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Original Article PT&R

Vitamin D status of children with cerebral palsy: Should vitamin D levels be checked in children with cerebral palsy?

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ABSTRACT

OBJECTIVE: We aimed to investigate the vitamin D status of children with cerebral palsy (CP).

METHODS: A total of 274 children (111 females and 163 males), aged between 1 and 19 years with CP, who came to the Physical Medicine and Rehabilitation, Pediatric Rehabilitation Outpatient Clinic between October 2013 and March 2017, were included in our study. Demographics, data concerning the details of each child's comorbidity, the Gross Motor Function Classification System (GMFCS), and Manual Ability Classification System (MACS) scores were recorded. The serum 25 hydroxy vitamin D [25(OH)D], calcium (Ca), phosphate (P), and parathormone (PTH) levels were also recorded.

RESULTS: The mean age of children with CP was 7.59±6.09 years. The distribution by the CP type was 24.8% spastic unilateral, 59.8% spastic bilateral, 1.4% dyskinetic, 0.7% ataxic, 7.6% mixed, and 5.1% unclassified. The serum 25(OH)D levels of the 235 children with CP were measured. There were 79 children at the 25(OH)D level ≤12 ng/ml, regarded as vitamin D deficiency; 62 children at the 25(OH)D level 12-≤20 ng/ml, considered as vitamin D insufficiency, 43 children at the 25(OH)D level 20-≤30 ng/ml, considered as vitamin D sufficiency, and 15 children at the 25(OH)D level >30 ng/ml. A total of 36 children were already taking vitamin D supplements. There was a significant correlation between the 25(OH)D levels and GMFCS and MACS levels and associated impairments such as the epilepsy history, intellectual delay, teeth problems, and growth retardation ($p<0.05$).

CONCLUSION: Our results revealed that the children with CP who are not ambulatory (GMFCS levels IV–V) and have associated impairments were prone to vitamin D deficiency, and thus should be checked for vitamin D.

Keywords: Anti-epileptics; cerebral palsy; gross motor function classification system; vitamin D.

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Cerebral palsy (CP) refers to a group of disorders in the development of motor and posture, occurring as a result of a non-progressive impairment of the brain, and it can have a wide range of consequences for the child. Various manifestations of the impaired brain may appear more significant in different children or at different life periods, for example, some aspects of the motor impairment, sensory loss, intellectual disability, epilepsy, musculoskeletal dysfunction, and many others may be more prominent at different stages of the life of a child with CP [1].

Children with CP present as a heterogeneous population and often have associative and co-mitigating conditions that also impose additional challenges. There are

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also many potential variables that may affect their growth and development of the bony skeleton.

Children with CP can be prone to low bone mineral density (BMD) for several reasons, such as poor nutritional status, vitamin D deficiency, non-ambulation, reduced weight-bearing activity, anti-epileptic drug (AED) intake, and pubertal delay [2].

Vitamin D deficiency is one of the important causes of low BMD in children with CP. Children with CP have inadequate dietary intake of calcium and vitamin D, due to feeding problems. They are usually housebound and have poor sunlight exposure. Epilepsy frequently coexists with CP, and many studies reported that the AED use contribute to low vitamin D status [3–6].

Adequate vitamin D levels are essential for normal skeletal system development and mineralization. There isn't enough scientific evidence on the prevalence and severity of the vitamin D deficiency in children with CP. We aimed to investigate the vitamin D status of children with CP and also its relation with the functional level and associated impairments.

MATERIALS AND METHODS

In this retrospective study, 274 children (111 females and 163 males), aged between 1 and 19 years with CP, who applied to the Physical Medicine and Rehabilitation, Pediatric Rehabilitation Outpatient Clinic between October 2013 and March 2017, were included. Demographics, data concerning the details of each patient's comorbidity, Gross Motor Function Classification System (GMFCS), and Manual Ability Classification System (MACS) scores were recorded. The serum 25-hydroxy-vitamin D [25(OH)D], calcium (Ca), phosphate (P), and parathormone (PTH) levels during autumn, winter, and beginning of the spring (from October until the end of March) were recorded. Children whose serum 25(OH)D levels were measured during summer were not included.

For the biochemical analysis, 10-hour fasting blood samples were collected in the morning using a vacutainer system (Becton–Dickinson, NJ, USA). The samples were then centrifuged for 10 minutes at 3000 rpm and further analyzed for biochemical parameters (Ca and P) using the Abbott Architect C16000 model autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA). The PTH and 25(OH)D measurements were performed by the chemiluminescent microparticle immunoassay method using the ARCHITECT system brand kits on the Abbott brand i2000SR immunological analyzer.

