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Short Communication

Association of functional levels and serum vitamin D among children with cerebral palsy

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Abstract

Children with cerebral palsy are more susceptible to deficiency of vitamin D due to less sunlight exposure, poor dietary intake, and long-term use of anti-epileptic drugs, which disrupt their metabolism, resulting in changes in bone mineral density, osteopenia, and rickets. The aim of this study was to investigate the association between gross motor functional levels and vitamin D status in cerebral palsy children. A cross-sectional study was conducted among cerebral palsy patients aged 2–6 years at Haji Adam Malik Hospital, Medan, Indonesia, from November 2022 to April 2023. The levels of the gross motor function classification system (GMFCS) were classified into two groups: ambulatory (GMFCS I, II, III) and non-ambulatory (GMFCS IV, V). Vitamin D status was classified based on serum 25(OH)D levels as normal (30–100 ng/mL), insufficiency (21–29 ng/mL), and deficiency (<20 ng/mL). A total of 85 children with cerebral palsy were included in this study, categorized as ambulatory (n=28, 32.9%) and non-ambulatory (n=57, 67%). The mean serum vitamin D level was 21.92±9.07 ng/L. As many as 54.1% (n=46) of the total children were categorized as vitamin D deficient, followed by insufficient (n=25, 29.4%) and normal vitamin D level (n=14, 16.5%). Age (p=0.310), sex (p=0.590), nutritional status (p=0.269), and types of cerebral palsy (p=0.271) were not associated with vitamin D status. However, there was a significant association between GMFCS levels and circulating vitamin D levels (p<0.001). In a logistic regression model, children classified as ambulatory were more likely to have better vitamin D status, with odds ratios of 12.30 (95%CI: 3.61–41.90) for deficient versus insufficient and 10.93 (95%CI: 2.67–44.69) for deficient versus normal. In conclusion, there was a significant association between functional levels and vitamin D status among children with cerebral palsy.

Keywords: Cerebral palsy, 25(OH)D, vitamin D, GMFCS, ambulatory

Introduction

Cerebral palsy is a disorder characterized as a non-progressive and persistent motor disorder with impaired motor function and posture due to brain damage that leads to lifelong disability [1]. Cerebral palsy has a high morbidity rate and causes a significant disability burden worldwide [2]. Its prevalence from population-based studies ranges from 2–4 per 1000 live births [3-5]. Unfortunately, the disease epidemiology in Indonesia is still lacking [6].

Cerebral palsy may be accompanied by various disorders or abnormalities, including perceptual, sensory, musculoskeletal, cognitive, and behavioral disorders, as well as communicative defects, epilepsy, feeding difficulties, nutritional disorders, and reduced bone density due to deficiencies in vitamins and minerals, particularly 25(OH)D and calcium [7,8].

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Vitamin D deficiency is an increasing public health concern across all age groups. It can lead to hypocalcemia, metabolic bone disease, osteopenia, and rickets. In cerebral palsy children, it is a crucial cause of poor bone mineral density and can result in pathological fractures even with minor trauma [9].

Vitamin D deficiency is higher among cerebral palsy children compared to children without limitation of activity, due to lack of sun exposure, limited physical activity, use of anti-epileptic drugs and low dietary intake of calcium and vitamin D related to oral/motor dysfunction [8,10]. Previous studies in multiple countries have reported that 50–60% of cerebral palsy children have vitamin D deficiency [8,10-12]. However, Indonesia has yet to publish its data regarding the case. Vitamin D supplementation might be necessary for individuals who are prone to vitamin D deficiency, including those with cerebral palsy [13,14]. Hence, the aim of this study was to explore the correlation between functional levels and vitamin D status in children with cerebral palsy.

Methods

Study design

A cross-sectional study was conducted at the pediatric outpatient clinic of Haji Adam Malik Hospital, Medan, Indonesia. The objective was to evaluate the relationship between gross motor function and serum vitamin D status in children with cerebral palsy. The study employed total and consecutive sampling from November 2022 to April 2023, screening 101 children with cerebral palsy. Of these, 85 children met the inclusion criteria, while 16 were excluded because they either received vitamin D supplements (n=8) or did not receive parental permission (n=8).

Eligibility criteria

The study included children with cerebral palsy aged 2 to 6 years who attended the pediatric outpatient clinic of Haji Adam Malik Hospital, Medan, Indonesia, between November 2022 and April 2023. The diagnosis of cerebral palsy was confirmed by a neuro-pediatrician based on the World Health Organization (WHO) guidelines, which defined cerebral palsy as a group of permanent movement and posture disorders caused by non-progressive disturbances in the developing brain. The diagnostic process included a detailed clinical evaluation of motor impairments, a review of developmental history, and neuroimaging studies to identify brain abnormalities and exclude other progressive or genetic conditions. Children who had consumed vitamin D supplements at doses of 400 IU/day or higher, as well as those receiving medications such as systemic corticosteroids, rifampicin, or antiretrovirals known to affect vitamin D metabolism, were excluded from the study.

