

## COMPARISON OF SERUM VITAMIN D LEVELS IN FEBRILE CHILDREN WITH AND WITHOUT SEIZURE

### Nöbetin Eşlik Ettiği ve Etmediği Febril Çocuklarda Serum D Vitamini Düzeylerinin Karşılaştırılması

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#### ABSTRACT

**Objective:** The pathogenesis of febrile seizures in children is unknown. The aim of this study was to show the correlation between febrile seizures and serum vitamin D levels in children.

**Material and Methods:** Boys and girls aged 6 months to 5 years with a fever  $\geq 38^{\circ}\text{C}$  with or without seizures in the Paediatric Emergency Clinic were included in the study. The patients were divided into two main groups: with febrile seizures and without febrile seizures. Patients in the febrile seizures group were subdivided into simple febrile seizures—complicated febrile seizures, first febrile seizures—repetitive febrile seizures characteristics.

**Results:** There was no statistically significant difference between febrile seizures group and febrile group in terms of serum vitamin D levels and other laboratory parameters. (For vitamin D, median was 14.95 (IQR:10.88), 19.08 (IQR:11.38), respectively,  $p = 0.077$ ). No statistically significant difference was found between the simple febrile seizures group and the complicated febrile seizures group in terms of serum vitamin D levels ( $p = 0.198$ ). There was no significant difference between the group with recurrent seizures and the group that had febrile seizures for the first time in terms of serum vitamin D levels ( $p = 0.848$ ).

**Conclusion:** No significant relationship was found between FS and vitamin D levels in this study. There are few studies in the literature that support and do not support the relationship. Our study is different in terms of evaluating the seizure type and recurrence. More studies with a similar methodology, with a large number of cases, are needed.

**Keywords:** Febrile Seizure; Vitamin D; Child

#### ÖZET

**Amaç:** Çocuklardaki febril nöbetin patogenezi halen kesin olarak bilinmemektedir. Bu çalışmanın amacı, çocuklardaki febril nöbetler ile serum D vitamini düzeyleri arasındaki ilişki düzeylerini ortaya koymaktır.

**Gereç ve Yöntemler:** Bu çalışmaya, çocuk acil kliniğinde nöbetle birlikte veya nöbetsiz  $\geq 38^{\circ}\text{C}$  ateş saptanan 6 ay-5 yaş arası kız ve erkek çocuklar dahil edildi. Hastalar febril nöbete sahip olanlar ve olmayanlar olarak iki ana gruba ayrıldı. Febril nöbet grubundaki hastalar, basit febril nöbet-komplike febril nöbet ve ilk febril nöbet-tekrarlayıcı febril nöbet özelliklerine göre alt gruplara ayrıldı.

**Bulgular:** Febril nöbet grubu ile febril grup arasında serum D vitamini düzeyleri ve diğer laboratuvar parametreleri yönünden istatistiksel olarak anlamlı bir farklılık saptanmadı. (D vitamini için, ortanca değer 14,95 (IQR:10,88) vs. 19,08 (IQR:11,38)  $p = 0,077$ ). Basit febril nöbet grubu ile komplike febril nöbet grubu arasında serum D vitamini düzeyleri yönünden istatistiksel olarak anlamlı bir farklılık saptanmadı ( $p = 0,198$ ). Tekrarlayan nöbete sahip olan hasta grubu ile ilk kez febril nöbet geçiren grup arasında serum D vitamini düzeyleri yönünden anlamlı fark saptanmadı ( $p = 0,848$ ).

**Sonuç:** Bu çalışmada, febril nöbet ile serum D vitamini düzeyleri arasında anlamlı bir ilişki saptanmadı. Literatürde ilişkiyi destekleyen ve desteklemeyen az sayıda çalışma bulunmaktadır. Çalışmamız nöbet tipi ve tekrarlayıcılığını değerlendirmesi yönüyle farklıdır. Bu konuda olgu sayısının fazla olduğu, benzer metodolojiye sahip daha fazla sayıda çalışmaya ihtiyaç vardır.

**Anahtar Kelimeler:** Ateşli Nöbet; D Vitamini; Çocuk

## INTRODUCTION

Febrile seizure (FS) is one of the most common acute neurological conditions seen in children aged 3 months to 5 years. The incidence of this condition, which is not accompanied by any metabolic abnormality or central nervous system (CNS) infection, is 2–5% in children with fever  $\geq 38^{\circ}\text{C}$ . FS recurs in 30–50% of febrile patients (1). It is most common between 18 and 24 months. Simple FSs (SFS) are generalized seizures that last less than 15 minutes, do not recur in the first 24-hour period and do not show pathological findings in the postictal trial. Complicated FSs (CFS) are generalized seizures that last longer than 15 minutes, recur within the first 24-hour period following the first seizure; they are focal in nature or pathological findings are observed during the postictal period (1,2).