The serum 25(OH)D levels were considered deficient if 25(OH)D was ≤12 ng/ml, insufficient if 25(OH)D was in the range of 12–20 ng/ml, and sufficient if 25(OH)D was in the range of 20≤30 ng/ml [7].

The GMFCS-E&R is a widely used method for classifying the movement ability of children with cerebral palsy. It consists of 5 levels; Level I indicates independent mobility, and Level V indicates full dependency. The questionnaire is available for four different age groups: 2 to <4 years, 4 to <6 years, 6 to <12 years, and 12 to 18 years [8]. The Turkish version of the expanded and revised GMFCS was translated by Kerem-Gunel et al., and reliability was demonstrated by El et al. [9, 10].

The MACS was developed to describe how children with CP aged between 4 to 18 years use their hands when handling objects in daily activities [11]. Later on, the Mini-MACS for children with CP aged between 1 to 4 years was created by making adjustments to the MACS [12]. The MACS is a five-level system, where Level I represents the best manual ability, and Level V indicates that the child does not use his or her hands for functional purposes. Adaptation of the MACS to Turkish children with CP was done by Akpinar et al. [13]. Turkish versions of the MACS and the Mini-MACS can be found at www.macs.nu.

This study was approved by the Institutional Ethics Committee, and informed consent was obtained from the parents of each child (Approval number: 2017/6).

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics 22 software package (IBM Turk Limited Company, Istanbul, Turkey). The Shapiro–Wilk test was used to check whether the data were normally distributed. The chi-square test and Fisher Freeman Halton test were used for comparison of qualitative data, and Continuity (Yates) correction was used to determine the group causing the difference. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of 274 children with CP was 7.59±6.09 years. The distribution by the CP type was 24.8% spastic unilateral, 59.8% spastic bilateral, 1.4% dyskinetic, 0.7% ataxic, 7.6% mixed, and 5.1% unclassified. One hundred ninety-six (71.5%) children with CP were ambulatory

Table 1. Descriptive data of children (Types of CP and associated impairments)

	n=235	%
Types of CP		
Spastic unilateral (hemiplegic) CP	61	25.95
Spastic bilateral	142	60.42
Diplegic CP	89	
Quadriplegic CP	25	
Triplegic CP	28	
Dyskinetic CP	3	1.27
Ataxic CP	0	0.0
Mixed CP	16	6.80
Unclassified CP	11	4.68
Associated impairments		
Epilepsy	95	40.4
Intellectual delay	96	40.9
Hearing impairment	12	5.1
Visual impairment	59	25.1
Strabismus	83	35.3
Growth retardation	81	34.5
Behavioral problems	35	14.9
Respiratory dysfunction	28	11.9
Dysphagia	36	15.3
Drooling	45	19.1
Teeth problems	45	19.1
Metabolic disorders	8	3.4

CP: Cerebral palsy; n: Number.

Table 2. Serum 25(OH)D, PTH, Ca, and p levels

	n	%
25(OH)D (ng/ml) (n=235)		
≤12	79	33.6
>12 – ≤20	62	26.4
>20 – ≤30	43	18.3
>30	15	6.4
Taking already	36	15.3
Ca (mg/dl) (n=83)		
Low	2	2.4
Normal	80	96.4
High	1	1.2
P (mg/dl) (n=28)		
Low	1	3.6
Normal	27	96.4
High	0	0
PTH (pg/ml) (n=50)		
Low	1	2.0
Normal	41	82.0
High	8	16.0

25(OH)D: 25-hydroxy-vitamin D; PTH: Parathormone; Ca: Calcium; P: Phosphor; n: Number.

Table 3. The GMFCS and MACS levels

	n=235	%
GMFCS level		
I	31	13.2
II	59	25.1
III	79	33.6
IV	39	16.6
V	27	11.5
MACS level		
I	53	22.6
II	85	36.2
III	41	17.4
IV	33	14
V	23	9.8

GMFCS: Gross motor function classification system; MACS: Manual ability classification system; n: Number.

(GMFCS Levels I–III), and 78 (28.5%) children were non-ambulatory (GMFCS Levels IV–V).

The serum 25(OH)D levels of the 235 children with CP were recorded. The types of CP and associated impairments of these 235 children are shown at Table 1. There were 79 children at the 25(OH)D level ≤12 ng/ml regarded as vitamin D deficiency, 62 children at the 25(OH)D level 12-≤20 ng/ml regarded as vitamin D insufficiency, 43 children at the 25(OH)D level 20-≤30 ng/ml regarded as vitamin D sufficient, and 15 children at the 25(OH)D level >30 ng/ml. Thirty-six children were already taking vitamin D supplements. The serum 25(OH)D, PTH, Ca, and P levels are shown in Table 2.

