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Evaluation of Serum 25-hydroxyvitamin D Levels in Children with The First Episode of Seizures

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Abstract

Background

Seizures have been prevalent among children leading to critical complications and death in some cases, investigation of the reasons for seizures is of great importance. We aimed to assess the influence of 25-hydroxyvitamin D deficiency in children with the first episode of on seizures.

Materials and Methods: This study was a case control study and carried out on 1 to 16-year-old children of Besat Hospital of Sanandaj, Kurdistan province, Iran, with the first episode of seizures (case), and children who were referred for routine laboratory checkup (control) in the year 2020. Serum 25-hydroxyvitamin D level was measured by chemiluminescence immunoassay methods of blood sample for both case and control groups. The required data were collected and entered in SPSS software version 21.0 to be analyzed.

Results: Total individuals of 120 children [72 (60%) boys] with an average age of 46.77±40.5 months were selected. Sixty-two patients (51.7%) of the children received an appropriate vitamin D supplement, and prevalence of vitamin D supplementation use was higher in case group (P=0.011).The average serum level of 25-hydroxyvitamin D in individuals was 31.36±19.01 and the average serum level of vitamin D in the patient group was greater than that of the control group (P=0.003).The frequency of 25-hydroxyvitamin D deficiency was higher in the control group (P=0.001).

Conclusion

Based on the obtained results, an important conclusion can be reached that seizures in children were not effectively prevent by normal vitamin D supplements.

Key Words: Children, Seizures, 25-hydroxyvitamin D.

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1- INTRODUCTION

Seizures, known to be one of the most prevalent neurological disorders in children, are experienced by 3-4% of them once in a lifetime (1); also, 1% of all hospital's emergency room visits in children are because of seizures caused by benign to life-threatening factors (2). Among the different types of this disease, febrile seizure, as the most prevalent seizure type between children is not often complicated; The International League against Epilepsy defines the First Unprovoked Seizure as the first experienced seizure or added seizures happening during 24 hours of one month of age with no stimuli, including head injury or fever (3). Seizures are an anxious and frightening phenomenon for the family, many studies have concentrated on studying the causes of seizures (4). There have been several reasons for occurring seizures resulting in increased nervous activity. These reasons are bleeding, electrolyte disorders, including calcium and sodium disorders, 25-hydroxyvitamin D deficiency, trauma, ischemia, fever, and infections of the central nervous system, including meningitis (5-8). As an electrolyte disturbance, hypocalcemia can result in occurring seizures. The healthy operation of nerve cells relies on extracellular calcium ions. The production of such hemostatic systems is facilitated via parathyroid hormone as well as 25-hydroxyvitamin D (9). Despite providing symptomatic therapy in patients diagnosed with seizures, antiepileptic drugs are not capable of treating seizures (10). Several diets and remedies have been found effective for curing epilepsy, such as the modified diet, the ketogenic diet, and omega-3 fatty acids. Vitamin D3 is poorly investigated as a successful remedy for curing epilepsy (11). Vitamin D3 supplementation reduces the frequency of seizures by regulating anticonvulsant factors and negatively regulating cytokine IL-6 (7). Sunlight is accounted for the principal source of vitamin D meaning that sunlight exposure for about 10 to 20 minutes supplies the required daily dose of the vitamin for the human body. Furthermore, this vitamin can be provided by other sources, including plant sources like cereals and animal sources, including milk, eggs, and sardine (12). There have been numerous investigations focused on the assessment of 25-hydroxyvitamin D content in patients with epilepsy who received anticonvulsant medications (13-16). According to a study published in 2012, correcting 25-hydroxyvitamin D deficiency led to the improvement of controlling seizures in patients with epilepsy (17). Moreover, a vitamin D deficiency of between 4% and 75% in children with epilepsy was reported by six studies. Bone mineral density or bone biomarkers have been found to be related to epilepsy (18). Since seizures have been prevalent among children leading to critical complications and death in some cases, investigation of the reasons for seizures is of great importance. The aim of this investigation was to Evaluation of Serum 25-hydroxyvitamin D levels in children with the first episode of seizures.

