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# Evaluation of vitamin D status in children with cerebral palsy

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## Abstract

### Objective

The current study was conducted to evaluate vitamin D status in children with cerebral palsy (CP) and its relations with associated risk factors.

### Patients and methods

The present research included 50 children with CP of both sexes compared with a control group of 20 healthy children with matched age and sex. Serum 25-hydroxyvitamin D, serum calcium, and phosphorus were measured and compared in cases and controls. The Gross Motor Function Classification System (GMFCS) was recorded, and children with GMFCS level I–III were considered ambulatory, whereas children with level IV–V were considered nonambulatory.

### Results

Median (interquartile range) serum vitamin D levels exhibited a significant decrease in the CP group (22.2 (14.48) ng/dl) as compared with the controls (33.1 (7.8) ng/dl). Twenty-two (44%) children with CP were vitamin D deficient versus two (10%) control groups. A significant difference was found in serum vitamin D level in those who were nonambulatory, had feeding problems in comparison with those who were ambulatory, and had no feeding problems. At the same time, there was no significant difference regarding antiepileptic drugs (AEDs) use. Serum vitamin D level was inversely correlated with nonambulation and feeding problems, whereas the correlation was not significant regarding AEDs use.

### Conclusion

Children with CP are susceptible to vitamin D deficiency, especially those who are nonambulatory, having feeding problems, whereas those who used AEDs are not.

**Keywords:** Ambulation, antiepileptics, cerebral palsy, vitamin D

## INTRODUCTION

Cerebral palsy (CP) represents the most prevalent reason for physical disability in childhood. It is characterized by an abnormality in fine and gross motor function, resulting in activity limitations and reduced participation [1]. Children with CP frequently undergo musculoskeletal disorders, such as spasticity, contractures, and bony deformities. Although CP represents a nonprogressive neurological disorder, reports showed that musculoskeletal disorders and function worsen with age [2].

CP has a different effect on functional status. The child may show variation in the ambulation, intellectual function, and tone disability. Growth and nutrition disorganization are considered secondary to health conditions in CP. Regardless

of the degree of motor impairments, children with CP are at risk for malnutrition [3].

Children with CP are susceptible to vitamin D deficiency due to inadequate intake, feeding problems, lack of sun exposure, nonambulation, reduced weight-bearing activity, anticonvulsants drugs interfering with vitamin D metabolism, associated obesity, and in institutionalized children [4].

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In addition, vitamin D deficiency could eventually lead to a loss in bone mineral density that is increasingly recognized as a risk factor for fractures [5]. It is also linked to hypovitaminosis D myopathy and poor muscular coordination [6].

## Aim

The current study evaluated vitamin D status among children with CP and its relation with associated risk factors.

## PATIENTS AND METHODS

The present work included 50 children with CP (diagnosed according to Bax *et al.*) [7] recruited from those attending the outpatient clinic of Physical Medicine and Rehabilitation in the National Institute of Neuromotor System, Giza, Egypt. The diagnosed children with CP were compared with 20 control participants recruited from Ahmed Maher Teaching Hospital, Cairo, Egypt. The Ethical Committee of GOTHI approved the study and written informed consent was provided by each child’s parents.

Children of both sexes below 18 years of age with confirmed CP were included. Those with chronic disease (renal, hepatic, or metabolic disease), clinical features of rickets, and who received any calcium or vitamin D supplements were excluded. The study was carried out from August 2020 to January 2021.

Evaluation of patients with CP in the form of general, musculoskeletal, and neurological examination was performed and recorded. History taking, including antiepileptic drugs (AEDs) use and feeding problems in the form of dysphagia, drooling, or teeth problems, was also documented.

Gross Motor Function Classification System (GMFCS) is a standard observational tool for assessing children’s ambulation having CP. GMFCS measures movement capabilities, including sitting, walking, and climbing stairs. Based on such a scale, children are classified into five grades (I–V), and their lower levels represent better gross motor skills, with I as the lightest and V as the most severe level [8]. Children with GMFCS level I–III were considered ambulatory, whereas children with level IV and V were considered nonambulatory.

Children with CP were categorized based on Surveillance of Cerebral Palsy in Europe into dyskinetic, ataxic, spastic unilateral, and spastic bilateral. Spastic bilateral was further subdivided into quadriplegia and diplegia [9].

