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Evaluation of Vitamin D Level in Children With Febrile Seizure Referred to Amirkola Children's Hospital, Babol

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Abstract

Objective. This study aim to evaluate the level of vitamin D with the incidence of febrile seizure. *Method.* This case-control study was conducted on 90 febrile children referred to Amirkola Children's Hospital from 19 February to 21 August 2021. Febrile children with and without seizures were considered as case and control groups, respectively. Vitamin D, calcium, phosphorus, and alkaline phosphatase were evaluated. *Results.* The mean level of vitamin D was not significant between the 2 groups ($P = .62$), but the mean level of alkaline phosphatase was higher in the case group, statistically ($P = .04$). 46.75% and 15.6% of case group, 28.9% and 26.7% of control group had deficiency and insufficiency levels of vitamin D, respectively ($P = .17$). *Conclusion.* In this study the mean level and deficiency of Vitamin D were not significant between the 2 groups. No correlation was also found between Vitamin D levels and the incidence of Febrile Seizure.

Keywords

febrile seizure, vitamin D, children

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Introduction

Febrile seizure (FS) are the most common form of convulsion in children, occurring in 2% to 5% of infants and children aged 6 to 60 months. Generalized FS is defined as a 24-hour period of fever without any evidence of metabolic abnormalities or a history of previous epilepsy.[1,2] For a child with a FS, there are 4 potential adverse outcomes: IQ deficiency,[2] increased risk of epilepsy,[2] the risk of frequent FS,[3] and death.[2]

Vitamin D (VD) deficiency in children is an important and global health issue. The causes of VD deficiency include: children with a mother's VD deficiency, darker skin color, lack of exposure to sunlight, living in northern latitudes, malnutrition, exclusive breastfeeding after 6 months, chronic use of medications (such as antifungals, antacids containing aluminum, rifampin, isoniazid, antiretrovirals, and glucocorticoids), liver failure, chronic kidney disease, obesity, cystic fibrosis, inflammatory bowel disease, asthma, and sickle cell hemoglobinopathy).[4]

VD status varies among different European, Asian, and Middle Eastern countries. The difference may be due to the amount of sun exposure and VD supplementation.[5] The prevalence of VD deficiency in our country is reported to be around 50% to 80%.[6]

Synthesis of VD in the skin is from 7-dehydrocholesterol, under the influence of ultraviolet radiation. To complete the activity, the resulting compound needs 2 hydroxylation reactions in the liver and kidney to form 25-hydroxyvitamin D and 1, 25-dihydroxy vitamin D, respectively. If the VD level changes, it is necessary to check the calcium and phosphorus levels to find the cause and monitor the treatment in some cases.[7] In

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addition to calcium-related reactions such as seizures, tetanus, and spasms, VD also has calcium-unrelated reactions, which include improving the function of the body's immune system, neurological system, and neurotransmitters responsible for convulsions.[7]

Symptoms and diseases associated with VD deficiency in children include hypocalcemia, convulsion, rickets, osteomalacia, growth retardation, infectious diseases, and autism.[4] VD and its receptors as well as the enzyme (1-alpha hydroxylase) that creates its active form, widely exist in the brain. VD deficiency has been linked to some diseases such as dementia, depression, diabetes mellitus and schizophrenia and its correction can prevent many health problems.[8] VD affects the central nervous system through calcium and non-calcium reactions, which the recent reaction is a result of the difference in gene expression in response to the VD binding to its receptor.[9] In some studies, Prescribing VD has had anticonvulsant effects in such a way that it reduces the duration of convulsion, decreases the mortality rate caused by convulsion, and delays the incidence of seizures.[7]

The common causes of infection in FS are otitis media and viral infections such as roseola, norovirus, and enterovirus.[10] VD plays an important role in the context of the innate immune system and decreasing the incidence and intensity of viral infections. The findings showed that a normal level of VD has a protective effect against otitis media and viral infections, especially in the respiratory system.[11]

Due to the great importance of preventing FS to decrease morbidities such as recurrence of FS, turning into status convulsion, and the risk of exposure to hypoxia, epileptic syndromes, developmental delay, and the need for long-term treatment with anticonvulsant drugs, as well as to prevent the incidence of FS affected by the complications of VD deficiency, this study was conducted to investigate the level of VD in children with FS referred to Amirkola Children's Hospital, Babol.

