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Clinical features of vitamin D deficiency in children: A retrospective analysis

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ABSTRACT

Vitamin D is very important for children's health. Previous studies have shown that vitamin D deficiency leads to a series of diseases in adults. However, pediatricians are mostly aware of rickets caused by vitamin D deficiency in children and poorly aware of other symptoms. This study aimed to retrospectively analyze the different clinical features of vitamin D deficiency to enhance identification by pediatricians, thus minimizing misdiagnosis. In this study, we retrospectively analyzed the clinical features of vitamin D deficiency in 268 children aged 0–14 years from June 2016 to May 2018 in the Third Affiliated Hospital of Zhengzhou University. Serum 25-hydroxy vitamin D [25(OH)D] levels were determined using the chemiluminescence method. Of the 268 cases, 101 cases showed movement disorder (37.7%) and 167 nervous system abnormalities (62.3%). Among all cases, 6 were misdiagnosed as febrile seizures (2.23%), 5 as epilepsy (1.86%), 2 as Tourette syndrome (0.74%), and 2 as developmental retardation (0.74%). There were significant differences in patients with clinical characteristics of movement disorder and nervous system abnormalities partly between Pre-and post-vitamin D treatment. This analysis revealed that vitamin D deficiency occurs not only in children but also in adolescents, with diverse clinical features. Therefore, pediatricians should pay more attention to clinical different signs and symptoms, and future studies should be conducted to confirm the mechanisms of these processes.

1. Introduction

Vitamin D, an important hormone with a steroid structure during development, is a fat-soluble vitamin that has substantial function in maintaining calcium and phosphorus equilibrium and bone health. It has been reported that vitamin D deficiency is considerably common with a prevalence of 25–50% among the general population [1,2].

Vitamin D is very important for human health, especially that of children. Circulating 25(OH)D levels greater than 50 nmol/L are required to maintain healthy vitamin D levels. Adequate vitamin D is not only beneficial for calcium and phosphorus metabolism, bone and skeletal muscle health, and preventing falls, but also for reducing the incidence of some diseases and cancers [3–5]. There are several reports stating that vitamin D deficiency is related to obesity [6,7] and diabetes in adults [8,9].

Vitamin D deficiency is particularly pronounced in children [10,11] and has been reported in China [12]. Vitamin D deficiency is associated with many diseases [13–15]. However, clinicians are only aware of rickets caused by vitamin D deficiency in children and poorly aware of other symptoms. This study describes possible non-skeletal effects of vitamin D deficiency and retrospectively analyze the different clinical features of vitamin D deficiency to enhance the ability of pediatricians to identify them in children, thus minimizing misdiagnosis.

2. Subjects

A total of 268 cases tested with vitamin D deficiency owing to various causes from June 2016 to May 2018 in the Third Affiliated Hospital of Zhengzhou University were included in this study. Among them, 140 cases (52.2%) were male and 128 (47.8%) cases were female. In this analysis, we included juveniles (patients) in the age group of 1–14 years. Patients were classified into four age groups (Table 1). The time of onset are shown in Table 1.

3. Study design and methods

3.1. Judging criteria

With reference to the hospital clinical laboratory kit standard, the plasma level of 25(OH)D was measured using chemiluminescence.

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Table 1
General characteristics of patients (n = 268).

Age (years)	
Mean ± SD	2.3 ± 0.52
Median (interquartile range)	2.1 (1.8)
Sex n (%)	
Female	128 (47.8%)
Male	140 (52.2%)
Onset time (%)	
2 weeks	38 (14.2 %)
2 months	116 (43.3%)
6 months	50 (18.7%)
1 year	36 (13.4 %)
2 years	28 (10.4%)
Onset season distribution (%)	
November to April	188 (70.1%)
May to October	80 (29.9%)

Levels of 25(OH)D from 50 to 250 nmol/L were considered as normal, 50–37.5 nmol/L as relatively inadequate, and less than 37.5 nmol/L as deficient. Oral calcium supplements were needed approximately 3 days before vitamin D was injected, because of the fear that a large dose of vitamin D could lead to a reduction in calcium ions and further lead to convulsion [16–18].

3.2. Observation index

25(OH)D levels were tested after 1 month, and the symptoms had either resolved or were still present.

4. Statistical analysis

Data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Data were presented as percentage (%) and mean ± standard deviation (SD). Pre- and post-treatment changes in clinical characteristics of patients with movement system disorder and nervous system abnormalities were compared using the Chi-square test, and P values < 0.05 were considered statistically significant.

5. Result

Of the 268 children with vitamin D deficiency, there were 101 cases with movement disorder (37.7%) and 167 cases with nervous system abnormalities (62.3%). Movement disorders included limb shaking, hand shaking, body stiffness, standing unsteady, abnormal posture, falling over easily, and thrill of popliteal space. Nervous system abnormalities included headache, fatigue, pain in limbs, dizziness, numbness of fingers, sweating, febrile seizures, pass out, epileptic seizure, nightmare, developmental retardation, and irascibility. A detailed comparison of the clinical characteristics of movement disorders and nervous system abnormalities is presented in Table 2.