Data collection

The sociodemographic data were collected through interviews during outpatient clinic visits and from patients' medical records. These data included age, sex, nutritional status, type of cerebral palsy, presence of epilepsy, use of anti-epileptic drugs, and functional levels. Nutritional status was assessed using the WHO child growth standards, with malnourished defined as a weight-for-height z-score below -3 standard deviations (SD), moderately nourished as a z-score between -2 and -3 SD, and adequately nourished as a z-score above -2 SD. The type of cerebral palsy was classified into spastic, hypotonic, and dyskinetic. Spastic cerebral palsy, characterized by increased muscle tone, was further categorized into three subtypes according to previously published guidelines [1]. These subtypes include spastic hemiplegia, affecting one side of the body; spastic diplegia, primarily affecting the lower extremities; and spastic quadriplegia, involving all four limbs and often the trunk. Hypotonic cerebral palsy was defined as reduced muscle tone and significant muscle weakness, while dyskinetic cerebral palsy involved extrapyramidal symptoms such as involuntary movements, dystonia, or choreoathetosis.

Functional levels were assessed using the Gross Motor Function Classification System (GMFCS), which evaluates gross motor function in children with cerebral palsy. GMFCS includes five levels: level I for children who can walk without limitations, level II for those who can walk with limitations in balance or coordination, and level III for children requiring assistive mobility devices or orthoses to walk. Level IV is for children who can function in a sitting position with

limited self-mobility but cannot walk, while level V is for those who require support for sitting and are entirely dependent on mobility. For analytical purposes, GMFCS levels were grouped into two categories: ambulatory (GMFCS levels I–III), representing children capable of walking either independently or with assistance, and non-ambulatory (GMFCS levels IV–V), representing children unable to walk and requiring support for mobility.

Serum 25-hydroxyvitamin D [25(OH)D] levels were measured from a 5 ml venous blood sample obtained from each participant. The samples were analyzed using the Enzyme-Linked Fluorescent Assay (ELFA) in the central laboratory of Haji Adam Malik Hospital. Vitamin D status was classified based on 25(OH)D levels into normal (30–100 ng/mL), insufficient (21–29 ng/mL), and deficient (<20 ng/mL) categories in accordance with a published recommendation [14].

Data analysis

The normality of the data distribution was tested using Shapiro-Wilk. Bivariate analysis was carried out using Chi-square for categorical data and Kruskal Wallis for continuous data. Logistic regression was further performed to analyze the relationship of vitamin D status with anti-epileptic drug intake history and GMFCS categories (ambulatory versus non-ambulatory). The threshold for statistical significance in all analyses was $p<0.05$. All statistical analyses were conducted using SPSS version 23.0 (IBM, New York, US).

Results

Characteristics of patients

A total of 85 children with cerebral palsy were included in the study, with their characteristics are presented in **Table 1**. The patients had a median age of 2.58 (2.25–4.25) years and consisted of 44 boys and 41 girls. Most of the children were moderately nourished (n=35, 41.2%), while 34.1% (n=29) were malnourished. The majority of children had spastic cerebral palsy (n=64, 75.3%), with spastic quadriplegia and spastic diplegia being the most common subtypes. Over fifty percent of the children (n=49, 57.6%) had anti-epileptic drugs intake. Most of the children were non-ambulatory (n=57, 67%). The lowest vitamin D level was 9.07 ng/mL, and the highest was 55.6 ng/mL. Most of the subjects experienced a deficiency of vitamin D (n=46, 4.1%). The highest number of vitamin D deficiency cases was found among children with GMFCS level V (n=25, 86.2%). Non-ambulatory children had a higher prevalence of vitamin D deficiency (n=41, 72%) than those who were ambulatory (n=5, 17.8%).

