Original Article

Comparative Study of Serum Vitamin D Levels in Patients with Febrile Seizures and Febrile Illnesses Referred to Motahhari Hospital in Urmia

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Abstract

Background & Aims: Febrile Seizure reffered to seizures associated with febrile illness in the absence of central nervous system infection or acute electrolyte disturbance in children without a history of non-febrile seizures. The brain is one of the target tissues for the actions of vitamin D. This steroid hormone plays an important role in the nervous system. The aim of this study was to compare the serum levels of vitamin D in patients with febrile illness and febrile seizures admitted to Motahhari Hospital, Urmia, Iran.

Materials & Methods: The present study was a case-control study in which 50 children with febrile seizure were studied as thecase group and 50 children with febrile illness without seizure as the controlgroup. Inclusion criteria for the case group included age 6 months to 5 years, febrile seizure, no nervous system infection, and no electrolyte disturbance. Exclusion criteria were seizures without fever, epilepsy and neurological lesions. Inclusion criteria for the control group were febrile patients admitted to Motahhari Hospital, Urmia, Iran without a history of seizures.

Results: Out of 100 patients studied, 51 were boys and 49 were girls. The mean age of the whole study population was 31.5 ± 6.4 months. After comparing two groups, it was found that there was no significant difference between the two groups in anthropometric characteristics. The mean level of vitamin D among febrile patients was 30.83 ± 28.93 and the mean level of vitamin D among febrile seizure patients was 26.18 ± 12.44 ng / dl. There was no significant difference between two groups in this regard.

Conclusion: Based on the results of our study, there was no significant difference in the mean level of vitamin D between two groups of febrile patients without seizures and patients with febrile seizures, although the mean level of vitamin D in patients with febrile seizures was in the range defined as deficient.

Keywords: Fever, Febrile seizure, Vitamin D

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Introduction

Febrile Convulsion is defined as convulsions associated with febrile illness in the absence of central nervous system infection or acute electrolyte disturbance in children without a history of non-febrile seizures. Febrile Convulsion is age-related and is rare before 6 months of age and after 5 years of age. The highest incidence of seizures is among children aged 14 to 18 months (1).

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The prevalence of febrile seizures varies in different studies. The lowest prevalence reported belongs to China with one percent and the highest rate reported to Japan with 6 to 9 percent. The disease rate is estimated to about 3 to 4 percent worldwide (2, 3, 4). These seizures fall into two general categories: simple febrile seizures (generalized seizures without focal features, duration of seizures less than 15 minutes and occurrence of only one seizure within 24h) and complex febrile seizures (focal seizures, lasting 15 minutes or more, and repeated seizures within first 24 hours). Although the prognosis for febrile seizures is often good, sometimes the disease progresses to the type of complex or status epilepticus caused by the fever and leads to epilepsy or multiple neurological complications. Although febrile convulsion is the most common type of seizure in children, the physiopathology of this disease is still unclear (1). Risk factors for febrile convulsion include genetic factors, deficiency of certain micronutrients such as iron, zinc, and selenium, and immunological reactions (1, 5, 6). According to new studies, the brain is one of the target organs on which vitamin D is effective. This steroid hormone plays an important role in the nervous system (7,8). These include differentiation, regulation of calcium homeostasis, and regulation of neutrophils release which facilitates the activity of key brain genes and enzymes involved in the metabolism of neurotransmitters (9). Vitamin D receptors are abundant in the brain and spinal cord, indicating the importance of the function of vitamin D and its receptors in the nervous system (9, 10). $1,25\text{-}(OH)_{(2)}D_{(3)}$ is the main active metabolite of vitamin D and the main ligand of vitamin D receptor. The mechanism of function of this hormone is similar to the function of other steroid hormones (9, 11). Many studies have shown an association between vitamin D-related disorders and epilepsy. Low levels of vitamin D lead to hypocalcemia, which can lead to seizures due to excessive irritability of neuronal membranes (12). Convulsions associated with hypocalcemia and low levels of vitamin D are often seen in patients with hereditary or nutritional rickets (13, 14). Also, studies have shown that treatment with vitamin D and calcium by reducing hypocalcemia reduces seizures in patients with rickets (15). In addition, studies on laboratory animals have shown direct anticonvulsant effects of 1, 25-dihydroxyvitamin D (15).

