ORIGINAL ARTICLE

Prevalence of Vitamin D Deficiency and Associated Risk Factors in Cerebral Palsy, A Study in North-West of Iran

How to Cite This Article: Toopchizadeh V, Barzegar M, Masoumi SH, Jahanjoo F. Prevalence of Vitamin D Deficiency and Associated Risk Factors in Cerebral Palsied Children in North-West of Iran: A Case-Control Study. Iran J Child Neurol.Spring 2018; 12(2):25-32

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Received: 08-Oct-2016
Last Revised : 16-Apr-2017
Accepted: 06- May -2017

Abstract

Objective

This study aimed to compare the prevalence of 25-hydroxy vitamin D deficiency in cerebral palsied (CP) with healthy control children and evaluate possible correlations between serum level of 25-hydroxy vitamin D and severity of CP and motor function.

Materials & Methods

In this case-control study, serum levels of 25-hydroxy vitamin D were evaluated in 65 children with CP and compared with 65 healthy children referred to Tabriz Pediatric Hospital, Tabriz, northwestern Iran in 2015. Blood samples were taken to measure levels of 25-hydroxy vitamin D, calcium, phosphorus and alkaline phosphatase. Regarding 25-hydroxy vitamin D levels, patients were classified as sufficient (≥30 ng/ml), insufficient (20-30 ng/ml) and deficient (<20 ng/ml).

Results

Mean 25-hydroxy vitamin D levels were 28.03±24.2 ng/ml in patients and 30±1.94 ng/ml in control group. 25-hydroxy vitamin D deficiency was seen in 44.6% of CP and 18.5% of healthy children. There was no significant difference in 25-hydroxy vitamin D levels between boys and girls, CP types and use of antiepileptics in case group. There was significant negative correlation between age and 25-hydroxy vitamin D levels (P=0.007). The correlation between 25-hydroxy vitamin D and Gross Motor Function Classification System was not significant.

Conclusion

25-hydroxy vitamin D deficiency is common in children with CP in comparison with healthy children. There was significant negative correlation between age and 25-hydroxy vitamin D levels. Routine measurement of 25-hydroxy vitamin D levels and its proper treatment is recommended to prevent its deficiency and subsequent consequences.

Keywords: Cerebral Palsy; Children; 25-hydroxy vitamin D; Motor function

Introduction

Cerebral palsy (CP) is the most common developmental disabilities in childhood which persist throughout the lifespan, is a clinical syndrome characterized by a persistent disorder in motor control and posture, and results from injury or dysfunction of the brain which is non-progressive (1, 2). The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication and behavior, epilepsy, and secondary musculoskeletal problems (3, 4). Children with CP experience limitations in their daily activities e.g. feeding, dressing, bathing, and mobility due to abnormal muscle tone, involuntary movement, unsteady gait, problems with balance, and poor social functioning (5, 6). They have also difficulties in swallowing. Feeding difficulty and malnutrition are two of the associated problems in cerebral palsy (7). These patients usually have poor overall nutrition and insufficient calcium and 25-hydroxy vitamin D intake (8).

In childhood, 25-hydroxy vitamin D is crucial for bone growth, mineralization, and musculoskeletal health because it promotes the assimilation of nutritional calcium and phosphate. It also regulated numerous cellular functions and would play an important role in the risk of metabolic syndrome, diabetes, autoimmune diseases, and some types of cancer (9). "Severe 25-hydroxy vitamin D deficiency (VDD) can result in rickets, metabolic bone disease, and hypocalcemia during infant and childhood growth" (10).

Because of nutritional deficiency, lack of sun exposure and sedentary behavior, osteopenia and rickets are common in children with CP. Patients have significantly decreased bone mineral density. In addition, painful fractures with minor traumas are common (11).

In this study, we aimed to assess prevalence of 25-hydroxy vitamin D deficiency in children with CP and possible correlations between 25-hydroxy vitamin D and severity of CP and motor function was evaluated.

Materials & Methods

In this case-control study, 25-hydroxy vitamin D status of 65 children with CP visiting outpatient clinics of Tabriz Pediatric Hospital, Tabriz, northwestern Iran in 2015 was evaluated and compared with healthy age and sex-matched children without history of chronic disease. Considering 95% confidence, power of 80% and according to the similar studies d=3.76, s_1=8.75 and s_2=6.24 we determined the sample size of 65 participants for each study group. Inclusion criteria were children of both sexes between 3-11 yr old with confirmed CP for case group and without any chronic disease for control group and no history of 25-hydroxy vitamin D or calcium supplement use in recent 2 months.