Despite many proposed mechanisms, the pathogenesis of FS is still not known exactly. It is assumed that genetic and environmental factors play a role in its mechanism. It may be due to electrolyte disturbances, especially febrile infections, and various conditions that stimulate the CNS such as head trauma (3,4). Fever is a very common finding in children, and the exact cause of FS associated with fever is still unclear.

Vitamin D is a fat-soluble vitamin and a group of steroids that can also be synthesized endogenously. Its most important effect is on calcium, phosphorus metabolism, and bone mineralization (5). Both vitamin D deficiency and insufficiency are likely to be the risk factors for broad-spectrum acute and chronic diseases (6). Vitamin D deficiency is associated with nutrition and rapid growth and is more common in infancy and adolescence. Today, although vitamin D deficiency is more common in developing countries, it continues to be an important public health problem all over the world (7). Previous *in vitro* studies have shown that vitamin D has a neuroprotective effect on brain cells, and a relationship between serum vitamin D levels and epilepsy has been revealed (8-10). However, there are very few studies in the literature investigating the relationship between FS and vitamin D levels (11-13). The aim of this study was to reveal the relationship between FS and serum vitamin D levels in children.

## MATERIAL AND METHOD

This prospective study was conducted between March

2019 and June 2019 at Konya Training and Research Hospital Paediatric Emergency Clinic. The study protocol was approved by the Ethics Committee of Necmettin Erbakan University Faculty of Medicine, with the decision dated March 15, 2019 and numbered 2019/1766. The study participants consisted of boys or girls aged 6 months to 5 years who were brought to the Paediatric Emergency Clinic with a fever  $\geq 38^{\circ}\text{C}$ . Those who signed an informed consent form from the legal parents of the participants were included in the study. The patients were divided into two main groups: with FS and without FS. Patients with FS were divided into two groups as simple or complicated FS.

Sociodemographic data, seizure type, duration, previous seizure, presence of additional disease, and drug history of all participants were recorded. Blood samples were taken within the first hour after the participants admitted to the emergency clinic. Complete blood count (CBC), calcium, phosphorus, and magnesium levels of the patients were measured at admission. Sera obtained from the participants were kept labelled at  $-80^{\circ}\text{C}$ , and vitamin D, alkaline phosphatase, and parathyroid hormone levels were studied at the end of the study. All measurements were made in a single laboratory and using a single method. 25 (OH) vitamin D levels were determined using a chemiluminescent immunoassay (Siemens Advia centaur xp, Siemens Healthcare Diagnostics, Erlangen, Germany). 25 (OH) Vitamin D levels lower than 20 ng/mL were defined as 'deficiency', levels between 20-30 ng/mL were defined as 'insufficiency' and levels over 30 ng/mL were defined as 'sufficient' (14).

The children between 1–6 months to 5 years, with or without febrile seizures (fever  $\geq 38^{\circ}\text{C}$ ) were included in the study. Detection of CNS infection (meningitis, encephalitis), hypoglycemia, hypocalcemia, hypernatremia or hyponatremia, co-existence of a metabolic disease or antiepileptic drug intake history were defined as exclusion criteria.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp.). The normal distribution of the data was checked using the Kolmogorov–Smirnov test. Descriptive statistics of the categorical variables were presented as frequencies and percentages, while normally distributed variables are presented as mean  $\pm$  standard deviation

(SD), and the non-normally distributed variables are presented as median and interquartile range (IQR). The chi-square test was used to evaluate the gender distribution of the groups. Independent samples t-test (Student's t-test) was used in normally distributed groups, and Mann–Whitney U test was used in non-normally distributed groups to compare the differences between groups with numerical variables. All statistical analyses were performed by formulating two-way hypotheses with a 5% significance threshold and a 95% confidence interval.

**RESULTS**

A total of 95 cases, 57 FS and 38 febrile, were included in the study. Of the FS group, 26 were girls (45.6%), 31 were boys (54.4%), and the median age was 23 (IQR: 20) months. In the F group, 16 were girls (42.1%), 22 were boys (57.9%), and the median age was 20 (IQR:

24) months. The two groups were similar in terms of age and gender (Table 1).

