ORIGINAL ARTICLE

Vitamin D Insufficiency in Children with Chronic Neurological Diseases: Frequency and Causative Factors

How to Cite This Article: Isik G, Ustundag B, Dogan Y. Vitamin D Insufficiency in Children with Chronic Neurological Diseases: Frequency and Causative Factors. Iran J Child Neurol. Spring 2023; 17 (2): 31-38

Gunes ISIK MD[1]
Bilal USTUNDAG MD[2],
Yasar DOGAN MD[3],

1. Adiyaman University Faculty of Medicine, Pediatric Nephrology Department, Adiyaman, Turkey
2. Firat University, Faculty of Medicine, Division of Clinical Biochemistry, Elazig, Turkey
3. Firat University, Faculty of Medicine, Division of Pediatric Gastroenterology, Hepatology and Nutrition, Elazig, Turkey

Corresponding Author
sik g. MD
Pediatric Nephrology, Adiyaman University Faculty of Medicine, Adiyaman, Turkey
Email:drgunes07@hotmail.com

Received: 26-Aug-2021
Accepted: 16-Jun-2022
Published: 15- Mar-2023

Abstract

Objective

Vitamin D insufficiency/rickets is a metabolic bone disease that leads to insufficient mineralization of bone. Chronic neurological diseases, including cerebral palsy (CP), convulsive disorders, neural tube defects, myopathy, immobility, lack of sun exposure, inadequate nutrition, and antiepileptic drugs (AEDs) can cause vitamin D insufficiency and osteopenia in children.

Materials & Methods

In this study, the authors searched the frequency and causative factors of vitamin D insufficiency in children with chronic neurological diseases such as CP, hypoxic-ischemic encephalopathy, mental motor retardation, epilepsy, neurodegenerative and neuromuscular diseases, meningitis-encephalitis sequelae, neural tube defects, paralysis, and paresis. This cross-sectional study included 108 children (forty-five [41.6%] females; sixty-three [58.4%] males), aged between one and 18 years with chronic neurological diseases, and a control group of thirty age-matched healthy children (16 [53.3%] females; 14 [46.7%] males.

Results

Vitamin D levels were significantly lower, and parathyroid hormone (PTH) levels were significantly higher in the patient group than in the control group ($p<0.05$). The patient group was divided into four subgroups: (i) Epilepsy (n=41; 38%), (ii) Neural tube defects (n=14; 13%), (iii) CP (n=21; 19%), and (iv) other diseases (neurodegenerative and neuromuscular diseases, meningitis sequelae, intracranial hemorrhage, psychomotor retardation, hypoxic-ischemic

encephalopathy) (n=32; 30%) to identify any differences in the measured levels. In the patient group, eighty-three (76.9%) had vitamin D deficiency, and 17 (15.7%) had vitamin D insufficiency, while in the control group, twenty-one (70%) had vitamin D insufficiency. The use of AEDs had no significant effect on serum Ca, P, ALP, PTH, or vitamin D levels ($p>0.05$), and serum Ca levels were significantly higher in ambulant patients than in non-ambulant patients ($p<0.05$). Vitamin D levels were significantly higher in the non-ambulant than in the ambulant patients ($p<0.05$). No rickets was determined in the control group, while in the patient group, nine (8.3%) had level-1 rickets, six (5.6%) had level-2 rickets, and two (1.9%) had level-3 rickets.

Conclusion

Children with chronic neurological diseases have low serum vitamin D levels, and vitamin D prophylaxis is essential in this group.

Keywords: Vitamin D Levels; Chronic Neurological Diseases; Pediatrics; Antiepileptic Treatment; Prophylaxis

DOI: 10.22037/ijcn.v17i2.35938

Introduction

The common causes of vitamin D deficiency and osteopenia in children with chronic neurological diseases (CP, convulsive disorders, neural tube defects, and myopathies) are; inadequate sunlight exposure, nutritional problems because of impaired chewing and swallowing functions, inadequate Ca intake and antiepileptic drugs (AED) use (3).

Rickets is a metabolic bone disease that causes inadequate mineralization of bone, remaining a critical health problem, particularly in developing countries. Vitamin D is essential for bone growth in children and prevents bone loss in adults. The clinical manifestation of nutritional vitamin D deficiency in children is rickets. Vitamin D deficiency is a clinically diagnosed vitamin D deficiency without clinical symptoms or signs of rickets (1).