Ethics Committee of Tabriz University of Medical Sciences approved the study, and the written informed consent was obtained from the parents or legal guardians of children.

Demographic findings, history of supplement use, anti-epileptic medications use and Gross Motor Function Classification System (GMFCS) were recorded. Calcium, phosphorus, alkaline phosphatase and 25-hydroxy vitamin D levels were measured.

A peripheral non-fasting venous blood sample was obtained for analysis of multiple factors relating to nutrition or bone metabolism. The hospital laboratory at the respective institutions determined serum levels of calcium, phosphate, alkaline phosphatase using Pars Azmoon DGKC spectrophotometry kits in case group. Serum 25-hydroxy vitamin D was measured in the Sheikh Al-Rais Laboratory using ELISA Diasource kits (Louvain-la-Neuve, Belgium) in both study groups. All evaluations were done in the same season (spring and summer). The values for 25-hydroxy vitamin D levels ≥30 ng/ml were considered as sufficient, between 20 and 30 ng/ml as insufficient and <20 ng/ml as deficient (12).

GMFCS

GMFCS is a standard observational tool for assessing children with cerebral palsy that evaluated the ability to perform movements such as walking, climbing stairs, running and sitting. According to this scale, children are placed into five grades from I to V in order to their gross motor skills and lower levels represent better gross motor skills, with I as the lightest and V as the most severe level (13).

Statistical Analysis

All statistical tests were performed using SPSS for Windows Ver. 17 (Chicago, IL, USA). Quantitative data were presented as mean ± standard of error (S.E), while qualitative data were demonstrated as frequencies and percentages (percentage). After determining of frequency distribution of variables using Kolmogorov-Smirnov test, independent t-test, one-way and two-way ANOVA, chi-square test or Fisher's exact tests and Pearson correlation test, as appropriate were used to compare data between groups of patients. Pearson correlation was used to evaluate the correlation between variables. A P-value of <0.05 was considered statistically significant.

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences and informed consents were obtained from all study participants. The registry number of confirmation letter was 5/4/2767 and ethical code of this study was 91/1-7/16. The measurement of serum levels of vitamin D were paid by the Research Center of Physical Medicine and Rehabilitation.

Results

Sixty-five children with CP were evaluated for 25-hydroxy vitamin D and compared with 65 healthy children. Table 1 demonstrates demographic and laboratory findings between groups. There was no significant difference in age or gender between groups. 44.6% of cerebral palsied and 18.5% of control children had deficient levels of 25-hydroxy vitamin D, including 9 patients (13.8%) with severe deficiency (25-hydroxy vitamin D levels <10 ng/ml) in case group. Using post-hoc analysis showed that children with CP compared to normal group had significantly higher rate of vitamin D deficiency (P=0.008). Correlation between 25-hydroxy vitamin D and age was evaluated and there was significantly negative correlation between 25-hydroxy vitamin D and age (P=0.007). Using Two-way ANOVA, there was not a significant interaction between the effects of gender and groups on 25-hydroxy vitamin D levels (Table 1). Although main effect analysis did not show statistically significant differences, boy's 25-hydroxy vitamin D levels were considerably higher in case group.

Table 1. Demographic and laboratory findings of the study subjects

Variable	Categories	Case (n=65) (Mean ± S.E*) Or n (%)	Control (n=65) (Mean ± S.E*) Or n (%)	P-value
Age (yr)		5.9±0.30	6.23±0.37	0.523*
Gender	Boys	37 (56.9)	38(58.5)	0.859**
	Girls	28 (43.1)	27(41.55)	
25-hydroxy vitamin D (ng/ml)		28.03±24.2	30.00±1.94	0.583*
	Deficient	29(44.6)	12(18.5)	0.008**
	Insufficient	15(23.1)	26(40.0)	
	Sufficient	20(30.8)	26(40.0)	
	Toxicity	1 (1.5)	1(1.5)	
Age *25-hydroxy vitamin D		Case (n=65) r (P value)	Control (n=65) r (P value)	
		-0.333(0.007***)	-0.239 (0.55***)	
Gender * 25-hydroxy vitamin D	Categories	Case (n=65) Mean ± S.E* 25-hydroxy vitamin D levels	Control(n=65) Mean ± S.E* 25-hydroxy vitamin D levels	
	Boys	30.69 ± 3.36	29.45 ± 3.31	0.506 †
	Girls	24.52 ± 3.86	30.78 ± 3.93	
	P-value	0.491†		0.303 †