5.1. Levels of serum 25(OH) D

25(OH)D levels were between 10 and 20 nmol/L in 33 cases (12.3%) and between 20 and 37.5 nmol/L in 235 cases (87.7%).

5.2. Misdiagnosis

Among all cases, 6 cases were misdiagnosed as febrile seizures (2.23%), 5 as epileptic seizures (1.86%), 2 as Tourette syndrome (0.74%), and 2 as developmental retardation (0.74%) (Table 3).

5.3. Follow-up

After vitamin D therapy, the clinical syndrome of the patients either improved or completely resolved, and the effect was satisfactory.

Table 2
Post-treatment comparison of changes in clinical characteristics of patients with movement system disorder (n = 101) and nervous system abnormalities (n = 167).

Symptoms	Number of cases	Clinical Symptom change		*p*
		Yes	No	
Movement disorder	101	98	38	< 0.001*
Limb shaking	80	78	2	< 0.001*
Hand shaking	8	8	0	< 0.004*
Body stiffness	4	3	1	0.175
Standing unsteady	3	3	0	0.246
Abnormal posture	3	3	03	0.246
Falling over easily	2	2	0	0.498
Thrill of popliteal space	1	1	0	0.317
Nervous system abnormalities	167	161	6	< 0.001*
Headache	46	44	2	< 0.001*
Fatigue	10	10	0	< 0.001*
Pain in limbs	39	39	0	< 0.001*
Dizziness	29	28	1	< 0.001*
Numbness of fingers	12	12	0	< 0.001*
Sweating	8	7	1	< 0.037*
Febrile seizures	7	6	1	0.067
Pass out	6	6	0	0.056
Epileptic seizures	6	5	1	0.121
Nightmares	3	3	0	0.267
Development retardation	2	2	0	0.498
Irascibility	2	2	0	0.498

* Statistically significant.

Table 3
Time to symptom resolution and misdiagnosis in patients.

Misdiagnosis	
As febrile seizures	6 (2.23%)
As epileptic seizures	5 (1.86 %)
As Tourette syndrome	2 (0.74%)
As development retardation	2 (0.74%)
Time to symptom resolution, n (%)	
3 days	30 (11.2%)
1 week	198 (73.8%)
2 weeks	22 (8.2%)
3 weeks	6 (2.2%)
4 weeks	8 (3%)

Table 3 shows clinical symptoms disappeared or relieved time. However, 4 cases (1.5%) were excluded from the study due to loss to follow-up. During the follow-up of the remaining 264 patients, 25(OH)D levels recovered to 50–70 nmol/L in 200 cases (75.7%), 71–90 nmol/L in 36 cases (13.6%), and 91–110 nmol/L in 2 cases (0.8%). Fifteen cases (5.7%) were close to the normal range (40–50 nmol/L) (Table 4). Eleven cases (4.2%) did not retest 25(OH)D, but the symptoms had improved (6 cases, 2.3%) or completely resolved (5 cases, 1.9%). On patient follow-up, it was observed that the symptoms resolved completely (250 cases, 94.7%) or lessen reduced (4 cases, 1.5%) after 3 months. However, 10 patients (3.8%) were lost to follow-up again, and the symptoms completely resolved in 254 cases (100%) after 6 months.

Table 4
Pre- and post-treatment comparison of distribution of vitamin D levels.

Serum concentration of 25 hydroxy vitamin D	Pre-treatment, n (%)	Post-treatment, n (%)
10–20 nmol/L	33 (12.3%)	–
20–37.5 nmol/L	235 (87.7%)	–
40–50 nmol/L	–	15 (5.7%)
51–70 nmol/L	–	200 (75.7%)
71–90 nmol/L	–	36 (13.6%)
91–110 nmol/L		2 (0.8%)

6. Discussion

Intake of vitamin D increases levels of 25(OH) D in the blood. Therefore, adequate vitamin D is essential to maintain healthy bones. Vitamin D deficiency is reportedly more common in infants and young children, as well as in neonates [19,20], and adversely affects growth and health. In addition to its historical skeletal functions, studies have found that vitamin D deficiency can lead to an array of problems in adults [13–15]. High-risk groups with a deficiency of vitamin D include newborns [19], infants, young children [21,22], pregnant women [23,24], and elderly individuals [25]. As growth and development in children is faster than that in adults, the demand for vitamin D is higher in children than that in other groups. If the children are less involved in outdoor activities and fail to supplement vitamin D in a timely manner, it may lead to vitamin D deficiency. In addition to rickets, vitamin D deficiency can lead to different clinical symptoms and signs, such as respiratory symptom [26] and muscle weakness [25]. Studies have shown that muscle reaction speed and strength improved with an increase in vitamin D levels [10]. A slight deficiency of vitamin D can often cause fatigue [27,28] and muscle pain [25,29] in patients. Patients with severe vitamin D deficiency and hypocalcemia develop neuromuscular sensitivity, such as numbness of the limbs and even convulsions [30]. The study also found numbness of fingers in 12 cases and pain in the limbs in 39 cases. Ten cases exhibited fatigue. On comparing pre-treatment and post-treatment symptoms, statistically significant differences in numbness and pain in the limbs and fatigue ($P < 0.05$) were observed. Symptoms disappeared or reduced gradually within 1–2 weeks. Subsequently, a month later, 25(OH)D levels had reached normal or close to normal levels. The results correspond with those reported in the literature [31].