The principal physiological function of vitamin D is to increase calcium (Ca) and phosphorus (P) absorption from the intestine for the maintenance of serum Ca-P levels within the normal physiological range, together with the parathyroid hormone (PTH). Vitamin D has metabolic and neuromuscular functions in the body and provides bone mineralization in the skeletal system (2). Vitamin D deficiency and osteopenia are common in children with chronic neurological diseases because of limited movement, inadequate sunlight exposure, nutritional problems due to impaired oro-motor functions, inadequate Ca intake,, and the side effects of AED (3).

This study aims to determine the prevalence of 25(OH) D3 deficiency/rickets and the influential

factors associated with 25(OH) D3 deficiency in patients with chronic neurological problems. As a further goal, the differences in vitamin D levels in the chronic neurological disease subgroups (epilepsy, neural tube defects, CP, and other diseases [neurodegenerative and neuromuscular diseases, meningitis sequelae, intracranial hemorrhage, psychomotor retardation, hypoxic-ischemic encephalopathy]) are investigated. The study also identifies the main factors contributing to vitamin D insufficiencies, such as nutrition, Ca intake, daily sun exposure, mobility, and AED use. Vitamin D is crucial in maintaining bone health, CNS neurotransmissions, and healthy children's immune functions. In epileptic patients, low vitamin D levels tend to increase the frequency of seizures, with the least occurring in the summer and the most during the winter (4-5).

In the present study, vitamin D levels were significantly lower, and PTH levels were significantly higher in the patient group than in the control group. The use of AEDs had no significant effect on serum Ca, P, ALP, PTH, or vitamin D levels. However, there was a positive effect of daily adequate calcium intake on vitamin D levels.

Materials & Methods

This cross-sectional study included 108 children with chronic neurological problems aged between one and 18 years and a control group of thirty age-matched healthy children who were admitted to the Pediatric Clinic of the Medical School Hospital of Firat University. Patients with CP, hypoxic-ischemic encephalopathy, mental motor retardation, epilepsy, neurodegenerative and neuromuscular diseases, meningitis-encephalitis sequelae, neural tube defects, neuronal migration defect, paralysis, and paresis, and those undergoing treatment with AEDs for at least the last two years, were included in the study. Patients taking vitamin D supplements and on Ca therapy, those with vitamin D-resistant rickets, chronic liver and kidney problems, other metabolic bone diseases, and skeletal dysplasia were excluded from the study. In addition to routine examinations, serum levels of Ca, P, alkaline phosphatase (ALP), PTH, and 25(OH) D3 were evaluated in each patient. The daily Ca intake calculated based on the participants' three-day diet lists. Vitamin D deficiency was defined as a serum 25(OH) D3 level of <20 ng/mL and insufficiency as a 25(OH) D3 level of 21–30 ng/mL. Cases with vitamin D deficiency with clinical, laboratory, and radiological findings were referred to as rickets. One physician examined cases for craniotabes, rachitic rosary, Harrison groove, pectus excavatus, pectus carinatus, kyphosis, lordosis, scoliosis, X- bine, 0-bine deformities, enlargement of the wrists and knees were noted. The radiological findings were also recorded. Rickets was classified as stages 1, 2, and 3 according to serum levels of Ca, P, alkaline phosphatase (ALP), PTH, and 25(OH) D3. Rickets stages were defined as mentioned; Stage I rickets; low serum 25-OH-D level and hypocalcemia and euphosphatemia; 1, 25-OH2-D is normal/high. Stage II rickets, low serum 25-OH-D level, high PTH, normocalcemia, hypophosphatemia, and a slight increase in the skeletal alkaline phosphatase level. Stage III rickets; severe 25-OH-D deficiency with hypocalcemia, hypophosphatemia, and increased alkaline phosphatase; bones have overt signs of demineralization (6). Normal serum calcium was defined as 8.8–10.8 mg/dl in 1-16 years. Normal serum phosphorus level was defined as 3.8-6.5 mg/dl for 1-3 years, as 3.7-5.6 mg/dl for 4-11 years, as 2.9-5.4 mg/dl for 12-15 years, as 2.7-4.7 mg/dl for 16-19 years. Normal

serum parathormone was defined as 12–65 pg/ml. Additionally, normal serum ALP levels in all ages and sex groups were evaluated separately (7).

The patients' daily sun exposure (hours/day during summer/winter) and ongoing physical therapies were recorded for each participant.

Statistical analysis

The data were analyzed using IBM SPSS Statistics for Windows (Armonk, NY: IBM Corp.). The normality of the distribution of continuous variables was assessed using a One-sample Kolmogorov-Smirnov test; parametric data were compared using a Standard t-test, and non-parametric data were compared with a Mann-Whitney U test. Group means were compared using an Independent Samples t-test, and the means for more than two groups were compared using a One-Way ANOVA test followed by a Post HOC LSD test. Correlations were determined using Pearson's and Spearman's Correlation Coefficients. A p-value of <0.05 was considered significant.