The GMFCS and MACS levels are shown in Table 3. There was a significant correlation between the 25(OH)D levels and the GMFCS and MACS levels ($p<0.05$) (Table 4). Non-ambulatory children with CP had lower 25(OH)D levels than the ambulatory children. Children who were at the MACS Levels I and III had higher serum 25(OH)D levels than the children who were at the MACS Levels IV and V. Children who have been already

Table 4. Correlation between the 25(OH)D levels and GMFCS and MACS levels

	25(OH)D (ng/ml)							
	≤12		12 – ≤20		>20		Taking already	
	n	%	n	%	n	%	n	%
GMFCS level								
I	9	29	13	41.9	8	25.8	1	3.2
II	10	16.9	22	37.3	17	28.8	10	16.9
III	29	36.7	16	20.3	22	27.8	12	15.2
IV	18	46.2	9	23.1	8	20.5	4	10.3
V	13	48.1	2	7.4	3	11.1	9	33.3
p				0.002*				
Ambulatory (GMFCS I, II, III)	48	28.4	51	30.2	47	27.8	23	13.6
Non-ambulatory (GMFCS IV, V)	31	47	11	16.7	11	16.7	13	19.7
p				0.009*				
MACS level								
I	14	26.4	14	26.4	20	37.7	5	9.4
II	28	32.9	29	34.1	15	17.6	13	15.3
III	12	29.3	12	29.3	13	31.7	4	9.8
IV	14	42.4	4	12.1	8	24.2	7	21.2
V	5	47.8	3	13	2	8.7	7	30.4
p				0.002*				

*p<0.05; GMFCS: Gross motor function classification system; MACS: Manual ability classification system; 25(OH)D: 25-hydroxy-vitamin D; n: Number.

taking vitamin D were mostly at the MACS Level V.

There wasn't any correlation between the 25(OH) D levels and the CP types, except children classified as spastic bilateral CP had significantly lower vitamin D levels than the children classified as spastic unilateral CP ($p<0.05$).

Table 5 shows significant relations between the 25(OH)D levels and the associated impairments. There was a significant correlation between the 25(OH)D levels and AED use. Children who used AEDs also had lower 25(OH)D levels than the children who did not use AEDs. Children who had intellectual delay, teeth problems, and growth retardation had lower 25(OH)D levels than the children who didn't have intellectual delay, teeth problems, and growth retardation.

Nine children with CP had a history of previous fracture. Six of the 9 children had vitamin D deficiency, 2 had vitamin D insufficiency, and 1 have already been taking vitamin D. Five of the 9 children had an epilepsy history. Five children were ambulatory, and 4 children were non-ambulatory.

DISCUSSION

In this study, we investigated the vitamin D status of children with CP and its relation to the functional level and associated impairments to find an answer to the question if the investigation of vitamin D levels is necessary in this population. In our study population, 33.6% of the 235 children with CP were vitamin D deficient. Our results demonstrated that children with CP who were not ambulatory and had associated impairments such as epilepsy history, intellectual delay, teeth problems, and growth retardation were prone to vitamin D deficiency. This is in agreement with earlier studies, which revealed that non-ambulation and the AED use affect vitamin D levels [2, 3, 14].

Vitamin D deficiency is an increasing public health concern among individuals of all ages. The endocrine society recommends that children and adults at high risk of vitamin D deficiency, with factors or conditions that reduce the synthesis or intake of vitamin D, were candidates for preventative vitamin D supplementation [7].

Table 5. Correlation between the 25(OH)D levels and associated impairments

	25(OH)D (ng/ml)							
	≤12		12 – ≤20		>20		Taking already	
	n	%	n	%	n	%	n	%
Epilepsy								
(+)	45	47.4	26	27.4	6	6.3	18	18.9
(-)	34	24.3	36	25.7	52	37.1	18	12.9
p				0.001*				
Intellectual delay								
(+)	45	46.9	23	24	16	16.7	12	12.5
(-)	34	47.4	39	28.1	42	30.2	24	17.3
p				0.003*				
Growth retardation								
(+)	30	37	12	14.8	19	23.5	20	24.7
(-)	49	31.8	50	32.5	39	25.3	16	10.4
p				0.003*				
Teeth problems								
(+)	24	53.3	15	33.3	4	8.9	2	4.4
(-)	55	28.9	47	24.7	54	28.4	34	17.9
p				0.001*				

*p<0.05; 25(OH)D: 25-hydroxy-vitamin D; n: Number.

