RESEARCH PAPER

Vitamin D, Bone Mineral Density and Serum IGF-1 Level in Non-ambulatory Children With Cerebral Palsy

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Objective: To compare serum 25-hydroxy vitamin D (25-OHD) status, bone mineral density and Insulin-like growth factor (IGF-1) level among children with cerebral palsy (CP) aged 1 to 8 years with age- and gender-matched controls. **Methods:** A cross-sectional study enrolled 30 children in each group: CP with epilepsy, CP without epilepsy, and healthy controls. Bone mineral density (BMD), serum 25-OHD levels, and serum insulin like growth factor (IGF)-1 levels were measured. **Results:** *z*-scores of BMD [-1.80 (1.03), -2.12 (0.85) vs -1.40 (0.90); *P*<0.01], 25-OHD levels [19.26 (8.28), 20.59 (8.92) Vs 26.79 (12.76) ng/mL; *P*<0.01] and IGF-1 levels [20.90 (6.42), 23.37 (8.11) vs 31.77 (11.21) ng/mL; *P*<0.01] were significantly low among children with CP with epilepsy, CP without epilepsy when compared to controls . **Conclusion:** Children with CP with or without comorbid epilepsy were prone to vitamin D deficiency, low bone mineral density and growth hormone axis suppression with low IGF-1 levels.

Keywords: *Antiepileptic drugs, BMD, Dyskinetic cerebral palsy, Epilepsy, Osteoporosis.*

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Cerebral palsy (CP) is a group of non-progressive disorders of movement and posture that result in activity limitation [1]. The motor disorder of cerebral palsy is often accompanied by disturbance of sensation, cognition, behavior, and epilepsy [2]. The risk factors that predispose children with CP to low bone mineral density include physical inactivity, lack of adequate sunlight exposure, poor nutrition, and intake of antiepileptic drugs [3-6]. Low bone mineral density predisposes to osteoporotic fractures leading to further inactivity and functional loss [7]. Non-ambulatory children with CP are also prone to vitamin D deficiency, low intake of calcium and low sunlight exposure [3,8].

Insulin like growth factor-1 (IGF-1) stimulates the synthesis of bone-specific proteins and osteoblasts in cell and organ cultures [9,10]. Both bone mineral density (BMD) and IGF-1 levels were found significantly low in children with spastic CP with higher gross motor functional classification system GMFCS [11]. Few antiepileptic drugs (AEDs) can cause decrease in BMD attributed to the increased enzyme induction and expression of CYP21 leading to increased inactivation of vitamin D [12]. The spectrum of CP in India is shifting from quadriplegic CP to more of diplegic CP over last 10 years [13]. Indian children with cerebral palsy are also at high risk of malnutrition [14]. There is limited literature on BMD among Indian children with CP. Hence, the present study was conducted to evaluate the vitamin D levels, IGF-1 levels, and BMD in non-ambulatory patients with CP.

METHODS

This was a cross-sectional study conducted in a tertiary care hospital from January, 2018 to April, 2019. Patients were recruited from pediatric and pediatric neurology outpatient units. Clearance was obtained from the institutional ethics committee and a written informed consent was obtained from the caregiver.

Thirty children aged 1-8 years were recruited in each of the following three groups: Group I – CP with GMFCS III-V with epilepsy (on AEDs for at least two years), Group II - CP without epilepsy, and Group III – age- and gender-matched healthy controls who belonged to same community. Children on vitamin D or calcium supplementation in last six months, and those with ambiguity in clinical diagnosis were excluded from the study.

After taking a thorough history, each participant underwent detailed clinical evaluation including anthropometric and functional ability assessment GMFCS. Bone mineral density **(**BMD) of lumbar vertebrae (L2-L4) was determined by dual energy *X*-ray absorptiometry (DXA). Serum 25-hydroxy vitamin D (25-OHD) levels were measured by radioimmunoassay (RIA). Serum IGF-1 levels

were measured by ELISA method using DRG IGF-1 600 ELISA (EIA-4140) kit.

Considering the proportion of vitamin D deficiency to be 66% in children with CP and 36.7% in healthy controls based on previous published data [3], a sample size of 28 (rounded to 30 in each group) was computed assuming an alpha error of 0.05 and power of 90%.

Statistical analysis: Outcome variables were compared between the three groups by using analysis of Variance (ANOVA) for multi-group comparisons followed by Tukey test. Logistic regression analysis was performed to determine the predictors of low BMD. A *P* value <0.05 was considered as significant.

RESULTS

A total of 90 children (30 in each of three groups) were enrolled in the study. Baseline characteristics were mostly comparable between the groups **(Table I)**. Of the 30 children with comorbid epilepsy, 21 (70%) were on valproate, 2 (2.1%) were on levetiracetam, 10 (33.3%) children were on clonazepam, 3 (10%) on vigabatrin and one child was on phenytoin.