Results

The study included 108 patients with chronic neurological disorders and thirty healthy controls. The patient group comprised forty-five (41.6%) females and sixty-three (58.4%) males, and the control group comprised 16 (53.3%) females and 14 (46.7%) males. No significant difference was found between the patient and control groups regarding age and gender ($p>0.05$). Although no significant difference was found between the two groups in terms of Ca, P, and ALP levels ($p>0.05$) (Table 1), vitamin D levels were significantly lower, and PTH levels were significantly higher in the patient group than in the control group ($p<0.05$) (Table 2) when the patient group was divided into four subgroups: (i) Epilepsy (n=41; 38%), (ii) Neural tube defects (n=14; 13%), (iii) CP (n=21; 19%), and (iv) other diseases (neurodegenerative and neuromuscular diseases, meningitis sequelae, intracranial hemorrhage, psychomotor retardation, hypoxic-ischemic encephalopathy) (n=32; 30%). Vitamin D levels were significantly lower in epilepsy and other groups than in the CP group ($p<0.05$), while no significant difference was found among other groups ($p>0.05$) (Table 2).

The positive effect of an adequate daily calcium intake on vitamin D levels was statistically significant ($p<0.05$). Seventy-six (70.3%) patients were using AEDs, with twenty-seven (35%) on valproic acid, 16 (21%) on phenobarbital, six (8%) on Tegretol, four (5%) on clonazepam and five (6.5%) on other AEDs (three [3.9%] on oxcarbazepine, one [1.3%] on topiramate, and one [1.3%] on phenytoin), while 18 (23%) patients were using multiple AEDs. However, no significant differences were found between the AED types in serum P and ALP levels ($p>0.05$). Serum Ca levels were significantly lower in patients treated *with* valproic acid compared to *those* using other AEDs (oxcarbazepine, topiramate, phenytoin) and those not using AEDs ($p<0.05$ for both). No significant difference was identified between the patients regarding body weight and height percentiles or serum Ca, PTH, and vitamin D levels ($p>0.05$ for all).

No significant correlation was found between the duration of sun exposure (hours/day) and vitamin D levels. In the control group, vitamin D levels were 21–30 ng/ml in twenty-one (70%) and ≥31 ng/ml in nine (30%) of the participants. In the patient group, vitamin D levels were <20 ng/ml in eighty-three (76.9%), 21–30 ng/ml in 17 (15.7%), and ≥31 ng/ml in eight (7.4%) of the participants.

No rickets was detected in the control group, whereas in the patient group, stage I rickets were detected in nine (8.3%), stage II rickets in six (5.6%), and stage III rickets in two (1.9%) patients.

Table 1. Comparison of serum Ca, P, ALP, PTH, and vitamin D levels

	Patient group (n=108)	Control group (n=30)	p
Ca (mg/dl)	9.6±0.8	9.7±0.5	>0.05
P (mg/dl)	4.0±0.9	4.1±0.6	>0.05
ALP (U/L)	173.9±85	171.3±66	>0.05
Vitamin D (ng/ml)	13.2 (2.6-38)	26.1 (21.4-42.9)	**<0.05**
PTH (pg/ml)	48.8 (8.1-863)	30 (12.6-95.8)	**<0.05**

Table 2. Comparison of vitamin D levels according to comorbidities

Patient group (n=108)	Vitamin D level (ng/ml)
Epilepsy (n=41) (38%)	11.8 (2.6-36)
CP (n=21) (19%)	17.6 (7.2-38)
Meningomyelocele (n=14) (13%)	14.9 (6.1-35)
Others (n=32) (%30)	12 (3.9-37.8)

The use of AEDs had no significant effect on serum Ca, P, ALP, PTH, and vitamin D levels (p>0.05) (Table 3). Serum Ca levels were significantly higher in ambulant patients than in non-ambulant patients (p<0.05). In contrast, vitamin D levels were significantly higher in the non-ambulant patients than in the ambulant patients (p<0.05).