A quantitative enzyme immunoassay was performed on serum samples to be assayed for 25-hydroxyvitamin D [25-OH-D] [10]. In the present study, we followed the Endocrine Society Guidelines [11], where vitamin D deficiency, insufficiency, and sufficient concentration corresponded to 25-OH-D less than 20, 20–29.9, and greater than equal to 30 ng/ml, respectively. Sampling was done during the summer and autumn seasons to minimize seasonal variations due to changes in exposure to sunlight.

Besides, calcium and phosphorus were assayed in serum, with reference of 8.4–10.2 and 2.5–4.9 mg/dl, respectively.

## Statistical analysis

All results were collected, tabulated, and subjected to statistical analysis using SPSS software, version 23. After normal distribution, the continuous data were displayed as mean ± SD. Categorical data were summarized as numbers and percentages. The Shapiro-Wilk test of normality was utilized to test the normality hypothesis of all quantitative variables toward further selecting proper parametric and nonparametric tests. Non-normal distributed data were described as median as well as the interquartile range (IQR). Mann-Whitney test and Kruskal-Wallis test were employed as the distribution of all variables was not normal. Bonferroni test was used for multiple comparisons, and the  $\chi^2$  test was utilized to compare categorical data. The rank biserial (rb) correlation coefficient was used for the correlation of nominal and continuous variables.  $P < 0.05$  was considered significant.

## RESULTS

The present study assessed 50 clinically diagnosed children with CP including 32 (64%) boys and 18 (36%) girls. Their mean age was  $9.62 \pm 2.69$  years ranging from 6 to 15 years. The control group consisted of 20 healthy children, 13 (65%) boys and 7 (35%) girls. Their mean age was  $8.9 \pm 2.2$  years ranging from 7 to 15 years. No significant differences were found between the patient and control groups regarding age ( $P = 0.3$ ) and sex ( $P = 0.9$ ) [Table 1].

Twenty-two patients (44%) belonging to the CP group had vitamin D deficiency, 13 (26%) had vitamin D insufficiency, and 15 (30%) had normal vitamin D concentration, whereas 2 participants (10%) belonging to the control group had vitamin D deficiency, 4 (20%) had vitamin D insufficiency, and 14 (70%) had normal vitamin D concentration. The difference was statistically significant ( $P < 0.05$ ). The median (IQR) serum vitamin D levels in patients with CP were 22.2 (14.48) ng/dl compared with 33.1 (7.8) ng/dl in the control group ( $P < 0.05$ ). The median (IQR) serum calcium and serum phosphorus levels were 9.4 (0.8) and 3.8 (1.3) mg/dl, respectively, in the CP group, whereas it was 10 (0.5) and 3.1 (1.2) mg/dl, respectively, in the control group. These differences were also statistically significant ( $P < 0.05$ ) [Table 2].

Thirty-four (68%) of children with CP (GMFCS levels I–III) considered ambulatory, and 16 (32%) children (GMFCS levels IV and V) considered nonambulatory. Eighteen (36%) use AEDs, whereas 32 (64%) do not use AEDs. Feeding problems were detected in 9 (18%) patients, whereas 41 (82%) had no feeding problems. There were a significantly lower

**Table 1: Demographic data of the patient and control**

|         | Group 1 Patient (50) | Group 11 Control (20) | P   |
|---------|----------------------|-----------------------|-----|
| Age (y) | 9.62±2.69            | 8.95±2.24             | 0.3 |
| Sex     |                      |                       |     |
| Boys    | 32 (64%)             | 13 (65%)              | 0.9 |
| Girls   | 18 (36%)             | 7 (35%)               |     |

$P > 0.05$  nonsignificant.

**Table 2: Comparison of laboratory findings of study groups**

|                    | Group 1 Patient (50) |              | Group 11 Control (20) |              | P     |
|--------------------|----------------------|--------------|-----------------------|--------------|-------|
|                    | No (%)               | Median (IQR) | No (%)                | Median (IQR) |       |
| 25-OH-D (ng/ml)    |                      |              |                       |              |       |
| Deficiency         | 22 (44%)             |              | 2 (10%)               |              | 0.005 |
| Insufficient       | 13 (26%)             |              | 4 (20%)               |              |       |
| Sufficient         | 15 (30%)             |              | 14 (70%)              |              |       |
| Total              | 50 (100%)            |              | 20 (100%)             |              |       |
| Ca (total) (mg/dl) | 9.4 (0.8)            |              | 10 (0.5)              |              | 0.001 |
| Phosphorus (mg/dl) | 3.85 (1.3)           |              | 3.1 (1.2)             |              | 0.04  |

25-OH-D, 25-hydroxyvitamin D; IQR, interquartile range.  $P < 0.05$  significant.