Neuromuscular conditions like CP may put an individual at higher calcium and vitamin D deficiency, as well as under-nutrition in general [4]. Thus, investigation of vitamin D status and addition of vitamin D supplements may be necessary in children with CP.

For children with CP, skeletal maturation can be delayed or accelerated as a result of multiple factors that affect the onset of puberty, including hormonal imbalance, nutrition, and severity of impairment. Feeding problems due to swallowing difficulty, impaired control of the lips and tongue, dental problems, malabsorption syndromes, and hepatic, renal, and endocrine disorders may contribute to growth retardation and impaired skeletal development. Adequate vitamin D levels are essential for normal skeletal development and mineralization. In our study, children who had intellectual delay, teeth problems, and growth retardation had significantly lower 25(OH)D levels than the children who didn't have intellectual delay, teeth problems, and growth retardation. Moreover, 29 of the 36 children who were already taking vitamin D supplements had dysphagia and teeth problems.

Individuals with disabilities that limit mobility like CP are often housebound and have reduced sunlight exposure. Thus, they are prone to low serum vitamin D concentrations [15]. The sun exposure is known to be a strong determinant of vitamin D status: More than 90% of people's vitamin D requirement comes from casual exposure to sunlight [16]. In non-ambulatory patients with CP, the sunlight exposure is expected to be limited. In our study population, non-ambulatory children with CP had lower 25(OH)D levels than the ambulatory children with CP, which is parallel with the literature [3].

In addition, children with CP are already at an increased risk of developing symptomatic osteoporosis because of decreased weight bearing. Low vitamin D levels in children with CP are also associated with muscle weakness and with hypovitaminosis D myopathy, characterized by decreased muscle strength and balance, muscle pain, paresthesias, and poor muscular coordination [15, 17]. Vitamin D also plays a role in host defense, and hypovitaminosis D may predispose to infections [18]. Therefore, sufficient vitamin D supplementation may have significant health benefits.

Furthermore, the AED intake can contribute to re-

duced serum vitamin D concentrations. Vitamin D deficiency is common in children who use AEDs. The AEDs commonly reported to affect vitamin D levels and bone health are the inducers of cytochrome P450 enzyme: carbamazepine, phenytoin, phenobarbitone, and primidone. However, studies have found that even valproic acid, a P450 enzyme inhibitor, affects vitamin D levels apart from accelerating bone loss by activating the osteoclasts directly [3, 19]. Nettekoven et al. demonstrated vitamin D deficiency in 75% of children taking AEDs, and this deficiency was most pronounced in patients taking combinations of different AEDs [6]. In our study population, 40.4% of the 235 children with CP were applied AED, and 47.4% of them were vitamin D deficient. We found a significant correlation between the 25(OH)D levels and the AED use in line with the literature [3, 4]. Unfortunately, we didn't report the types of AEDs used in our study. Another limitation of our study is that the serum PTH, Ca, and P levels were not measured for all children. We referred the children who had abnormal serum PTH, Ca, and P levels to the pediatric endocrinologist.

Clarke and Page suggested prevention of fractures through the use of vitamin D supplementation in children with CP. They pointed out that the pathological fractures in this group of patients can be extremely difficult to treat conservatively or surgically [20]. The prophylactic use of vitamin D dramatically reduced the rate of pathological fractures in children with CP [21]. Only 9 patients had a history of previous fracture in our study population, but 6 of the 9 children had vitamin D deficiency, 2 had vitamin D insufficiency, and 1 has already been taking vitamin D. Although normal bone growth probably cannot be expected, facilitating bone development and reducing the fracture incidence is critical to ensure the optimal quality of life for these children.

Clinical researches involving children with CP tend to focus on common symptoms, such as spasticity, pain, and mobility issues, and the viability and effectiveness of respective medical interventions. There has been very little attention on bone health in children with CP. Most clinicians who treat children with CP do not check vitamin D levels on a consistent basis. Our study showed that children with CP who are not ambulatory and have associated impairments such as epilepsy history, intellectual delay, teeth problems, and growth retardation should be checked for vitamin D deficiency. Prospective research is needed to determine the appropriate timing and dosing of vitamin D in children with CP.

Conclusion

Investigation of the vitamin D status and addition of vitamin D supplements may be necessary in children with CP, especially those who are not ambulatory and have associated impairments, such as an epilepsy history, intellectual delay, teeth problems, and growth retardation to maintain a good health.

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