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# Exploring Vitamin D in Children with Febrile Seizure: A Preliminary Study

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***Abstract***

***Background:*** Febrile seizures are the most common convulsive disorder in children. There is growing evidence that vitamin D can affect gene expression and modulate various cell metabolisms. Also vitamin D may have a role in the etiology of febrile seizures. We aimed to explore vitamin D status in children with febrile seizure.

***Materials and Methods:*** This cross-sectional study was conducted on 40 children with first episode of febrile seizure referring to Children's Medical Center in Tehran, Iran. A 5 ml blood sample was taken from the peripheral veins of each participant. Serum levels of vitamin D, calcium, phosphorus, parathyroid hormone (PTH), and alkaline phosphates (ALP) was recorded. Other variables that were recorded from each case were gender, age, parental consanguinity and family history of febrile seizure. Patients' skin color was categorized based on Fitzpatrick's scale. We asked the parents to complete a validated food frequency questionnaire including vitamin D sources in children.

***Results:*** The mean plasma calcium, phosphorous, PTH and ALP were in normal ranges; the mean vitamin D level was 24.41±11.21 ng/ml (in insufficient range). In 7.5% of patients, vitamin D level was in the deficient, 72.5% was in the insufficient and 20% was in sufficient levels. There was no significant difference in vitamin D level between two sexes (P=0.85). There was no significant correlation between vitamin D level and age (P=0.34). There was no significant correlation between vitamin D level and its metabolites (P>0.05).

***Conclusion***

There was a high prevalence of vitamin D insufficiency among our patients with febrile seizure. Further analytical studies are recommended to prove the relation between vitamin D deficiency and febrile seizure.

***Key Words:*** Children, Febrile seizure, Iran, Vitamin D.

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## 1- INTRODUCTION

Febrile seizures are the most common seizure disorder in children with a worldwide prevalence of 2 to 5% (1, 2). The disorder is characterized by seizure in children six to 60 months of age, with temperature ≥ 38ºC without any evidence of Central Nervous System (CNS) infection, electrolyte imbalance, or previous history of seizures (3). Febrile seizure is a multifactorial disorder, and various risk factors are attributed to its occurrence. However, genetic inheritance and some environmental factors are suggested to play a role in this regard (4).

Some theories about possible metabolic change during the rising phase of body temperature have been proposed, like electrolyte imbalance, vitamin B6 deficiency, and low gamma aminobutyric acid (5). Also, some studies reported trace elements can have roles in the etiology of febrile seizures (5-8). There is increasing concern that vitamin D deficiency is a major health problem in children and its worldwide prevalence has been estimated at about one billion (9-18).

There seems to be a growing interest concerning the role of this vitamin in various medical conditions such as diabetes, oncological, cardiovascular, and autoimmune and central nervous system disorders (19, 20). Although vitamin D deficiency is known to be highly prevalent among epileptic patients (21, 22), there are a few studies that have reported vitamin D deficiency rickets in a child with recurrent febrile seizures and incidence of Hypocalcemic Seizures due to vitamin D deficiency in children (23 - 25).

So, it has been hypothesized that vitamin D may be considered as the etiology of febrile seizures. The objective of this study was to explore vitamin D status in children aged six to 60 months with first episode of a febrile seizure.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

The study was cross-sectional. The study population consisted of patients admitted to two university hospital in Tehran, Iran (Ziyaiyan and Bahrami), during 2015 to ۲016. Considering the vitamin D deficiency (p) as 8% (26), q=0.92, d=0.09, α=0.0.5, β=0.8, z= 1.96 and 10% drop out, sample size was estimated 40 using following formula:

$$n = \frac{Z^{2}_{1-\frac{\alpha}{2}} pq}{d^{2}}$$

The study adopted convenience sampling approach. Enrolled patient were taken from who were admitted to pediatric emergency wards of two children hospitals in Tehran. The selection procedure followed the inclusion and exclusion criteria.

### 2-2. Inclusion and exclusion criteria

Inclusion criteria were children aged six to 60 months with first episode of a febrile seizure. Exclusion criteria were children with history of epilepsy, rickets, liver, renal or endocrine disorders and taking any medication that could interfere with vitamin D metabolism.