* Standard of Error *** Pearson Correlation Test * Independent-Samples t-test † Two-Way Anova
** Pearson Chi-Square Test ‡ Level of significance is considered to be <0.05

Patients were mostly spastic (73.8%) and quadriplegic type (43.1%). Antiepileptic medication was positive in 19 patients in case group (with phenobarbital). Most patients had GMFCS level II and III. The result from exact test indicated that prevalence of 25-hydroxy vitamin D Deficiency was the same between GMFC categories (GMFCI- II- III vs. IV-V). Lower calcium levels (<8.5 µg/dL) were observed only in one patient (15%). Elevated levels of alkaline phosphatase and high serum phosphorus (>4.5 µg/dL) were observed in 29 (44.61%) and 22 (33.84%), respectively. None of the cases had lower serum levels of phosphorus.

We found no significant difference between boys and girls, CP types and use of antiepileptics regarding 25-hydroxy vitamin D levels (Table 2). Correlation between 25-hydroxy vitamin D with GMFCS level, age, and laboratory findings was evaluated and there was only significantly negative correlation between 25-hydroxy vitamin D and age (r=-0.333, P=0.007).

Discussion

We evaluated the 25-hydroxy vitamin D levels in

Table 2. 25-hydroxy vitamin D levels between CP types, GMFCS groups, and Antiepileptic usage status

<table>
<tr><th>Variable</th><th>Categories</th><th>n (%)</th><th colspan="4">Mean ± S.E
25-hydroxy vitamin D levels</th><th>P-value</th></tr>
<tr><td rowspan="3">Type of CP, n (%)</td><td>Hemiplegic</td><td>14 (21.5)</td><td colspan="4">21.34 ± 5.29</td><td rowspan="3">0.220**</td></tr>
<tr><td>Quadriplegic</td><td>28 (43.1)</td><td colspan="4">35.02 ± 5.90</td></tr>
<tr><td>Diplegic</td><td>23 (35.1)</td><td colspan="4">23.60 ± 2.70</td></tr>
<tr><td rowspan="4">Type of CP, n (%)</td><td>Spastic</td><td>48 (73.8)</td><td colspan="4">24.84 ± 2.70</td><td rowspan="5">0.389**</td></tr>
<tr><td>Hypotonic</td><td>10 (15.4)</td><td colspan="4">36.42 ± 6.76</td></tr>
<tr><td>Dyskinetic</td><td>2 (3.1)</td><td colspan="4">25.12 ± 3.38</td></tr>
<tr><td>Mixed</td><td>5 (7.7)</td><td colspan="4">43.08 ± 27.06</td></tr>
<tr><td rowspan="2">GMFCS, n (%)</td><td>I,II,III</td><td>56 (86.2)</td><td colspan="4">28.61± 24.09</td></tr>
<tr><td>IV,V</td><td>9 (13.8)</td><td colspan="4">24.33 ± 20.87</td><td>0.174**</td></tr>
<tr><td rowspan="2">Antiepileptic use</td><td>Yes</td><td>19 (29.2)</td><td colspan="4">26.78 ± 4.11</td><td rowspan="2">0.791***</td></tr>
<tr><td>No</td><td>46 (70.8)</td><td colspan="4">28.55 ± 3.92</td></tr>
<tr><td rowspan="4">GMFCS Categories</td><td rowspan="2">Categories</td><td colspan="5">25-hydroxy vitamin D</td><td></td></tr>
<tr><td>Deficient</td><td>Insufficient</td><td>Sufficient</td><td>Toxicity</td><td></td><td></td></tr>
<tr><td>I- II- III</td><td>24 (42.85)</td><td>14 (25%)</td><td>17 (30.35)</td><td>1 (1.7)</td><td></td><td rowspan="2">0.664†</td></tr>
<tr><td>IV- V</td><td>5 (55.55)</td><td>1 (11.11%)</td><td>3 (33.33)</td><td>0 (0)</td><td></td></tr>
</table>

* Standard of Error. † Exact Test. ** Kruskal Wallis Test. ‡ Level of significance is considered to be <0.05.
*** Independent-Samples t-test.

cerebral palsied and healthy children and observed higher rate of 25-hydroxy vitamin D deficiency (44.6%) and severe deficiency (13.8%) in CP cases.