Materials and Methods

Study Design and Participants

This case-control study was conducted between 19 February to 21 August 2021 in children 6 to 60 months with simple FS referred to Amirkola Children's Hospital, Babol. After applying the inclusion and exclusion criteria, the required information was collected and recorded with the full consent of the parents through an interview. The inclusion criteria in the case group included: the presence of fever at the time of convulsion (fever in the form of an axillary temperature of 38°C and above), convulsion (lasts less than 15 minutes, occurs once in 24 hours and is not focal), regular use of VD supplements in children under 2 years of age according to the health protocol of the country, no history of head trauma, no known causes of convulsions such as meningitis, encephalitis, shigellosis, electrolyte abnormalities (such as hypocalcemia) and metabolic disorders, absence of neurological diseases (such as epilepsy) and history of seizure without fever, absence of underlying kidney and liver diseases and malabsorption syndromes, lack of use of therapeutic doses of VD in children with a previous history of VD deficiency, not receiving any anticonvulsant drugs, even benzodiazepine during fever. For each patient, 1 child of the same age and gender with fever without seizure who was admitted to the hospital due to viral infections (other than CNS infection), respiratory and gastrointestinal infections, was considered in the control group.

Sample Size and Sampling

In past studies, the prevalence of VD deficiency and insufficiency in community children[12] and with fever and convulsions were reported at 50% and 80%, respectively.[13] The sample size was estimated at 36 children in each group with a confidence interval of 95% and 80% test power (with the following formula). In order to increase the accuracy of the study, it was increased to 45 people. Sampling was done by the census.

$$n = \frac{(z_{1-a/2} + z_{1-\beta})^2 * [p_1(1-p_1)p_2(1-p_2)]}{(1-p_1)^2}$$

Data Collection

In both groups, blood levels of VD, calcium, phosphorus and Alkaline phosphatase (ALP) were measured. VD level was measured by ELISA method with Ideal Tashkhis kit made in Iran. Calcium level was measured by photometric method with Pars test kit made in Iran. Phosphorus level was measured by photometric method with Man kit made in Iran and ALP level was measured by DGKC method with Pars Azmoun kit made in Iran. Deficiency of VD as a level under 20 ng/mL (50 nmol/L), insufficiency as a level between 21 and 29 ng/mL (52.5-72.5 nmol/L) and sufficiency were considered at a level of more than 30 ng/mL (>75 nmol/L) and toxicity at levels above 150 ng/mL (375 nmol/L).[4,5] The normal level of calcium between 8.5 and 10.5 mg/dL and the normal level of phosphorus between 3 and 6 mg/dL were considered, according to the reference range of the kit used. The normal level of ALP in children was considered

Table 1. Comparison of VD- Calcium-Phosphorus and ALP Levels Between 2 Case and Control Groups.

Group			
Variable	Case (fever and convulsions)	Control (fever without convulsions)	*P*-value
V D (ng/mL)	27.04 ± 13.75	27.67 ± 12.53	.62
Calcium (mg/dL)	9.52 ± 0.50	9.46 ± 0.61	.57
Phosphorus (mg/dL)	3.90 ± 0.65	3.76 ± 0.71	.26
ALP (IU/L)	496.37 ± 171.48	428.60 ± 137.34	.04

between 150 and 1200 IU/L, according to the reference range of the kit used. The patient's information was kept confidential and was not given to any natural or legal person. No additional costs were imposed on the patient.

Statistical Analysis

Children information and laboratory test results were collected and statistically analyzed using SPSS version 22. Descriptive statistics indicators such as mean, standard deviation, frequency, percentage and descriptive statistics table were examined for the study variables. Also, chi-square and *t*-test, were used to check the relationship between the investigated variables. *P* values less than .05 were considered statistically significant.