2- MATERIALS AND METHODS

2-1. Study design, period, and area

This case control study was carried out on 1 to 16-year-old children of Besat Hospital of Sanandaj, Kurdistan province, Iran, with the first episode of seizures in the year 2020. The following formula was used to determine the sample size. In this study, a 95% confidence level was considered.

$$n = \frac{z^2_{1-\alpha/2} * p * q}{d^2}$$

Considering the seizure episode ratio of 0.04 and the maximum error of 0.05, the volume of each case and control studied group were equal to 60 people.

2-2. Data collection

Children referred to Besat Hospital in Sanandaj, Iran, from January 2020 to December 2020 with the first episode of seizures (case), and same number of healthy children who were coming for routine laboratory checkup (control) were selected to participate in the study. Diagnosing of Seizure was proved based on the history of patients and laboratory tests, and electroencephalogram (EEG). Children with history of previous history of seizures, an underlying disease affecting vitamin D and calcium metabolism, medication or drugs that affect calcium and vitamin D metabolism were excluded from participation in the study. Demographic data of children, such as gender, age, weight were recorded in the checklist for both case and control groups. Four cc of blood samples were taken from superficial veins of the upper limb for the measurement of serum 25-hydroxyvitamin D level and was transferred to the laboratory; In these study, related factors like serum phosphor, calcium, and hemoglobin levels that can affect serum vitamin D levels were also measured in patients (case); also these factors were measured in children who came for a routine checkup (control): serum vitamin D, phosphor, calcium and hemoglobin levels measured by chemiluminescence immunoassay methods. According to that the measurement of serum 25-hydroxyvitamin D, Hb, Ca, P level are routine in children checkup; no additional tests were forced to control group. In this study, serum Vit D level below 12 ng/mL was considered a deficiency, serum Vit D level 12-20 ng/mL considered insufficiency, Vit D ≥20 ng/mL defined as sufficient vit D≥100 ng/mL as toxicity (19). Also, anemia was defined based on the age; less than 9 g/dl in 2 months, less than 9.5 g/dl in 2– 6 months, less than 10.5 g/dl in 6-24 months, less than 11.5 g/dl in 2 -11 years old, and (f<12 g/dl and M<13 g/dl) in >12 years old patients (20). The obtained data were collected and submitted to the statistical consultant for analysis. The data collection was followed by ethical principles and without entering the identity card information in all stages.

2-3. Ethics approval and consent for participation

For participants under 16 year-old written consent was received from their parents. This manuscript obtained ethical approval from the Ethics Committee of Kurdistan University of Medical Sciences, Sanandaj, Iran. Ethical approval ID is IR.MUK.REC.1398.265.

2-4. Data analysis

The required data were collected and entered in SPSS software version 21.0 to be analyzed. Central indicators and qualitative variables were described using graphs and tables (frequency and percentage), and quantitative variables were analyzed using Chi-square and independent sample t-test. A p-value less than 0.05 was considered as the significance level.

3- RESULTS

According to the evaluations, 72 (60%) of the studied samples were boys, and 48 (40%) were girls. Based on the results of the Chi-square test, a similar distribution in terms of gender is evident in the two groups (p = 0.136) (**Table.1**). The average age in case samples is 46.77±40.5 months. The mean weight of 17.42 ± 11.09 kg, the minimum value of 5 kg, and the maximum value of 60 kg were calculated. Furthermore, similar values for the average weight were measured between the two groups (p = 0.156) (**Table.1**). Moreover, the minimum age observed of two months, and the maximum of 156 months (13 years) were considered. Furthermore, a notable variation was evident between the average age between the two groups (p=0.031) (**Table.1**).

Table-1: Demographic characteristics of participants.

Variables		Case, n=60	Controls, n=60	P-value
Gender	Boy	66.7%	53.3%	0.136
	Girl	33.3%	46.7%	
Weight (kg)		15.98±11.87	18.86±10.15	0.156
Age (month)		38.84±40.13	54.70±39.63	0.031

Case: The children with the first episode of seizures.