On the other hand, chronic treatment with anticonvulsant drugs disrupts mineral homeostasis in patients with epilepsy, which in turn causes hypocalcemia and decreased plasma levels of vitamin D in these patients (14). Based on these grounds, it can be concluded that vitamin D has positive effects on mineral and hormonal homeostasis, which has led to the design and implementation of several studies on the anticonvulsant role of vitamin D. Also, many studies have shown that in addition to seizures, vitamin D also plays an important role in the physiological mechanisms associated with some other brain disorders. The most important of these disorders that have been considered so far are multiple sclerosis, schizophrenia, anxiety, and depression (9, 10, 16). So far, several studies have been performed to compare the levels of some laboratory parameters such as zinc, magnesium, and selenium in patients with febrile convulsion and patients with fever without seizure. The results of these studies indicate a significant difference between these parameters between patients in these two groups (8, 17).

Also, some experimental studies in laboratory animals have shown that vitamin D may have anticonvulsant effects and reduce the severity of seizures in mice in which chemical seizures have been induced (18, 19). Given these cases and the fact that so far no studies have been conducted on vitamin D levels in children with febrile convulsion, we designed this study to compare the serum levels of vitamin D in patients with febrile seizures and febrile illness without seizure.

Materials & Methods

The present study was a case-control study that was performed to compare the serum levels of vitamin D in patients with febrile seizures referred to Motahhari Hospital, Urmia, Iran. In this study, 50 children with febrile convulsion were studied as the case group and other 50 children with febrile illness without seizure as the control group. All diagnostic kits were purchased from Aria Pharmed Company and all tests were performed by an experienced technician familiar to ELISA method and the results reported in ng / ml, with Values of vitamin D (<10 ng/ml being considered as Deficient, 10-30 ng/ml as Insufficient, 31-100 ng/ml as Sufficient, and >100 ng/ml as toxicity). Demographic and clinical information of patients including age, sex, etc. were extracted from patients' files. Inclusion criteria for the case group included age 6 months to 5 years, febrile convulsion, no nervous system infection, and no electrolyte disturbance. Exclusion criteria were seizures without fever, epilepsy and neurological lesions. Criteria for inclusion in the control group were a febrile patient without a history of seizures admitted to Motahhari Hospital, Urmia,Iran. Children in both groups were matched based on age, sex, weight, height, head circumference, and fever intensity. Weight, height, head circumference, and temperature (axillary) were also measured using standard methods. Serum levels of vitamin D were compared between two cohorts using statistical tests. Quantitative variables were stated using central indices and dispersion (mean and standard deviation), and qualitative variables were mentioned as frequency and frequency percentage. Charts and statistical tables were used to display the data as needed. To make comparisons, appropriate statistical tests in terms of data distribution (normality) such as t-test, chi-square, ANOVA, or their non-parametric equivalent have been used. All analyses were performed using SPSS 21 software and the significance level for judging in all statistical tests was less than 0.05.

Ethical considerations

The proposal was approved by the Urmia University's Ethics Committee

(Code: IR.UMSU.REC .1399.040).

The patients' dignity was prioritized. All data of the patients were confidential. Informed consent was obtained from the infants' parents.

Results

The present study was a case-control study performed to compare the serum levels of vitamin D in patients with febrile seizures referred to Motahhari Hospital, Urmia, Iran. In this study, 50 children with febrile convulsion were studied as the case group and 50 children with febrile illness without seizure as a control group.

In the present study, the mean age of the total study population was31.8± 10.2 months. In Patients with febrile seizures, the mean age was 31.5±6.4 months and among febrile patients was 32.1± 16.2 months. After statistical analysis, it was found that there was no significant relationship between case and control groups in terms of mean age (P = 0.88) (Table 1).

Table 1: Average age in the total population

	Mean age ± standard deviation(months)	P-Value
Patients with febrile seizures	31.5±6.4	
Patients with febrile illness	32.1± 16.2	0.88
total	31.8± 10.2	

In this study, there was no difference between the two groups of patients in terms of anthropometric characteristics (height, weight and head circumference) (Table 2).