There is different reported prevalence of 25-hydroxy vitamin D deficiency around the world varying from 40% to 52.4% (14, 15). Among Iranian normal school-aged children and adolescents, two studies have reported high prevalence rate (16, 17). Children with CP have higher rate of 25-hydroxy vitamin D deficiency compared to normal children. However, in our study, it was similar to studies in other countries (14,15). The higher rate of 25-hydroxy vitamin D deficiency among children is suggested to be related to insufficient sun exposure, low physical activity, advancing age and pubertal stage (14-17). Recommended mechanisms among children with CP are poor nutritional status, oral motor dysfunction, feeding problems, insufficient calcium intake, non-ambulatory status, and anticonvulsant use (18). Antiepileptic drugs are associated with reduced 25-hydroxy vitamin D levels, rickets, and osteomalacia (19, 20). Anti-epileptic drugs, especially enzyme-inducing ones, may result in accelerated vitamin D metabolism and so vitamin D levels are decreased and consequently result in bone mineral density reduction (21). However, we found no significant difference regarding 25-hydroxy vitamin D levels in children treated or not with antiepileptics. Due to the small sample of the study and patients in the groups with and without antiepileptic drug use, these results should be interpreted with caution.

25-hydroxy vitamin D insufficiency is more prevalent among girls (22). 25-hydroxy vitamin D deficiency is higher in girls than boys in normal population are

(15). However, in this study, although girls had lower 25-hydroxy vitamin D levels, the difference between boys and girls was not significant. In our region, the girls are dressed as most parts are covered and so have less sun exposure, which could be a cause for this finding.

We also found that with increase in the subjects' age, the 25-hydroxy vitamin D levels are reduced and are more prone to 25-hydroxy vitamin D deficiency. Similarly, the frequency of 25-hydroxy vitamin D deficiency was increased with age (15). Lower outdoor activity and consequently lower sun exposure are regarded as one of the causes for higher 25-hydroxy vitamin D deficiency rate in older age (23).

We also found no correlation between significant difference in 25-hydroxy vitamin D levels among spastic, dyskinetic, mixed and hypotonic CP as well as quadriplegic, hemiplegic and diplegic types. In addition, there was no significant difference between GMFCS level and 25-hydroxy vitamin D levels. GMFCS was not associated with 25-hydroxy vitamin D levels (8). However, children in GMFCS level I to II have less severe bone deficits than children in GMFCS level III to IV (24). Most cases in our study were in GMFCS level II and III and levels I, IV and V constituted only 12 cases, which may be reason for not finding significant association.

Some limitation of our study should be considered as follows: The large sample for GMFCS II and III was the main cause limited our analysis. The data with regard to degree of sun exposure could not be objectively assessed. The study was done on small sample of patients and in an area with different climates and cultures.

In conclusion, prevalence of 25-hydroxy vitamin D deficiency was higher in this study population in comparison with healthy control children. There was significant negative correlation between age and 25-hydroxy vitamin D levels Routine measurement of 25-hydroxy vitamin D levels and proper treatment if needed, is recommended to prevent 25-hydroxy vitamin D deficiency and subsequent consequences. Future research should focus on the benefits of 25-hydroxy vitamin D supplementation for this population.

Acknowledgment

This research was supported by Physical Medicine and Rehabilitation Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. We are especially grateful to the patients and their parents for participation and cooperation in this research. We take responsibility for the integrity and accuracy of the data. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences and informed consents were obtained from all study participants. The registry number of confirmation letter was 5/4/2767 and ethical code of this study was 91/1-7/16. The measurement of serum levels of vitamin D were paid by the Research Center of Physical Medicine and Rehabilitation.

Authors' Contribution

Vahideh Toopchizadeh participated in the design of the study and drafted the manuscript. Mohammad Barzegar conceived of the study, and participated in its design and coordination and helped to draft the manuscript. Shahab Masoumi participated in data collection. Fatemeh Jahanjoo performed the statistical analysis.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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