Among the individuals, 62 (51.7%) of them had appropriate supplementation, and 58 (48.3%) of children did not receive supplementation or absorbed it inadequately. A meaningful variation was observed between supplementation in healthy and unhealthy individuals (p=0.011) (**Table.2**). The average serum level of 25-hydroxyvitamin D in individuals was equal to 31.36 ±19.01(ng/mL), with the minimum serum level of 4 and the maximum value of 108 (ng/mL). A higher value of the average serum level of vitamin D was observed in the patient group compared to the control group (p = 0.003) (**Table.2**). An average value of 11.67 ± 1.76 (g/dl) were calculated for hemoglobin (Hb) in children with a minimum value of 3.5 (g/dl) and a maximum value of 17.8(g/dl). The mean phosphorus (P) in children is 4.81 ± 1.13(mg/dl), the minimum value of 1.5(mg/dl), and the maximum value of 9 (mg/dl) (**Table.2**). The average value of 8.54 ±1.21(mg/dL), a minimum value of 5.9 (mg/dL), and the maximum value of 10.5 (mg/dL) were measured for calcium (Ca) in children (**Table.2**).

Table-2: Mean distribution of variables by case and control groups

		Mean	Standard deviation	P-value
Use of Vitamin D supplementation	Case	63.3%	-	0.011
	Control	40.0%	-	
Serum vit D level (ng/mL)	Case	36.50	20.48	0.003
	Control	26.23	16.00	
Serum Hb level (gr/ dL)	Case	11.69	1.72	0.926
	Control	11.66	1.81	
Serum P level (mg/dl)	Case	5.03	1.25	0.013
	Control	4.42	0.77	
Serum ca level (mg/dL)	Case	8.51	1.39	0.716
	Control	8.60	0.86	

Case: The children with the first episode of seizures.

According to the obtained results, a considerable variation was observed between the individuals who received vitamin D supplements and individuals who did not (did not receive or their consumption was inadequate). A higher average serum level of vitamin D was evident for individuals who received supplements (p = 0.0001) (**Table.3**).

Table-3: Relationship between serum 25-hydroxyvitamin D levels and vitamin D supplement use.

Variable	Vitamin D supplement use	Mean	Standard deviation	P-value
Serum 25-hydroxyvitamin D levels(ng/mL)	Yes	38.0	21.75	0.0001
	No	24.26	12.22	

Independent sample t-test was used for analyzing.

Among the investigated individuals, Abnormal serum phosphorus level [<4 (mg/dL), and > 4 (mg/dL)] were observed for 27 cases (22.5%), and 67 cases (55.8%), respectively. Also, abnormal serum Ca level (less than 8 (mg/dL), and more than 8 (mg/dL) were evident for 34 cases (28.3%) and 62 cases (51.7%), respectively. Among the investigated individuals, 5 cases (4.2%) suffered from vitamin D deficiency, 63 cases (52.5%) were deficient which 51 cases (42.5%) had enough vitamin D and 1 case (0.8%) had vitamin D poisoning. Among the investigated individuals, 99 cases had normal hemoglobin and 21 cases (17.5%) had anemia (**Table.4**).

Table-4: Frequency distribution of studied variables based on normal range.

Variables	Groups	Frequency (%)
Phosphor (mg/dl)	Hypophosphatemia (<4 mg/dL)	27 (22.5%)
	Normal (>4 mg/dL)	67 (55.8%)
	Uncertain	26 (21.7%)
Calcium (mg/dL)	Hypocalcemia(<8 mg/dL)	34 (28.3%)
	Normal(>8 mg/dL)	62 (51.7%)
	Uncertain	24 (20.0%)
25-hydroxyvitamin D (ng/mL)	Deficiency	5 (4.2%)
	Insufficiency	63 (52.5%)
	Normal	51 (42.5%)
	Toxicity	1 (0.8%)
Hb (gr/dl)	Normal	99 (82.5%)
	Anemia	21 (17.5%)

Based on the obtained results, no meaningful variation was evident between the two groups in terms of calcium, phosphorus, and hemoglobin (**Table.5**). Among individuals, the majority of patients (58.3%) had adequate vitamin D, and in the control group, the maximum number of 40 subjects (66.7%) suffered from vitamin D deficiency. Vitamin D inadequacy was greater in control group (**Table.6**).