Results

Ninety eligible people participated in this study. There were 45 people in the case group with a mean age of 17.9 ± 9.97 months and 45 people in the control group with a mean age of 18.6 ± 9.90 months. There was no statistically significant difference between the 2 groups in terms of mean age ($P=.71$). In the case group, there were 22 (48.9%) boys and 23 (51.1%) girls, and in the control group, 19 (42.2%) boys and 26 (57.8%) girls. Statistically, no significant difference was found between the 2 groups in terms of gender through chi-square test. ($P=.52$)

In this study, the laboratory factors of calcium, phosphorus and ALP were investigated in addition to VD in 2 groups (Table 1).

The mean level of the above laboratory factors in girls and boys was also evaluated separately. The mean level of VD in the boys in the case and control groups were 27.73 ± 15.55 and 28.63 ± 12.99 ng/mL respectively, which was not statistically significant ($P=.61$). The mean level of calcium and phosphorus in the boys in the case group was 9.52 ± 0.40 and 3.81 ± 0.53 mg/dL respectively, and the level of these 2 factors in the boys in the control group was 9.44 ± 0.68 and 3.63 ± 0.59 mg/dL, respectively. No significant difference was found between the mean levels of calcium and phosphorus between the 2 groups ($P=.62$ and 0.27, respectively). The mean level of ALP in the boys in the case and control groups were 492.90 ± 155.09 and 432.21 ± 147.08 IU/L respectively, and no significant relationship was found ($P=.11$).

Also, the above values were examined in the group of girls and the following results were obtained: the mean level of VD in girls in the case and control groups were 26.37 ± 12.09 and 26.96 ± 12.40 ng/mL respectively, which was not statistically significant ($P=.73$). The mean level of calcium and phosphorus in girls in the case group was 9.53 ± 0.59 and 4.00 ± 0.74 mg/dL respectively, and the level of these 2 factors in girls in the control group was 9.48 ± 0.56 and 3.86 ± 0.79 mg/dL, respectively that showed no significant difference between 2 these groups ($P=.78$ and 0.50, respectively). The mean level of ALP in the girls in the case and control groups were 499.69 ± 189.29 and 425.96 ± 132.68 IU/L respectively, which was not found to have a significant relationship ($P=.19$).

In the case group, 21 (46.7%), 7 (15.6%), and 17 (37.8%) of children had deficient, insufficient and sufficient levels of VD respectively, and these data in the control group was 13 (28.9%), 12 (26.7%), and 20 (44.4%) respectively, which in the statistical analysis between the 2 case and control groups, no significant difference was found in terms of VD levels ($P=.17$). Also, a comparison was made between children with VD deficiency in 2 groups. In the case group 21 (46.7%) people had VD deficiency and in the control group, 13 (28.9%) people had VD deficiency, but in the statistical analysis by Chi-square method between the 2 groups, no significant difference was found ($P=.08$).

In this research, a comparison was also made between children with normal levels of VD (VD >30 ng/mL) and patients with abnormal levels of VD (VD <30 ng/mL). In the case group, 17 (37.8%) people had normal levels of VD and a total of 28 (62.2%) people had an abnormal level (insufficient and deficient levels) of VD, while in the control group, 20 (44.4%) people had a normal level of VD and a total of 25 (55.6%) people had abnormal VD levels, with no significant difference ($P=.52$).

Discussion

The results of this study showed that 46.7% of children in case group and 28.9% of children in control group had VD deficiency, and children with VD deficiency had more convulsions, but this difference was not statistically significant. The mean level of VD in the case and control groups was 27.04 ± 13.75 and 27.67 ± 12.53 ng/mL respectively, which did not indicate a significant difference between the 2 groups.

The mean level of ALP was 496.37 ± 171.48 IU/L in the case group and 428.60 ± 137.34 IU/L in the control group, which was significantly higher in the case group.

In a study conducted by Heydarian et al, the aim was to investigate the level of VD in 51 children with FS and 53 children with fever without seizure who were between 6 and 60 months old. The results showed that the mean level of VD in the group with seizure was 41.9 ng/mL and in the group without seizure it was 48.4 ng/mL. Similarly to the present study, despite being lower in the group with seizures, no statistical difference was seen between the 2 groups.[14]

In a study conducted by Bağci et al, the serum level of VD in children with FS was 14.95 and 19.08 ng/mL in the group of children with fever, which did not show a significant difference ($P = .07$),[15] which is in line with the results of the present study.