Table 2: Comparison of anthropometric characteristics (height, weight and head circumference) in the patients with febrile illness and febrile seizures

	Mean± standard deviation			P-Value
	Patients with febrile illness	Patients with febrile seizures	total	
Height(cm)	90.1± 11.5	88.9±12.9	89.5± 11.2	0.88
Weight(kg)	12.7±2.4	13.9± 2.3	13.3±3.3	0.78
head circumference(cm)	46.7± 3.4	49.7± 3.3	48.2± 3.3	0.84

Based on the data in Table (2), the mean height in febrile patients and patients with febrile seizure was 90.1± 11.5 cm and 88.9±12.9 cm, the mean weight of febrile patients and febrile seizure were 12.7±2.4 kg and 13.9± 2.3 kg, respectively, the mean head circumference of febrile patients and patients with febrile seizures were 46.7± 3.4 cm and 49.7± 3.3 cm, respectively. There was no significant difference between two groups in terms of anthropometric characteristics.

The mean level of vitamin D in boys with febrile seizures was lower than girls with febrile seizures, but this difference was not statistically significant. Also, in our study, boys with febrile illness without seizure had lower levels of vitamin D than girls with febrile illness without seizure, but this difference was also not statistically significant.

Table 3: serum level of Vitamin D in febrile patients

	Mean± standard deviation	At least	Maximum	P-Value
Total patients with febrile illness	30.83±28.93	4	141	
females with febrile illness(ng/ml)	38.09±32.27	4	141	0.3
Males with febrile illness(ng/ml)	29. 49 ± 17.36	10.2	87.4	

According to the data in Table (3), the average level of vitamin D among patients with fever was 30.83±28.93 ng / ml. This amount was 38.09± 32.27 ng / ml in girls with febrile illness and 29.49 ±17.36 ng / ml in boys with febrile illness. Kolmogorov-Smirnov test was used to determine the distribution of serum vitamin D levels among these patients. Due to the normal distribution of serum vitamin D levels among these patients, an independent parametric t-test was used to compare vitamin D levels between girls and boys. The result of independent t-test was 0.3, so there was no significant relationship between sexes in terms of mean vitamin D levels.

Table 4: serum level of Vitamin D in patients with febrile seizure

	Mean± standard deviation	At least	Maximum	P-Value
Total patients with febrile seizure	26.18±12.44	10	60	
females with febrile seizure (ng/ml)	29.32±12.42	10	60	0.7
Males with febrile seizure (ng/ml)	23.04 ± 11.87	10	46.40	

According to the data in Table (4), the average level of vitamin D among patients with febrile seizure was 26.18±12.44 ng / mL. This amount was 29.32±12.42 ng / ml in girls with febrile seizures and 23.04 ± 11.87 ng / ml in boys with seizures. Kolmogorov-Smirnov test was used to determine the distribution of serum vitamin D levels among these patients. Due to the normal distribution of serum vitamin D levels among these patients, an independent parametric t-test was used to compare vitamin D levels between girls and boys. The result of independent t-test was 0.7, so there was no significant relationship between sex and mean serum level of vitamin D.

The mean level of vitamin D in Patients with febrile seizure was 26.18 ± 12.44 ng/ml and in febrile patients without seizures was 30.83 ± 28.93 ng/ml. There was no significant difference between two cohorts in terms of vitamin D levels (P = 0.3). Though, the vitamin D levels in patients with febrile seizures fell in vitamin D deficient category, while in children with fever without seizures vitamin D levels were in the normal range. (Table 5). Unfortunately, our search for similar studies on the relationship between febrile seizures and vitamin D levels turned nothing. However, animal studies such as the study by Kalueff et al. in Finland in 2005 to investigate the anticonvulsant effects of 1,25-dihydroxyvitamin D in mice showed that vitamin D could play a direct anticonvulsant role in the brain (18). In another study by Kalueff et al. a comparative study of seizure severity was performed in mice in whom the vitamin D receptor gene was partially deleted. The results of this study showed that vitamin D receptors play a regulatory role in seizures and that the endocrine system of vitamin D may be involved in the pathogenesis of epilepsy (19).