### 2-3. Measurements

A 5 ml of blood sample was taken from the peripheral veins of each participant by a laboratory technician. The sample put into plastic tubes. Blood samples were transferred in cold boxes to a laboratory. It should be mentioned that all measurements were performed in a single laboratory and by a single method. Calcium, phosphorus, and alkaline phosphatase were measured by the photometric method, whereas 25(OH) vitamin D level was detected using chemiluminescent immunoassay (HP, Hewlett Packard, Germany).

PTH levels were measured by electrochemiluminescence assay (IDS, England). Other variables that were recorded from each case were gender, age, parental consanguinity and family history of febrile seizure. Patients' skin color was categorized based on Fitzpatrick's scale (27). We asked the parents to complete a validated food frequency questionnaire (28) including vitamin D sources that are available for the Iranian people (such as egg, fish) to assess the children's dietary intake of vitamin D.

Also, parents completed three questions about their children's sun exposure that were frequency of sunlight exposure (One to three times daily, one to two times per week, three to five times per week); time of sunlight exposure (10 am - 3 pm), and using sunscreen (29). In order to categorize various degrees of vitamin D deficiency, we used criteria that were defined by the Iranian Ministry of Health in a national survey of micronutrient status in both pregnant women and 15 to 23-month-old children. Based on these criteria, sufficient is defined as 30 – 100 ng/ml, insufficient as 10 – 29 ng/ml, and deficient as ≤ 10 ng/ml; hypovitaminosis levels are defined as <30 ng/ml (30).

### 2-4. Ethical consideration

This study was approved by Ethics Committee of Tehran University of Medical Sciences (ID-code: 93-02-167-25676). Written informed consent was obtained from all parents who allowed their children to participate in the study.

### 2-5. Data Analyses

The SPSS software (version 18.0) was used for data analysis. Frequency and percentage were used for qualitative variables, and means and standard deviations were calculated for quantitative variables. Independent T-tests was used for the comparison of vitamin D level between two sexes. Pearson correlation was reported for vitamin D level and the other quantitative variables. For the statistical analysis, P-value <0.05 was considered as significant.

## 3- RESULTS

Forty subjects were included in this analysis. Twenty-four (60%) were male. Mean age was 2.05±1.38 years. **Table.1** shows the information on family history, parental consanguinity and sun exposure for subjects. The patients had type 3 skin color. Mean dietary intake of vitamin D in patients was 54.67 ± 13.69 IU/day. It should be noted it is recommended that all children under two years of age have a daily intake of 400 IU of vitamin D from the third birthday in Iran (31).

The mean vitamin D level was 24.41±11.21ng/ml that was in insufficient range. In 3 (7.5%) of patients, 25 (OH) vitamin D level was in the deficient, 29 (72.5%) was in the insufficient and 8 (20%) was in sufficient levels. There was no significant difference (P= 0.85) in vitamin D level between two sexes (**Table.2**). Although all three cases of vitamin D deficiency were female.

The mean, standard deviations and ranges of vitamin D metabolites are summarized in **Table.3** which were all in normal ranges. The correlation between levels of vitamin D and its metabolites or age are presented in **Table. 4.** The level of vitamin D was decreased by increasing of age but this correlation was not significant (P=0.34). There was no significant correlation between vitamin D level and calcium (P=0.07), phosphorus (P=0.19), PTH (p=0.06) and ALP levels (P=0.78).

**Table-1**: Information on family history, parental consanguinity and sun exposure for subjects

| Variables | | Frequency | Percent |
|---|---|---|---|
| Positive family history of febrile seizure | | 24 | 60 |
| Parental consanguinity | | 6 | 15 |
| Frequency of sunlight exposure | Two times per week | 23 | 57.5 |
| | Three to five times per week | 9 | 22.5 |
| | Three times daily | 8 | 20 |
| Time of sunlight exposure | Before 10 a.m. | 16 | 40 |
| | 10 a.m. – 3 p.m. | 10 | 25 |
| | After 3 p.m. | 14 | 35 |

**Table-2**: The mean of vitamin D level in two sexes of participants

| Gender | Mean ± Standard deviation(ng/ml) | Minimum 25(OH)D(ng/ml) | Maximum 25(OH)D(ng/ml) | P-value |
|---|---|---|---|---|
| Male | 24.1 ± 7.9 | 13.6 | 42 | 0.85 |
| Female | 24.8 ± 14.2 | 5.3 | 68 | |