Table-5: Evaluation of the relationship between 25-hydroxyvitamin D, P, Ca, and Hb variables with case and control groups in children under two years of age.

Variables	Groups	Mean	Standard deviation	P-value
Serum 25-hydroxyvitamin D level(ng/mL)	Case	38.61	19.78	0.191
	Control	31.79	19.21	
Hb (gr/dl)	Case	11.44	1.62	0.180
	Control	12.00	1.43	
P (mg/dl)	Case	5.05	1.25	0379
	Control	4.67	0.61	
Ca (mg/dL)	Case	8.33	1.68	0.494
	Control	8.71	0.63	

Chi-square test was used for analyzing, Case: The children with the first episode of seizures, CA: calcium, P: Phosphorus, Hb: Hemoglobin.

Table-6: Relationship table between 25-hydroxyvitamin D in case and controls groups.

serum 25-hydroxyvitamin D groups	Case	Control	P-value
Deficiency	1 (1.7%)	4 (6.7%)	0.001
Insufficiency	23 (38.3%)	40 (66.7%)	
Normal	35 (58.3%)	16 (26.7%)	
Toxicity	1 (1.7%)	0 (0.0%)	

The total number of subjects studied for six months to 5 years is 78, of which 41 (52.6%) were in case group, and 37 (47.4%) were in the control group. Among six months to 5 years old children, Twenty-five patients (61%) had a fever (T> 37.5 ℃). There was no significant relationship between fever with serum vitamin D level (p = 0.443) in six months to 5 years old patients (**Table.7**). Also, there was no significant relationship between anemia and having fever in patient group (p = 0.119) (**Table.7**).

Table-7: Relationship between serum 25-hydroxyvitamin D, and hemoglobin level with fever in 6 months to 5 year-old case group patient.

Variables		Having fever		P-value
		Yes	No	
Serum 25-hydroxyvitamin D	Deficiency	0	1	0.443
		0.0%	6.3%	
	Insufficiency	6	6	
		24.0%	37.5%	
	Normal	18	9	
		72.0%	56.3%	
	Toxicity	1	0	
		4.0%	0.0%	
Anemia	Not having anemia	23	27	0.119
		92.0%	77.1%	
	Having anemia	2	8	
		8.0%	22.9%	

Independent sample t-test was used for analyzing, Case: The children with the first episode of seizures.

4- DISCUSSION

Epilepsy is known to be one of the most prevalent neurological diseases observed in children more commonly in the first year of life. To determine the reason for seizures, effective tools, such as neuroimaging and electroencephalography are of major importance. Genetic testing has also been found to be an effective study particularly in the early stages of epilepsy. Drug-resistant seizures have been prevalent in up to a quarter of children with epilepsy. Common comorbidities, such as mental retardation in almost a quarter of cases and attention deficit/hyperactivity disorder as well as learning disabilities in a noteworthy minority have been seen in children with epilepsy (19). Also, brain development has been found to be influenced by Vit D (20). Serum 25-hydroxyvitamin D level may be decreased by long-term therapy with valproate in children. Hence, it is necessary to control 25-OH-Vit D levels in children receiving long-term therapy using valproate. Proper supplements are also essential to be applied if levels become low (21). SINGH et al. reported that low levels of Vitamin D are evident among simple febrile seizure cases (22). Greater average serum levels of vitamin D were observed for the patients who received supplements in our survey. Furthermore, higher values of the average serum level of 25-hydroxyvitamin D were evident in the patient group in comparison to the control group. On the other hand, a higher frequency of vitamin D deficiency was observed in the control group despite having normal 25-hydroxyvitamin D. Consequently, serum 25-hydroxyvitamin D deficiency has been found to be related to the occurrence of the first seizure in children without a history of seizures. Moreover, it is capable of protecting them against the disease. Similarly, Razazizan et al, Compared the 25-hydroxy vitamin D,