Table 3. Effect of AED use on serum Ca, P, ALP, PTH, and vitamin D levels in the patient group

	AED use		*p*
	Yes (n=76)	No (n=32)	
P (mg/dl)	4.05±0.8	3.9±1.1	>0.05
ALP (U/L)	187±77	142±94	>0.05
Vitamin D (ng/ml)	12.2 (2.6-38)	14.9 (5.4-35.7)	>0.05
Ca (mg/dl)	9.8 (7.4-11.3)	9.6 (6.9-10.9)	>0.05
PTH (pg/ml)	49.7 (8.1-863)	44.6 (13.8-186)	>0.05

Discussion

The effect of AEDs on bone health and vitamin D concentrations in epileptic patients remains a primary concern. In this study, AEDs were found to have no significant effect on serum Ca, P, and ALP levels ($p>0.05$). Giray et al. (8) compared fifty epileptic children, aged 5-14 years with no physical impairment, who were using AEDs (carbamazepine, valproic acid, and phenytoin) with a control group of forty age-matched healthy children and reported no significant difference between the two groups in terms of serum Ca and P levels ($p=0.1$). However, serum ALP and PTH levels were significantly higher in the patient group than in the control group ($p=0.0001$ for both). No difference was identified in the carbamazepine or valproic acid effect on serum ALP levels. In the present study, AEDs had no significant effect on serum PTH or ALP levels ($p>0.05$). Farhat et al. (9), similar to this study, found no significant difference between patients on single or multiple AEDs in serum P levels. Caksen et al. (10) found no significant increase in PTH levels in patients using antiepileptic drugs for ten months to five years. Similarly, Tsuhukara et al. (11) found no significant increase in serum PTH levels in patients using AEDs. Yildiz et al. (12) evaluated the potential risk to vitamin D levels related to the medium and long-term use of antiepileptic drugs in childhood in a study group aged one to 18 years who had been treated with AEDs for at least one year. The baseline vitamin D levels before administering AEDs are reported to be low in the study. No statistically significant difference was found in Ca, P, and ALP serum levels before and after antiepileptic medication. No significant difference was determined between the AED types in vitamin D status. Similarly, in this study, the use of AEDs had no significant effect on serum Ca, P, ALP, PTH, or vitamin D levels ($p>0.05$). In Toopchizadeh et al.'s (13) study of sixty-five children with CP and sixty-five healthy children as a control group, the mean 25(OH) D3 levels were 28.03±24.2 ng/ml in the patient group and 30±1.94 ng/ml in the control group. In contrast, 25(OH) D3 deficiencies were seen in 44.6% of the CP and 18.5% of the healthy controls. The authors reported no significant effect of antiepileptics on 25(OH) D3 levels. In this study, the use of AEDs also had no significant effect on serum vitamin D levels ($p>0.05$).

Siniscalchi et al. (14) drew attention to the effects of AEDs on bone health and their influence on bone metabolism through the induction of CYP450 enzymes and direct effects on bone cells. AEDs inhibit intestinal calcium absorption, osteoblastic cell growth, and calcitonin secretion. The authors underlined the importance of multifactorial pathophysiological mechanisms regarding the impact of AEDs on bone health, such as AED types, the dose of AEDs, gender, age, and sun exposure of patients.

In this study, in line with the literature, AED use had no significant effect on serum PTH levels ($p>0.05$). Baek et al. (15) evaluated 143 patients aged seven to 15 years who had been using AEDs for more than one year. They reported significantly lower 25(OH)D3 levels in patients using AEDs for more than two years than in those using them for less than two years ($p<0.03$). In the same study, the serum levels of 25(OH) D3 were lower in patients receiving oxcarbazepine than those taking valproic acid. Vitamin D insufficiency was detected in two-thirds of the patients. Patients on single therapy had similar vitamin D levels to those on multiple therapies. In the present study, multiple AEDs

were associated with decreased serum vitamin D levels ($p<0.05$). Chaudhuri et al. (16) compared 100 epilepsy patients aged below 18 years with a fifty age- and gender-matched control group. They reported a prevalence of vitamin D deficiency of 45% and 24%, respectively, with the highest prevalence, detected in the carbamazepine group, followed by the sodium valproate group. George et al. (17) reported that the prevalence of vitamin D deficiency increased in patients with cognitive and movement disabilities. Of the ninety children enrolled in the study, forty-six had cognitive (intellectual) disabilities, forty-four had movement disabilities, and forty-six were on antiepileptic medication. The mean serum vitamin D levels were below 30 ng/L in both the cognitive disability and the movement disability groups.

In another study (18) involving sixty-nine CP patients aged two to 12 years, the mean 25(OH) D3 concentration was 24.3 ng/mL (range, 5.4–48.7). Fifteen patients (21.8%) presented with vitamin D sufficiency, thirty-three (47.8%) with vitamin D insufficiency, and twenty-one (30.4%) with vitamin D deficiency. Vitamin D levels were suboptimal in 78.2% of the patients. In this study, vitamin D levels were significantly lower, and PTH levels were significantly higher in the patient group than in the control group ($p<0.05$).

