticonvulsant drugs on vitamin D3-activating cytochrome P-450-linked monooxygenase systems. *J Steroid Biochem Mol Biol*. 1991; 39:479-85.
17. Uitterlinden AG, Fang Y, Bergink AP, van Meurs JB, van Leeuwen HP, Pols HA. The role of vitamin D receptor gene polymorphisms in bone biology. *Mol Cell Endocrinol*. 2002; 197:15-21.
18. Coppola G, Fortunato D, Auricchio G, Mainolfi C, Operto FF, Pascotto A, *et al.* Bone mineral density in children, adolescents, and young adults with epilepsy. *Epilepsia*. 2009; 50:2140-6.
19. Mikati MA, Dib L, Yamout B, Sawaya R, Rahi AC, Fuleihan Gel-H. Two randomized vitamin D trials in ambulatory patients on anticonvulsants: impact on bone. *Neurology*. 2006; 67:2005-11.

TABLE I DEMOGRAPHIC CHARACTERISTICS OF CHILDREN RECEIVING ANTIEPILEPTIC DRUGS AND CONTROLS

Variable	CBZ (n= 28)	VPA (n=28)	Control (n=109)	P
Age (y)	8.0 (2.9)	8.2 (2.9)	8.9 (2.2)	0.17
Male gender, n (%)	15 (53.6)	13 (46.4)	62 (56.9)	0.61
Weight (kg)	23.2 (7.37)	25.2 (10.49)	27.7 (9.9)	0.06
Height (cm)	124.3 (15.95)	126.7 (18.23)	129.7 (12.0)	0.86
BMI (Kg/ m ²)	14.7 (2.4)	15.1 (2.8)	16.2 (4.0)	0.09
Exposure to direct sunlight (hr/wk)	2.8 (2.1)	2.7(1.6)	3.01(1.83)	0.61
Duration of Epilepsy	23.4	24.9	-	0.79
Duration of AED therapy (months)	23.4 (6-86)	24.9 (6-84)	-	0.78

All values in mean (SD); AED: Antiepileptic drugs; BMI: Body mass index.

TABLE II VITAMIN D STATUS OF CASES AND CONTROLS

Drug	Vitamin D (ng/mL), no (%)		
	<12 (n=17)	12-20 (n=40)	>20 (n=108)
CBZ	5 (17.9)	12 (42.9)	11 (39.3)
VPA	4 (14.3)	6 (21.4)	18 (64.3)
Controls	8 (7.3)	22 (20.2)	79 (72.5)

P=0.02; (<12NG/ML– DEFICIENT, 12-20NG/ML INSUFFICIENT >20NG/ML-SUFFICIENT) [4].

TABLE III CALCIUM, PHOSPHORUS AND ALKALINE PHOSPHATASE LEVELS IN THOSE RECEIVING ANTIEPILEPTIC DRUGS AND CONTROLS

	<i>Carbamazepine</i> (n=28)	<i>Valproate</i> (n=28)	<i>Control</i> (n=109)	<i>P</i>
Calcium (mg/dL)	9.6 (0.6)	10.2 (0.8)	9.6 (1.4)	0.026
Phosphorus (mg/dL)	4.8 (0.6)	5.8 (5.2)	4.5 (0.7)	0.031
Alkaline phosphatase (IU/L) (267.8 (72.3)	191.2 (52.3)	219.2 (68.4)	<0.001

All values in mean (SD).

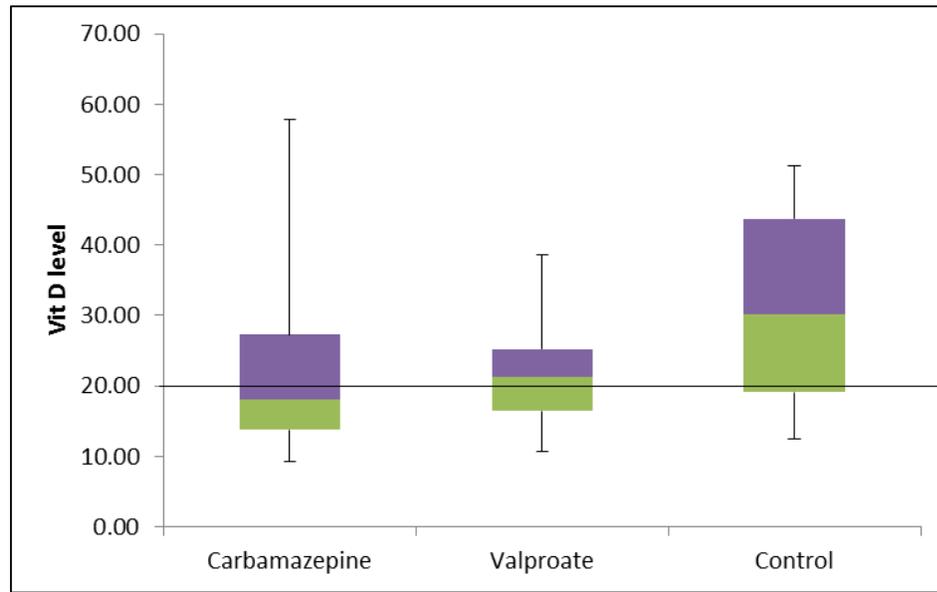


FIG. 1 Box and whisker plot showing vitamin D levels in children on valproate
Or carbamazepine monotherapy.