Although the vitamin D levels of the FS group were higher than that of the F group, no statistically significant difference was found between the two groups in terms of serum vitamin D levels. (For vitamin D, median was 14.95 (IQR:10.88), 19.08 (IQR:11.38), respectively, p = 0.077). The two groups were statistically similar in terms of parathormone (p = 0.474), alkaline phosphatase (ALP) (p = 0.487), phosphorus (p = 0.840), calcium (p = 0.429) and magnesium (p = 0.125) levels (Table 2). Fifty of the children with FS were diagnosed with simple FS, seven of them were diagnosed with CFS. No statistically significant difference was found between the Simple FS and the CFS groups in terms of serum vitamin D (p = 0.198), parathormone (p = 0.803), ALP (p = 0.497), phosphorus (p = 0.410), calcium (p = 0.933), and magnesium (p = 0.714) levels (Table 3).

**Table 1.** Baseline characteristics of febrile patients with and without seizure.

|             | Febrile seizure<br>n = 57 (60%) | Fever without seizure<br>n = 38 (40%) | p value |           |
|-------------|---------------------------------|---------------------------------------|---------|-----------|
| Age (month) | Median (IQR)                    | Median (IQR)                          | 0.456*  |           |
|             | 23 (20)                         | 20 (24)                               |         |           |
| Gender      | n (%)                           | n (%)                                 | 0.736** |           |
|             | Female                          | 26 (45.6)                             |         | 16 (42.1) |
|             | Male                            | 31 (54.4)                             |         | 22 (57.9) |

IQR: Interquartile range, \*Mann Whitney-U test, \*\*Chi-Square test

**Table 2.** Comparison of vitamin D levels and other laboratory parameters of febrile patients with and without seizure.

|                             | Febrile seizure<br>n = 57 (60%)<br>median (IQR), mean ± SD | Fever without seizure<br>n = 38 (40%)<br>median (IQR), mean ± SD | p value |
|-----------------------------|--|--|---------|
| Vitamin D (ng/mL)           | 19.08 (11.38)  | 14.95 (10.88)  | 0.077*  |
| Parathyroid hormone (ng/L)  | 11.1 (13.4)  | 12.15 (13.9)   | 0.474*  |
| Alkaline phosphatase (IU/L) | 126 (77)   | 137.5 (69)   | 0.487*  |
| Phosphorous (mg/dL)         | 4.82 (0.92)  | 4.65 (1.29)  | 0.840*  |
| Calcium (mg/dL)             | 9.60 (±0.56)   | 9.69 (±0.48)   | 0.429** |
| Magnesium (mg/dL)           | 2.09 (±0.18)   | 2.15 (±0.19)   | 0.125** |

The data were given as median (IQR) or mean ± SD. IQR: Interquartile range, SD: Standard derivation, \*Mann Whitney-U test, \*\*Student-t test. Nanogram (ng); millilitre (mL); decilitre (dL); milligram (mg); international unit (IU)

**Table 3.** Comparison of vitamin D levels and other laboratory parameters of complicated FS and simple FS groups

|                                    | Complicated FS<br>n = 7 (12.3%)<br>median (IQR), mean ± SD | Simple FS<br>n = 50 (87.7%)<br>median (IQR), mean ± SD | p value |
|------------------------------------|--|--|---------|
| Vitamin D (ng/mL)                  | 20.57 (13.68)  | 18.59(11.01)   | 0.198*  |
| Parathyroid hormone (ng/L) (pg/mL) | 11.5 (14.7)  | 11.05 (13.2)   | 0.803*  |
| Alkaline phosphatase (IU/L)        | 163 (66)   | 126 (74)   | 0.497*  |
| Phosphorous (mg/dL)                | 4.68 (0.53)  | 4.84 (1.05)  | 0.410*  |
| Calcium (mg/dL)                    | 9.62 (±0.24)   | 9.60 (±0.59)   | 0.933** |
| Magnesium (mg/dL)                  | 2.06 (±0.21)   | 2.09 (±0.18)   | 0.714** |

The data were given as median (IQR) or mean ± SD. IQR: Interquartile range, SD: Standard derivation, \*Mann Whitney-U test, \*\*Student-t test. Nanogram (ng); millilitre (mL); decilitre (dL); milligram (mg); international unit (IU)

Eleven of the children with FS had experienced FS at least once before, and 46 of them experienced FS for the first time. Serum calcium levels of the patient group with recurrent FS were found to be statistically higher than the group with non-recurrent FS (respectively,  $9.92 \pm 0.57$ ),  $(9.52 \pm 0.57)$ ,  $p = 0.033$ ). The two groups were statistically similar in terms of 25 (OH) vitamin D ( $p = 0.848$ ), parathormone ( $p = 0.570$ ), ALP ( $p = 0.551$ ), phosphorus ( $p = 0.225$ ) and magnesium ( $p = 0.234$ ) levels (Table 4).