**Table 3: Serum vitamin D 25-OH-D according to associated risk factors**

|                           | n (%)   | 25-OH-D (ng/ml) Median (IQR) | P      |
|---------------------------|---------|------------------------------|--------|
| Ambulatory status (GMFCS) |         |                              |        |
| Yes                       | 34 (68) | 27.15 (13.8)                 | 0.0000 |
| No                        | 16 (32) | 16.4 (6.15)                  |        |
| AED use                   |         |                              |        |
| Yes                       | 18 (36) | 21.1 (11.6)                  | 0.1340 |
| No                        | 32 (64) | 24 (14.5)                    |        |
| Feeding problems          |         |                              |        |
| Yes                       | 9 (18)  | 16.6 (1.65)                  | 0.0000 |
| No                        | 41 (82) | 25.1 (13.5)                  |        |

25-OH-D, 25-hydroxyvitamin D; AED, antiepileptic drug; GMFCS, Gross Motor Function Classification System; IQR, interquartile range.

serum vitamin D level in those who were nonambulatory, had feeding problems in comparison with those who neither were nonambulatory nor had no feeding problems, whereas there was no significant difference in those who used AEDs compared with those who did not use AEDs [Table 3].

The distribution of CP subtypes was: 42% diplegic, 24% quadriplegic, 16% hemiplegic, 10% ataxic, and 8% dyskinetic. Spastic CP represents 82% of cases. There was a significant difference between CP subtypes and serum vitamin D level ( $P < 0.05$ ) [Table 4]. Using Bonferroni test showed that children with spastic unilateral had significantly higher vitamin D levels than children with spastic bilateral (diplegic and quadriplegic;  $P < 0.05$  each).

Our results showed that all cases (100%) with hemiplegia, 15 (71.4%) of diplegic and 2 (16.7%) of quadriplegic, were present in level I–III on the GMFCS scale. In comparison, 6 cases (28.6%) of diplegic and 10 (83.3%) of quadriplegic were present in level IV and V on the GMFCS scale.

Serum 25-OH-D levels showed a statistically significant negative correlation with nonambulant and feeding problems ( $P < 0.05$ ), whereas with AEDs use did not ( $P > 0.05$ ) [Table 5].

## DISCUSSION

Neuromuscular conditions such as CP have a greater risk of malnutrition than a healthy pediatric population. Malnutrition

is linked to more severe gross motor dysfunction [12]. These individuals are at higher risk of vitamin D deficiency. Consequently, we aimed to investigate the status of vitamin D among children with CP and its relation with associated risk factors.

Vitamin D deficiency was widespread among the study group. The median serum level of 25-OH-D exhibited a significant decrease in our patients with CP (22.2) ng/dl in comparison with the control group (33.1) ng/dl ( $P < 0.05$ ). A total of 44% of patients with CP had vitamin D deficiency, whereas it was 10% in the control participants. This was similar to a study among Egyptian normal school children who reported vitamin D deficiency (serum 25-OH-D  $< 20$  ng/ml) in 23 patients (11.5%)[13] and stated that this prevalence was lower than reported from different countries and attributed this difference to the sunny climate in Egypt in comparison with that in Europe as well as the USA.

The prevalence of vitamin D deficiency among children with CP in previous publications varies between 19% and 60%, compared with 44% in ours [4,14,15]. Presumably, these discrepancies in the prevalence of these studies result from variation in patients' selection factors, the cut-off point for 25-OH-D deficiency and climate differences, and thereby different exposure to sunshine.

Similar findings were reported by Toopchizadeh *et al.*[16] in their study, where 44.6% were deficient compared with 18.5% in the control group. However, our findings (44%) were lower than Seth *et al.* (60%)[15] and higher than Baer *et al.* (17%) [17]. In their study, Seth *et al.* [15]. attributed their high prevalence than Baer *et al.*[17] to darker skin pigmentation and absence of food fortification.

Although children from both groups were at risk of low vitamin D levels, those in the patient group had statistically significant lower levels. Low vitamin D concentrations have been reported previously in children with CP by many authors [4,14–17]. The recommended mechanisms among children with CP are multifactorial and include poor nutritional status, feeding problems, insufficient calcium intake, AEDs use, and nonambulatory status [18].