Table I Baseline Characteristics of Children With Cerebral Palsy and Controls

Baseline characteristics	*Cerebral palsy with epilepsy (n=30)*	*Cerebral palsy without epilepsy (n=30)*	*Controls (n=30)*
Age in years[a]	3 (1.75-5.25)	3.5 (2-7)	4 (2-6.25)
Male gender	22 (73.3)	21 (70)	19 (63.3)
BMI[b,c]	14.89 (2.58)	14.07 (2.29)	16.21 (2.6)
WFA <-3 SD[d]	4 (13.3)	8 (26.7)	1 (3.3)
WFH <-3 SD	5 (16.7)	7 (23.3)	2 (6.7)
HFA <-3 SD[e]	4(13.3)	11(36.7)	12 (40.0)
Type of cerebral palsy			
Diplegia	6 (20)	7 (23.3)	-
Hemiplegia	6 (20)	2 (6.7)	
Quadriplegia	13 (43.3)	18 (60)	
Dyskinetic	1 (3.3)	2 (6.7)	
Mixed	4 (13.3)	1 (3.3)	
Etiology			
HIE	21 (70)	18 (60)	-
Prematurity	5 (16.7)	5 (16.7)	
Kernicterus	0	2 (6.7%)	
Meningitis	1 (3.3)	5 (16.7%)	
GMFCS			
Grade III	12 (40)	8 (26.7)	-
Grade IV	16 (53.3)	20 (66.7)	
Grade V	2 (6.7)	2 (6.7)	

Data expressed as no. (%), [a]median (IQR) or [b]mean (SD). GMFCS:Gross motor functional classification system. [c]P<0.001, [d]P<0.05, [e]P=0.05, BMI: body mass index; WFA: weight for age; WFH: weight for height; HFA: height for age; HIE: hypoxic ischemic encephalopathy.

The serum 25-OHD levels, IGF-1 levels and BMD *z*-score in the three groups are shown in **Table II**. Post hoc analysis revealed that BMD *Z*-scores (*P*=0.37), serum IGF-1 levels (*P*=0.53) and 25-OHD levels (*P*=0.87) were comparable between CP with epilepsy and CP without epilepsy. There was a significant correlation between serum IGF-1 levels and serum 25-OHD levels (r=0.88; *P*<0.001). Regression analysis model revealed that low BMD was predicted by lower age [OR (95% CI): 1.05 (1.02-1.08); *P*=0.005] and GMFCS level [OR (95% CI): 0.86 (0.71-1.01); *P*=0.038].

DISCUSSION

The present study revealed that comorbid epilepsy in children with CP did not affect BMD and serum 25-OHD levels. However, children with CP without epilepsy had significantly lower BMD when compared to age-matched controls. 25-OHD levels and IGF-1 levels were significantly low in children with CP with or without epilepsy when compared to controls.

The present study findings are in concurrence with another study which found that severity of functional ability (GMFCS level 4,5) correlated negatively with BMD [15]. However, majority of patients in the present study belonged to GMFCS IV and III.

Children with CP are prone to vitamin D deficiency owing to lower sunlight exposure, non-ambulatory status and poor nutritional intake. Findings of low vitamin D level among children with CP in this study were consistent with previous studies [8,12,15]. Similar serum vitamin D levels in those with or without epilepsy could be with use of non-enzyme inducing drugs in the epilepsy group in this study.

Table II Bone Mineral Density and Other Markers in Children With Cerebral Palsy (CP) and Healthy Controls

Variable	*CP with epilepsy (n=30)*	*CP without epilepsy (n=30)*	*Control (n=30)*
BMD (*z*- score)[a]	-1.80 (1.03)	-2.12 (0.85)	-1.40 (0.90)
25-OHD, ng/mL[b]	19.26 (8.28)	20.59 (8.92)	26.79 (12.76)
IGF-1, ng/mL[b]	20.90 (6.42)	23.37 (8.11)	31.77 (11.21)

Data expressed as mean (SD). [a]P<0.01 for CP without epilepsy and control and P=0.23 for CP with epilepsy and control; [b]P <0.01 for both CP with epilepsy and controls and CP without epilepsy and control. BMD – Bone mineral density; 25-OHD -25 hydroxy vitamin D; IGF-1-Insulin like growth factor.

WHAT THIS STUDY ADDS?

- Non-ambulatory children with cerebral palsy with or without epilepsy have low bone mineral density, low serum vitamin D levels, and low IGF-1 levels as compared to healthy controls.

GH and IGF-1 are principal regulators of bone-cell function. IGF-1 has stimulatory effects on the synthesis of bone specific proteins and osteoblastic proliferation in cell and organ cultures. Patients with CP have significantly low levels of IGF-1 and low BMD which makes them prone for osteoporotic fractures [4,11,15]. Low levels of IGF-1 in children with CP could also be attributed to malnutrition and liver disorders. In this context, GH level estimation would have been more useful than IGF-1 level. However, GH levels were not estimated as the procedure is tedious and there is need for hospital admission.

Selection of age- and gender-matched controls in the present study served as comparator for the observations of BMD, IGF-1 and vitamin D levels in children with CP. This study analyzed bone mineral metabolism in terms of suppression of growth hormone axis (IGF-1), bone mineralization (BMD) and nutritional status (vitamin D). Limitations of the study include cross-sectional descriptive study design with limited sample size and absence of liver function tests. Most of the enrolled children were non-ambulatory where factors like sunlight exposure, presence of feeding difficulties and history of use of dairy products would have been useful; however, these were not recorded in the study.

The study concludes that spinal BMD, serum vitamin D levels and serum IGF-1 levels were decreased in children with CP with and without epilepsy when compared to healthy controls. Future longitudinal studies are suggested with larger sample size looking for efficacy of interventions like structured exercise program, vitamin D, calcium, and GH supplementation among children with CP.

Ethics clearance: Institutional ethics committee, PLBD Sharma, PGIMS; No. BREC/Th/19/Ped 15; dated March 06, 2020.
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