Association between functional levels and vitamin D status

Bivariate analysis indicated that age ($p=0.310$) and sex ($p=0.590$) were not associated with vitamin D status among children with cerebral palsy (**Table 1**). Being malnourished, moderately nourished, and adequately nourished were not associated with vitamin D status. Similarly, no association was found between the type of cerebral palsy and vitamin D status ($p=0.271$). Median values of 25(OH)D levels were 16.0 (9.4–19.8) ng/mL, 23.2 (20.0–29.6) ng/mL, and 35.8(29.5–44.5) ng/mL in those with deficient, insufficient, and normal vitamin D status, respectively. While there was no association between anti-epileptic drug intake and vitamin D status ($p=0.218$), a strong association was observed in GMFCS levels ($p<0.001$) (**Table 1**). These results were further confirmed by the logistic regression analysis, where the results are presented in **Table 2**. The analysis suggested that the anti-epileptic drug intake is not associated with vitamin D status (*p*-values of 0.662 and 0.301, respectively). As compared to deficient vitamin D levels, children with ambulatory status were found to be associated with higher odds of insufficient vitamin D levels (OR: 12.30 (95%CI:3.61 to 41.90)) with *p*-value <0.001. Similarly, those with ambulatory were more likely to have normal vitamin D levels compared to those without ambulatory (OR: 10.93 (95%CI: 2.67 to 44.69), $p<0.001$).

Table 1. Association of vitamin D status with the subjects' characteristics

Variables	Total, n	Vitamin D status, n (%)			*p*-value [a]
		Deficiency (n=46)	Insufficiency (n=25)	Normal (n=14)	
Age, median (min-max) (year)	2.58 (2.25–4.25)	2.67 (2–6)	3.83 (2–6)	2.71 (2–6.89)	0.310[b]
Sex					
Male	44 (51.8)	26 (61.4)	12 (25)	6 (13.6)	0.590
Female	41 (48.2)	20 (48.8)	13 (31.7)	8 (19.5)	
Nutritional status					
Malnourished	29 (34.1)	19 (65.5)	4 (13.8)	6 (20.7)	0.269
Moderately nourished	35 (41.2)	15 (42.9)	15 (42.9)	5 (14.3)	
Adequately nourished	21 (24.7)	12 (61.9)	6 (23.8)	3 (14.3)	
Type of cerebral palsy					
Dyskinetic	1 (1.2)	0	1 (100)	0	0.271
Hypotonic	20 (23.5)	9 (45)	7 (35)	4 (20)	
Diplegic spastic	6 (7.1)	13 (44.8)	11 (38)	5 (17.2)	
Hemiplegic spastics	29 (34.1)	2 (33.3)	3 (50)	1 (16.7)	
Quadriplegic spastics	29 (34.1)	22 (75.9)	3 (10.3)	4 (13.8)	
25(OH)D level, median (min-max) (ng/mL)	19.0 (9.40–44.8)	16.0 (9.4–19.8)	23.2 (20.0–29.6)	35.8 (29.5–44.5)	<0.001[b]
Anti-epileptic drugs					
Yes	49 (57.6)	27 (55.1)	16 (32.7)	6 (12.2)	0.218
No	36 (42.4)	19 (52.8)	9 (25)	8 (22.2)	
GMFCS levels					
II	3 (3.5)	0 (0)	1 (33.4)	2 (66.6)	<0.001
III	25 (29.4)	5 (20)	14 (56)	6 (24)	
IV	28 (32.9)	16 (57.1)	7 (25)	5 (17.9)	
V	29 (34.1)	25 (86.2)	3 (10.3)	1 (3.5)	
GMFCS categories					
Ambulatory (levels II and III)	28 (32.9)	5 (17.8)	15 (53.6)	8 (28.6)	
Non-ambulatory (levels IV and V)	57 (67)	41 (72)	10 (17.5)	6 (10.5)	<0.001

[a] Otherwise stated, the *p*-value was estimated based on Chi-square test
[b] Analyzed using Kruskal-Wallis test

Table 2. Association of vitamin D and anti-epileptic drug intake or GMFCS based on logistic regression

Vitamin D status	Anti-epileptic drug intake		GMFCS categories	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Deficiency (n=46)	Ref.	Ref.	Ref.	Ref.
Insufficiency (n=25)	1.25 (0.46 to 3.42)	0.662	12.30 (3.61 to 41.90)	<0.001
Normal (n=14)	0.53 (0.16 to 1.77)	0.301	10.93 (2.67 to 44.69)	<0.001

Discussion

Herein, more than half of the children with cerebral palsy in this study were vitamin D deficient, followed by those who were insufficient. Similarly, a case-control study in Iran reported a deficiency rate of 44.6% among children with cerebral palsy [8]. In contrast, a study from Turkey found lower rates of vitamin D deficiency (28.8%) and insufficiency (22.6%), attributed to the stricter threshold for deficiency (≤12 ng/mL) used in that study [12]. Functional levels, assessed using the GMFCS, were found to be significant predictors of vitamin D status in the present study. Non-ambulatory children with cerebral palsy had significantly lower 25(OH)D levels and higher rates of vitamin D deficiency compared to ambulatory children. These findings are consistent with previous studies that linked severe motor impairments to an increased risk of vitamin D deficiency [10,18-20]. A Turkish prospective study concluded that the severity of motor impairment, as graded by GMFCS, is a strong predictor of low vitamin D levels and reduced bone mineral density [19]. Another study noted that non-ambulatory children with cerebral palsy and a history of epilepsy are particularly vulnerable to vitamin D deficiency [18].