Children with disabilities that limit mobility such as CP are often housebound and have reduced sunlight exposure that

**Table 4: Serum vitamin D 25-OH-D according to CP subtypes**

|             | Categories                    | n (%)   | 25-OH-D (ng/ml) Median (IQR) | P       |
|-------------|-------------------------------|---------|------------------------------|---------|
| CP subtypes | Spastic bilateral Diplegic    | 21 (42) | 21 (9.95)                    | 0.00002 |
|             | Quadriplegic                  | 12 (24) | 16.9 (5.25)                  |         |
|             | Spastic unilateral Hemiplegic | 8 (16)  | 32.95 (1.03)                 |         |
|             | Ataxic                        | 5 (10)  | 27.1 (9.45)                  |         |
|             | Dyskinetic                    | 4 (8)   | 25.6 (14.9)                  |         |

25-OH-D, 25-hydroxyvitamin D; CP, cerebral palsy; IQR, interquartile range.  $P < 0.05$  significant.

**Table 5: Correlation between serum vitamin D 25-OH-D and risk factors**

| Parameter        | Rank biserial | P      |
|------------------|---------------|--------|
| Nonambulant      | -0.51         | 0.0000 |
| Feeding problems | -0.44         | 0.000  |
| AED use          | -0.2          | 0.08   |

AED, antiepileptic drug.

is the primary vitamin D source [6]. Outdoor activities are also significantly diminished among children with severe CP (GMFCS IV and V), which could cause low serum 25-OH-D concentrations in these patients [19].

In line with Akpınar[4] and Seth *et al.* [15], nonambulatory CP children in our study exhibited lower 25-OH-D levels than the ambulatory children with CP. In contrast to this, Finbråten *et al.*[20] reported lower vitamin D concentration in walkers than nonwalkers and explained this by extra vitamin D supplements to the latter group.

Besides nonambulation and inadequate exposure to sunlight, feeding problems also contribute to low vitamin D status. Our study showed significantly lower vitamin D levels in children with feeding problems than those without feeding problems; this was similar to the Akpınar study [4]. In addition, feeding problems influence nutrition and augment in parallel with severe gross motor dysfunction [21]; this was confirmed in our study, where 7 of 9 (77.7%) patients with GMFCS level IV–V had feeding problems.

The administration of AEDs remains another factor contributing to reduced vitamin D levels. Several AEDs induce hepatic CYP450 metabolism, remarkably increasing hepatic vitamin D metabolism, which leads to low vitamin D levels. Nevertheless, nonenzyme-inducing AEDs (e.g., valproic acid) have also been linked to low vitamin levels and, in turn, with poor bone health [22].

The present study showed that 18 patients (36%) were applied AEDs, and 8 (44.4%) of them were vitamin D deficient. This proportion (44.4%) is consistent with a previous Turkish study (47.4%) [4]. However, this proportion is higher than reported by Henderson (19%)[14] and lower than Tosun *et al.*[5] and Nettekoven *et al.* [23], who demonstrated vitamin D deficiency with 63% and 75%, respectively. They reported that this deficiency was most pronounced in patients taking combinations of different AEDs.

Although our study showed no significant difference regarding vitamin D level between AED and non-AED use, similar to some investigators [16,17,24], others had reported a significant difference [4,25]. Baer *et al.*[17] attributed this significant difference to the inclusion of nonambulatory among their study participants and did not evaluate them separately.

Herein, serum vitamin D levels were significantly negatively correlated with nonambulation and feeding problems ( $P < 0.05$ ), whereas there was no significance with AEDs use ( $P > 0.05$ ). This was in accordance with Henderson [14], who showed no correlation regarding AEDs, and Baer *et al.* [17], who reported a stronger negative association between nonambulant and vitamin D than AEDs. Also, Tosun *et al.*[5] proposed that lower serum vitamin D levels in CP and epilepsy patients are correlated with severe physical inactivity as well as insufficient sunlight exposure instead of AEDs. In contrast to our result, others found a significant correlation between vitamin D and AEDs [4,15,26].

Finally, our study showed a significant difference between CP subtypes regarding vitamin D levels. There were also significant differences between spastic hemiplegic and (either spastic diplegic or quadriplegic). This could be explained by GMFCS level, which is highly correlated with CP subtypes [27], where 100% of children with spastic hemiplegic were at level I–III, whereas 71% of children with spastic diplegic and 16% with spastic quadriplegic were at level I–III.

**Limitation**

This was a single-center study with small sample size.

**CONCLUSION**

Vitamin D deficiency is prevalent in children with CP in comparison with apparently healthy children. The presence of feeding problems and nonambulation was significantly linked to vitamin D deficiency in these children, whereas AEDs utilization was not.

**Conflicts of interest**

None.

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