Seth et al. (19) evaluated 120 children with CP aged two to 10 years with oral/motor dysfunction. Vitamin D deficiency was identified in 60% of children with CP, predominantly among immobile children and on AEDs. In this study, the patient group was divided into four subgroups: (i) Epilepsy (n=41; 38%), (ii) Neural tube defects (n=14; 13%), (iii) CP (n=21; 19%), and (iv) other diseases (n=32; 30%). Vitamin D levels were significantly lower in epilepsy and other groups than in the CP group ($p<0.05$). In contrast, no significant difference was found among the other groups ($p>0.05$). Serum Ca levels were significantly higher in the ambulant patients than in the non-ambulant patients ($p<0.05$), while vitamin D levels were significantly higher in the ambulant patients than in the non-ambulant patients ($p<0.05$). These findings could be attributed to the administration of enteral nutrition supplementation in some non-ambulant patients. The multifactorial nature of vitamin D deficiency may be related to factors such as AED type, patient age, dose, gender, and sun exposure.

Vitamin D is crucial in maintaining bone health, CNS neurotransmissions, and healthy children's immune functions. In epileptic patients, low vitamin D levels tend to increase the frequency of seizures, with the least occurring in the summer and the most during the winter (4, 5).

In conclusion

this study's results identified decreased vitamin D levels in patients with chronic neurological diseases. As vitamin D deficiency/insufficiency is multifactorial, such patients should receive prophylactic vitamin D supplementation and adequate nutritional support, while physically impaired patients should receive additional physical therapy with minimal AEDs if possible.

Acknowledgment

The authors want to thank all the patients and their families for participating in this study.

Author's Contribution

The study design was performed (Dr. Gunes Isik, Prof. Dr. Yasar Dogan).

Clinical evaluation of patients, determination of participants to study and collection of samples (Dr.

Gunes Isik)
Biochemical analysis and interpretation of samples (Prof. Dr. Bilal Ustundag)
Analysis of data, comments and literature data. (Dr. Gunes Isik, Prof. Dr. Yasar Dogan)

Conflict of Interest

None declared.

References

1. El-Hajj Fuleihan Vieth R. Vitamin D Insufficiency and Musculoskeletal Health in Children and Adolescents. International Congress Series 1297;2007: 91-108.
2. Gokcay G., Neyzi O., Ertugrul T. Avitaminosis and Hypervitaminosis. Pediatrics. Volume 1. Istanbul 2010: 265-276.
3. Henderson RC., Lark RK. Gurka MJ. Bone density and metabolism in children and adolescents with moderate to severe cerebral palsy. Pediatrics 2002; 110: 5-6.
4. Giray T, Vitrinel A, Comert S, Deniz NC, Ciler G, Kesler E, et al. Evaluation of the effects of antiepileptic drugs on bone metabolism. Turkish Archives of Pediatrics 2005; 40: 221-226.
5. Farhat G, Yamout B, Mikati MA, Demirjian S, Sawaya R, El-Hajj Fuleihan G. Effect of antiepileptic drugs on bone density in ambulatory patients. Neurology 2002; 58: 1348-1353.
6. Caksen H, Dulger H, Cesur Y, Odabas D, Tuncer O, Atas B. No effect of long-term valproate therapy on thyroid and parathyroid functions in children. Int J Neurosci 2002; 112: 1371- 1374.
7. Tsukahara H, Kimura K, Todoroki Y. Bone mineral status in ambulatory pediatric patients on long-term antiepileptic drug therapy. Pediatr Int 2002; 44: 466.
8. Jung-Hyun Baek. Young-Ho Seo. Gun-Ha Kim. Mi-Kyung Kim. and Baik-Lin Eun. Vitamin D Levels in Children and Adolescents with Antiepileptic Drug Treatment. Yonsei Med J 55(2):417-421. 2014
9. Chaudhuri IR, Mridula KR, Rathnakishore Ch, Balaraju B, Bandaru VCS. Association of 25-Hydroxyvitamin D Deficiency in Pediatric Epileptic Patients. Iran J Child Neurol. Spring 2017; 11(2):48-56.
10. George AS, Mathew MC, Mathew A, Jacob SS, Raj JM. The prevalence and risk factors of hypovitaminosis-D in children with cognitive and movement disorders. Indian J Pediatr. 2019.