Another study conducted by Aydin et al, with investigating the laboratory factors among children with and without FS, concluded that the mean level of VD in children with FS was 22 and 31 ng/mL in the control group, which had a statistically significant difference ($P = .01$), which was contrary to the results of the present study. The main difference with the present study was that in this study, the control group was healthy children who visited in the clinic for growth monitoring,[15] but in our study, the control group was febrile children.

In the research conducted by Singh et al, in the FS group, 73% of the children had an abnormal level of VD (total deficiency or insufficient amounts), which was 45.9% in the control group, and there was a significant difference between the 2 groups ($P = .01$). However, in our study, 62.2% of children in the case group and 55.6% of the children in the control group had abnormal levels of VD (VD <30 ng/mL), which showed no significant difference, contrary to the results of Singh's research. However, in the above research, there was no mention of the mean levels of VD in the 2 groups.[15] Of course, our study was conducted during the COVID-19 epidemic, which could have affected the number of our cases.

The number of studies in which FS patients have been compared with a control group is few and the present study is the fifth study that compares VD levels in patients with FS and patients with fever without seizure in 2 groups of cases and controls. The study of Bagci and Heydarian were in line and the 2 studies of Aydin and Singh were opposite to our study in terms of the relationship between FS with VD deficiency.

In the study of Julies et al, infants who had convulsions due to hypocalcemia were examined and 32% of them had VD deficiency, of which 20% were hospitalized with FS, so they concluded that hypocalcemia in the context of VD deficiency can show itself as the first time of FS. Considering that in our study, patients with electrolyte abnormalities such as hypocalcemia were excluded from the study, we did not see a significant difference in the level of calcium and phosphorus between the 2 groups, which is in line with the studies conducted in this field.[16]

The significantly higher ALP in the case group can be caused by the higher percentage of patients with VD deficiency in the case group compared to the control group (46.7% vs 28.9%), although this difference was not statistically significant ($P = .08$). In the study by Heydarian et al, which had the same working method and sample size as the present study, the mean level of calcium and phosphorus in the 2 groups of cases and controls was not significantly different.[14] Therefore, it was in line with the present study.

In the present study, among the other variables examined, only ALP was significantly higher in the FS group than in the control group. In the research conducted by Güneş et al, investigating risk factors related to the incidence of FS in children (as in the present study), a positive relationship between the incidence of FS and ALP level was found.[17] This could be due to the higher percentage of people suffering from FS with VD deficiency, and it is better to consider the measurement of ALP along with VD in children with fever. In a study conducted by Heydarian et al, the level of ALP in children with FS was 530 and 519 IU/L in children without FS; however, as in the present study, the level of ALP was found to be higher in patients with FS, but this difference was not significant.[14]

Typically, FS occurs between the ages of 6 months and 5 years, and shown previous have studies that the most common age of FS is between 18 and 22 months.[17] The present study and previous studies showed that the mean age of children with FS was 18 months. The limitation of this study was the small number of cases due to the COVID-19 pandemic.

Conclusion

In the present study, the patients with VD deficiency had more convulsions, but this difference was not statistically significant. The mean level of VD in the control group in comparison with the case group was not

statistically significant and there was no correlation between the level of VD and the incidence of seizures. It is suggested that future studies be conducted as a multicenter study and with a greater number of cases. Additionally, to determine the role of VD deficiency in the recurrence of convulsions, patients should have long-term follow-up. It is also suggested to compare the level of VD in children with their first seizure and children with a history of recurrent seizures.

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Authors' Contribution

All authors collaborated in all stages of the design, data collection, and writing of the article. Dr M.A. as the responsible author submitted the article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was approved by the Ethical Committee of Babol University of Medical Sciences. Approval ID: IR.MUBABOL.REC.1399.506. (Webpage of ethical approval code is: https://ethics.research.ac.ir/EthicsProposalView.php?id=186144). The written consent was obtained from all subjects or their parents.

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