**Table-3**: Ranges of vitamin D metabolites in participants

| Parameters | Mean ± Standard deviation | Normal range |
|---|---|---|
| Calcium (mg/dl) | 9.46 ± 0.46 | 9 -11 |
| Phosphorous (mg/dl) | 5.04 ± 0.71 | 3.1 - 6 |
| Alkaline phosphatase (IU/L) | 461.22 ± 137.95 | 180 - 1200 |
| Parathyroid hormone (pg/ml) | 28.23 ± 15.70 | 15 - 65 |

**Table-4**: The correlation between vitamin D level, age and the other parameters

| Variables | | Age | Calcium | Phosphorous | Parathyroid hormone | Alkaline phosphatase |
|---|---|---|---|---|---|---|
| Vitamin D level | Pearson Correlation | -0.15 | 0.28 | 0.21 | 0.64 | -0.04 |
| | P-value | 0.34 | 0.07 | 0.19 | 0.06 | 0.78 |

## 4- DISCUSSION

In this study we examined vitamin D status in children with their first episode of a febrile seizure. In accordance with results of other studies in Iran (26, 30, 32), the levels of calcium, phosphorus, and ALP were in the normal range for our participants. We observed a remarkably high frequency of vitamin D insufficiency, which was comparable to those reported by other studies. Rabbani et al. (30) reported the prevalence of an insufficient vitamin D level was 46.6%, and the vitamin D deficiency was 7.9% in children younger than two years old in Tehran. In the study by Motlaghzadeh et al. (32), the proportion of hypovitaminosis D was 66.7% in 2 to14-year-old, non-obese children, which is comparable to our results. In our study there was no significant difference in vitamin D levels between the two sexes; this was consistent with Motlaghzadeh's study (32). Julies et al. (25) reported vitamin D levels in

children with hypocalcemic seizures with clinical manifestations of febrile convulsion. In this study, 50 children under the age of 1,000 days who were referred to two hospitals in northern London were studied. 16 children had vitamin D deficiency, all of them Asian and under the age of one year. The researchers reported vitamin D deficiency as a risk factor for developing simple febrile seizures or hypocalcemic seizures, especially in children in the Asian region.

Hoecker et al. (23) reported a 13-month-old boy (from Somali) who was a case of undiagnosed nutritional rickets presenting with recurrent febrile seizures. The patient had severe hypocalcemia which resulted in a lowered seizure threshold and predisposing the patient to recurrences during febrile illnesses. In another study, Mantadakis et al. (24) reported a 5-month-old infant presented with afebrile seizures. For this patient, the diagnosis of hypocalcemic seizures as a result of vitamin D deficiency was confirmed. In contrast to the previous studies (23- 25), hypocalcemia was not present in our study patients. Also, Balasubramanian et al. and Salama and El-Sakka, reported cases of hypocalcemic seizures in breastfed infants with rickets secondary to maternal vitamin D deficiency (33, 34).

In another study Tekin et al. (35) studied the risk factors for fever in children. They reported that vitamin D deficiency can cause fever in children and adolescents. Since vitamin D deficiency remains a major public health problem in developing countries and its possible role in febrile seizures regard to our results and other studies (16-18, 26), it seems vitamin D screening in children hospitalized due to febrile seizure in order to treat this metabolic disorder is logical. It should be mentioned that our study had a major limitation, which was the lack of a matched control group due to ethical and technical problems as well as a strong parental declination in blood sampling from healthy children. Nonetheless, our study had the advantage of comprehensive evaluation of major vitamin D metabolites with an accurate laboratory method, and it had the advantage enrolling this category of patients who comprise a significant population of hospitalized children.

### 4-1. Limitations of the study

The most important limitations in our study was the necessity of taking blood samples from children, which was done by providing explanations about the study's objects for parents. The lack of control group was another limitation of this study.

## 5- CONCLUSION

There was a high prevalence of vitamin D insufficiency among our patients with febrile seizure. So we put forward the hypothesis that there is a relation between vitamin D deficiency and febrile seizure. Further analytical studies are recommended to prove this relationship.

## 6- ABBREVIATION

PTH: Parathyroid Hormone,

ALP: Alkaline Phosphates,

CNS: Central Nervous System.

**7- CONFLICT OF INTEREST:** None.

## 8- ACKNOWLEDGMENT

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