RESEARCH PAPER

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

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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 CBZ or VPA.

Keywords: *Adverse effect; Antiepileptic drugs; Hypo-vitaminosis D.*

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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, gluco-corticoids, 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 –20° C until vitamin D analysis was performed.

25 (OH) D level was analyzed using ELISA 96T kit (Diametra, Italy) 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].

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 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), 21.3 ng/mL (IQR 16.4 -25.2) and 30.1 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

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; CBZ: Carbamazepine; VPA: Sodium valproate.

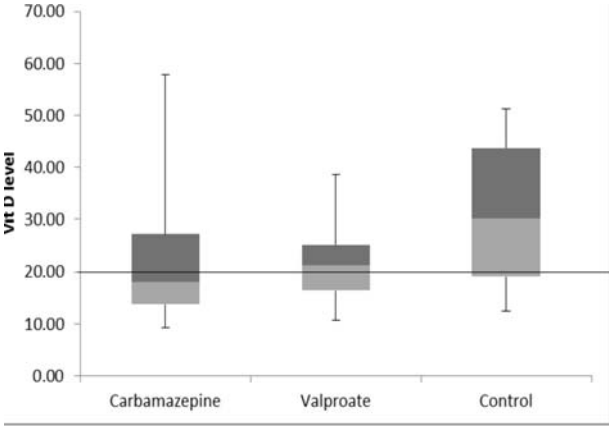

FIG. 1 *Box and whisker plot showing vitamin D levels in children on valproate Or carbamazepine monotherapy.*

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; (<12 ng/mL – Deficient, 12-20 ng/mL Insufficient, >20 ng/mL-Sufficient) [4], CBZ: Carbamazepine; VPA: Sodium valproate.

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 in levels was noted between the initial and the follow up after 6 months [8]. This suggested 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*. [10] found that 83% of non-ambulant children with cerebral palsy on antiepileptic drugs were vitamin D deficient. 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 also 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

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

	Carbamazepine (*n*=28)	*Valproate* (*n*=28)	*Control* (*n*=109)	*P*
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).

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 typically developing children on monotherapy with either Carbamazepine or Sodium valproate monotherapy.

identification of vitamin D deficiency and supplementation of calcium and vitamin D can help majority of children on long term anticonvulsants.

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