The susceptibility of children with cerebral palsy to vitamin D deficiency can be attributed to several factors, including reduced sun exposure, limited mobility, feeding difficulties, and the use of antiepileptic drugs [15-17]. Sunlight exposure, a critical source of vitamin D, is particularly

limited in non-ambulatory children with cerebral palsy, who often remain indoors due to mobility issues. With approximately 90% of vitamin D synthesis reliant on sunlight, these children are at a heightened risk of deficiency, especially in populations with poor dietary intake [10,18,22]. Feeding difficulties further exacerbate this risk. Abnormal muscle tone often leads to swallowing challenges, resulting in chronic malnutrition and reduced vitamin D and calcium intake over time [8,12,21]. These challenges are more severe in children with greater motor impairments. A prospective case-control study from India reported significant associations between vitamin D deficiency and factors such as feeding difficulties, poor sunlight exposure, malnutrition, antiepileptic drug use, cerebral palsy type, and functional levels [12].

Interestingly, the present study did not find a significant correlation between antiepileptic drug use and vitamin D status. This finding contrasts with other studies, which have associated antiepileptic drugs with higher rates of vitamin D deficiency, often leading to complications such as osteomalacia and rickets [10,12,21,23]. Discrepancies in findings may arise from differences in study populations, demographic factors, and the primary determinants of vitamin D status. For instance, in our population, vitamin D levels were primarily affected by mobility and physical activity, with less influence from nutritional status. This could be because vitamin D levels were already severely compromised, reducing the impact of nutritional factors. Variations in the types and dosages of antiepileptic drugs assessed, as well as inconsistent methods for measuring vitamin D levels, further contribute to these discrepancies. Antiepileptic drugs like carbamazepine, phenytoin, and phenobarbital, which induce cytochrome P450 enzymes, are known to interfere with vitamin D metabolism and bone health [21]. A systematic review and meta-analysis identified antiepileptic drugs with cytochrome P450 inducers as posing the highest risk for vitamin D deficiency [23]. Discrepancies in findings may arise from differences in study populations, demographic factors, and the primary determinants of vitamin D status. In our population, vitamin D levels were primarily influenced by mobility and physical activity, which overshadowed the potential effects of nutritional status. The severe baseline deficiency in vitamin D may have masked any additional contributions from nutritional intake. Moreover, demographic variations, such as differences in epilepsy prevalence and the type and duration of antiepileptic drug use, could further explain the inconsistencies. Antiepileptic drugs, particularly those inducing cytochrome P450 enzymes, can significantly alter vitamin D metabolism, yet their impact may vary depending on dosage, drug combinations, and underlying health conditions.

For a judicious interpretation, there are several limitations in this study that should be considered. The study did not assess the quantity or quality of sunlight exposure, nor did it evaluate bone metabolism markers or bone mineral density. Additionally, the study did not account for the duration, type, or dosage of antiepileptic drugs used, limiting its ability to fully evaluate the impact of antiepileptic drugs on vitamin D status. Furthermore, as a cross-sectional study, it captures data at a single point in time, making it challenging to establish causal relationships or observe changes over time. This design limitation may also affect the ability to understand the long-term impacts of mobility, antiepileptic drug use, and nutritional factors on vitamin D status.

Conclusion

Vitamin D deficiency is prevalent among children with cerebral palsy, particularly in non-ambulatory individuals. Functional levels, as assessed using the GMFCS, were significant predictors of vitamin D status. Future studies should adopt longitudinal designs to better assess causal relationships and the long-term impacts of various factors on vitamin D status. Additionally, comprehensive evaluations of sunlight exposure, bone metabolism markers, and the detailed effects of antiepileptic drug use are essential.

Ethics approval

This research was approved by the Clinical Research Ethics Committee of Universitas Sumatera Utara, Medan (No 991/KEPK/USU/2022). Informed consent was obtained from parents or legal guardians of all participants prior to their inclusion in the study.

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Competing interests

The authors have no known conflict of interest in relation to the publication of this work.

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Underlying data

Data underlying this study can be requested from the corresponding authors upon reasonable request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tools and methodologies in the following capacity for manuscript writing support: AI-based language models, such as ChatGPT was employed to language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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