One study reported that conventional treatment proved to be ineffective in patients with headache, and the symptoms gradually reduced with vitamin D supplementation, showing that headaches are correlated with vitamin D deficiency [32]. The mechanism of headache with vitamin D deficiency may relate to inflammation [33] and musculoskeletal pain [34]. A total of 46 patients with headache were included in the study. Vitamin D test results showed a severe deficiency in 38 cases and mild deficiency in 8 cases, accounting for 85.7% and 14.3%, respectively. At the 1-month follow-up after treatment, the symptoms had either completely resolved or were relieved. 25(OH)D reached normal or close to normal range and the results are in agreement with those reported. Excluding other systemic diseases, there were 28 patients with dizziness in this study. Among them, 25(OH)D levels were between 10 and 20 nmol/L in 19 cases (67.8%), and between 21 and 37.5 nmol/L in 9 cases (32.2%). In all, 22 cases (78.5%) showed excellent recovery and 8 cases (21.5%) showed minimal symptoms after 1-month supplementation with vitamin D. At the same time, 25(OH)D was retested after 1 month and the levels returned to normal range in 27 cases (90%), and close to the normal range in 3 cases (10%). Our findings are similar to those that have been well documented [35]. Statistically significant differences were observed regarding headache and dizziness ($P < 0.05$) before and after treatment (Table 2).

However, the study had 2 typical cases with irascibility and symptoms disappeared after vitamin D supplementation, which is in accordance with that reported in practice [36]. Three patients reported having nightmares during sleep. However, there are only a few reports with regard to the problem. On testing, 25(OH)D levels had severely reduced to 10–20 nmol/L. The symptoms disappeared after vitamin D supplementation, and the 25(OH)D levels were above 50 nmol/L after 1 month. However, statistically significant differences were not found after treatment because of the limited sample size ($P > 0.05$) (Table 2). In addition, there were other symptoms of vitamin D deficiency, and the difference was not statistically significant due to the limited sample size. Therefore, this study suggests that pediatricians should test 25(OH)D levels timely according to the symptoms and signs of the patients for establishing a clear diagnosis and further accumulating clinical experience.

In the recent years, vitamin D deficiency is becoming worse and is a well-known global problem [37]. The Vitamin D nutritional status of children in China is not optimistic, and the manifestations are variable. Our study found that vitamin D deficiency occurs not only in children but also in adolescents, and the results are in agreement with the reported abroad [38]. This confirms that vitamin D has extensive biological functions besides regulating calcium and phosphorus metabolism. With the development of industrialization, haze, and other environmental factors affect the air quality, and the cold season limits the outdoor activities of people. Therefore, vitamin D deficiency is more remarkable [39]. The study found that the incidence of vitamin D deficiency is lower in infants than in older individuals. This could be attributed to the faster growth and development in infants than that in older children and routine monthly check-ups and doctor's nutritional guidance for infants. However, when growth and development gradually slows down, the older children do not undergo regular check-ups and daily vitamin D supplements, causing increased incidence of vitamin D deficiency in older children [40]. Low levels of 25(OH)D are also linked to season [41]. In morbidity season distribution, among the 268 patients, incidence from November to April was obviously higher than that from May to October (Table1). Season and illumination time are the main reasons that cause this phenomenon. These results are consistent with previous findings [42]. However, in children, the onset based on sex is different from that in adults [29], which may be related to the physiological characteristics of different ages.

In conclusion, the study is an accumulation of clinical experience and is only based on clinical symptoms and 25(OH)D levels to establish a primary diagnosis. However, these studies are limited with a small number of cases and a short-term of follow-up; therefore, they are not established and there are still many problems that remain unsolved. The mechanisms of how these processes occur are still not fully understood. If we intensify our research efforts in these fields, it is only a matter of time that such mechanisms will be defined. Therefore, it is necessary to increase the sample size and extend the follow-up time to further verify the diagnosis and provide theoretical basis for the clinical diagnosis.

The study also suggests that pediatricians should test 25(OH)D levels in pre-school children, school-age children, and even adolescents frequently [38,43] and supplement vitamin D if necessary after excluding other systemic diseases according to the specific situation, while actively preventing and supplementing vitamin D in infants against rickets. Vitamin D deficiency can be prevented by vitamin D supplementation, which is both economical and safe. The clinicians should have the ability to identify the different clinical features of vitamin D deficiency. Early diagnosis and timely treatment are helpful, avoiding unnecessary economic and mental burden to patients' families and minimizing the rate of misdiagnosis.

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Declaration of Competing Interest

None.

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