calcium levels in epileptic and non-epileptic children and resulted that serum calcium and vitamin D levels are in normal ranges in epileptic children (23). Conversely, Lee et al. stated that a vitamin D deficiency was observed in children with epilepsy receiving anticonvulsant medications, particularly in adolescents over 12 years old (24). Based on another study published in 2012, vitamin D deficiency resulted in progressing seizures and correction. A reduction in seizure cases with epilepsy was evident related to vitamin D deficiency (25). Kija et al. assessed the effects of vitamin D on the children diagnosed with epilepsy in South Africa; According to the results, a higher level of vitamin D deficiency was evident in the group with epilepsy despite the existence of deficiency in both groups (26). In another study conducted by Tombini et al., lower vitamin D was observed in the group with epilepsy.

Nevertheless, refractory epilepsy was not significantly affected by vitamin D administration in the diagnosed patients (27). In terms of gender distribution, no considerable variation was found between the two groups, in the study contrary to the investigation of Abdullah et al. (28), in which a higher level of vitamin D3 was evident in boys with epilepsy compared to girls. According to a survey, lower levels of vitamin D3 were observed in a group that included healthy children, and lower vitamin D3 deficiency was evident in boys compared to girls (29). Furthermore, a higher prevalence of supplements was observed in unhealthy children, and a considerable variation was observed between supplements use in healthy and unhealthy ones. Age factor facilitates the reduction of the concentration of 7-dehydrocholesterol, a precursor to vitamin D3. Moreover, since vitamin D is a fat-soluble vitamin resulting in its deposition in fat parts of the body obesity factor leads to decreasing vitamin D (30). In our study, a notable variation was evident between the average ages of patients in the two groups. Furthermore, the average age of the control group was higher than that of patients. Nevertheless, in terms of the weight of the individuals in the two groups, similar results were obtained which was in good agreement with Pack et al. (31) Conversely, Baek et al. reported that increasing BMI led to reducing vitamin D3 levels (32). Iron has been found to be essential for human's health so that its deficiency can result in reducing hemoglobin production and causing iron deficiency anemia (33).

Conversely, the hemoglobin content was similar between the two groups in our investigation. There is no agreement between these findings and recent researches meaning that FS and seizure progression may be related to iron deficiency anemia (34, 35). Furthermore, in a study conducted by Jang et al., an increased risk of febrile seizures was observed related to anemia (36). Nevertheless, according to the results obtained by Yousefinejad et al., iron deficiency had a negative impact on febrile seizures progress in children. The reason for this was the increased threshold of neuronal stimulation in fever resulting in preventing febrile seizures in children (37).

The controlling of hyperphosphatemia can be facilitated by excretion via the kidneys. A reduction in serum calcium levels is capable of stimulating PTH secretion leading to renal reabsorption as well as decreasing urinary calcium excretion while simultaneously preventing tubular reabsorption of phosphorusat. On the contrary, high levels of calcium result in calcitonin releasing, decreasing phosphaturia while developing calcium excretion (38). Hypocalcemia (Ca <8.5 mEq / L) may result in reduced stimulation threshold, leading to increasing neurotransmission and increasing neuromuscular stimulation, causing

seizures (39-41). According to our results, higher levels of phosphorus were evident in the patient group in comparison to the control group. Nevertheless, similar levels of calcium were observed between the two groups. The hypercalciuria prevalence in children without seizures was found to be 37.8% (42). In another survey, no considerable variation was reported in the levels of P, Ca, and Hgb in children under 2 years old.

4-1. Study Limitations

Based on COVID-19 pandemic during 2020 we had problem with some laboratory data collection, and the phosphor and calcium level were remaining uncertain in some children of control group.

5- CONCLUSION

In this study despite having normal 25-hydroxyvitamin D, more frequency of 25-hydroxyvitamin D deficiency was observed in the control group. Also, Serum 25-hydroxyvitamin D deficiency is associated with the onset of the first seizure in children without a history of seizures. In addition, it can protect them against disease. Based on the results, it can be concluded that seizures in children are not effectively treated with natural vitamin D supplements. In addition, serum calcium levels did not have sufficient protection to treat the first seizure in children.

6- CONFLICT OF INTEREST: None.

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