Table 5: serum level of Vitamin D in patients with fever and febrile seizure

	Mean± standard deviation	At least	Maximum	P-Value
Patients with febrile seizures(mg/dl)	26.18 ± 12.44	10	60	
Patients with febrile illness(mg/dl)	30.83 ± 28.93	4	141	0.3
Total(mg/dl)	28.50 ± 22.28	4	141	

According to the data in Table (5), the mean level of vitamin D in the patients with febrile seizures was 26.18±12.44, compared to 30.83 ± 28.93 in febrile patients without seizures. The difference was not statistically significant (P = 0.3).

Discussion

Febrile seizure is considered as a benign condition affecting children from 6 to 60 month of age and is defined as a convulsive seizure fallowing a febrile illness without any signs of CNS abnormality, infection,

and any electrolyte abnormality. A lot of research has been conducted on determining its risk factors, especially modifiable ones, in an effort to identify at risk children and implement measures to prevent the seizures or at least cut the number of relapses. Research on the relationship between iron deficiency anemia and FC is a good example.

Vitamin D now is considered to be a multifunctional hormone with a wide variety of functions throughout the body. It`s widespread distribution of receptors in the brain and spinal cord is an indication of its being involved in its proper functioning. Some even suggest vitamin D to be a neurotransmitter.

While a lot of work has been accomplished regarding the role of vitamin D in preventing convulsions in epileptic patients, with the bulk of the evidence supporting the preventative role of vitamin D, to the best of our knowledge little has been done to find any possible relationship between vitamin D and febrile convulsions. Our study is one of the few limited studies in Iran that examines the possible relationship between vitamin D levels and FC. Tasleem Arif Bhat et al. in a study conducted in 2020 in India, studied the relation between serum levels of 25(OH) Vit D and recurrence rate of seizures in children with the febrile convulsions. They established a negative correlation between these two groups; the higher serum level of vitamin D, the lower recurrence rate of seizures. Serum level of Vitamin D in their study fell in insufficient, deficient, and sufficient categories, respectively in a descending manner. (20). In a study conducted by Heidarian et al. in Mashhad, Iran, 104 children were studied in 2 groups; 53 children with febrile convulsions and 51 children with fever without seizures, and the level of vit D3 in the two groups were compared. There was no statistically significant difference between febrile seizures and febrile group. This is homogeneous with our study (21).

A study conducted by Zafer BAĞCI in 2019 in Turkey and published in 2021 to compare serum levels of vitamin D in 38 febrile children with seizure and 95 without seizure. There was no statistically significant difference between febrile seizures group and febrile group in terms of serum vitamin D levels, which is similar to our study (22).

There was no significant difference between boys and girls in febrile patients without seizures in terms of vitamin D3 levels with P-value=0.3. So there was no significant relationship between sexes in terms of mean vitamin D levels which is similar to the study of Heidarian et al. and Zafer Bağci (21،22).

There was no significant difference between boys and girls in patients with febrile seizures in terms of vitamin D3 levels with P-value=0.7. So there was no significant relationship between sexes in terms of mean vitamin D levels ،which is similar to the study of Heidarian et al. and Zafer Bağci (21،22).

Our findings, on the other hand could not find any significant difference between serum levels of vitamin D in children with febrile convulsions and their controls with febrile illness without seizures, though the vitamin D levels in patients with febrile convulsions fell in vitamin D deficient category, while in children with fever without seizures vitamin D levels were in the normal range. But it was not statistically significant between the two groups; it was probably related to the smaller number of patients, which needs to be done with a large number of patients and in the form of multi-centers.

The seemingly contradicting results can be somehow contributed to the different design of the studies.

In conclusion, although our study was unable to find a relationship between serum levels of vitamin D and the febrile convulsions, the mean level of vitamin D among these patients turned out to be at insufficient range. We recommend implementing future studies to establish guidelines for monitoring and treatment of vitamin

deficiency in this vulnerable group of children aged 6 to 60 months in an attempt to prevent febrile seizures.

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Conflict of interests

The authors declare that there is no conflict of interest.

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Authors' Contribution

EA, AG and HF were the principal investigators of the study. EA and AG were involved in preparing the concept and design. HF and AG revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read, approved the content of the manuscript and confirmed the accuracy and integrity of any part of the work.

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