**DISCUSSION**

The exact prevalence of vitamin D deficiency is unknown in Turkey. The studies conducted so far have small sample sizes and the results cannot be generalized since the studies are regional. Andiran

et al. reported prevalence of vitamin D deficiency in 440 children and adolescents in Ankara as 25% and insufficiency as 15% (15). Meral et al. reported the average of 25 (OH) vitamin D levels as  $30.2 \pm 22.1$  (SD) in children aged 0–5 years in Istanbul (16).

Vitamin D deficiency is associated with various medical disorders related to the musculoskeletal as well as the immune, metabolic, neurological, and cardiovascular systems (6). There are no adequate studies on the effect of vitamin D deficiency on early brain development in humans. Vitamin D receptors and 1-alpha-hydroxylase are widely distributed in the brain (17). Although the relationship between vitamin D and epilepsy has been established, its role in FS has attracted attention only in recent years, and the number of studies on this subject is very few.

**Table 4.** Comparison of vitamin D levels and other laboratory parameters of repeated FS and non-repeated FS groups.

|                             | Repeated FS<br>n = 11 (19.3%)<br>median (IQR) mean ± SD | Non-repeated FS<br>n = 46 (80.7%)<br>median (IQR) mean ± SD | p value |
|-----------------------------|---|---|---------|
| Vitamin D (ng/mL)           | 17.82 (11.24)   | 19.2 (12.3)   | 0.848*  |
| Parathyroid hormone (ng/L)  | 15.3 (12.3)   | 11.05 (14.1)  | 0.570*  |
| Alkaline phosphatase (IU/L) | 126 (38)  | 139 (80)  | 0.551*  |
| Phosphorous (mg/dL)         | 4.92 (1.01)   | 4.78 (0.9)  | 0.225*  |
| Calcium (mg/dL)             | 9.92 (±0.37)  | 9.52 (±0.57)  | 0.033** |
| Magnesium (mg/dL)           | 2.15 (±0.15)  | 2.07 (±0.19)  | 0.234** |

The data were given as median (IQR) or mean ± SD. IQR: Interquartile range, SD: Standard derivation, \*Mann Whitney-U test, \*\*Student-t test. Nanogram (ng); millilitre (mL); decilitre (dL); milligram (mg); international unit (IU)

Hoacker et al. reported a previously undiagnosed case of nutritional rickets, who applied with recurrent FS in 2002 (18). It was suggested by the authors that the case with severe hypocalcemia lowered the FS threshold. In a study conducted by Shariatpanahi et al. of 40 children with their first seizure attack, vitamin D deficiency was reported in 7.5%, vitamin D insufficiency in 72.5% and normal vitamin D levels in 20% of the patients (11). The absence of a control group was the limitation of this study. Heyderian et al. compared 53 children with FS with 53 children with fever and without seizures in terms of serum vitamin D levels and reported that there was no difference between the two groups ( $p = 0.07$ ) (13). This study is methodologically similar to ours, and moreover, its results were consistent with our results. The difference between the results of the two studies was that, although not statistically significant, the mean serum vitamin D levels in children in the FS group in our study were higher than those with fever without seizures.

The status of serum vitamin D level and its relationship with recurrence of seizures was investigated in another study; with 223 children who had SFS, it was found that 30.85% of these children had vitamin D deficiency and 43.5% had vitamin D insufficiency. It has been reported to be negatively correlated with repetitive FS (12). In our study, children who had a seizure for the first time were compared with those who had recurrent seizures in terms of serum vitamin D levels, and no difference was found between the two groups.

Children with complicated FS and simple FS have never been compared in terms of serum vitamin D levels in any of the studies conducted so far. Our study was the first study in the literature in this respect. Even if the number of patients with complicated FS was small, our results showed that there was no statistical difference between these two groups.

## CONCLUSION

There are few studies in the literature that report a correlation between FS and vitamin D levels. In this study, we found that 25 (OH) vitamin D levels in children with FS were not statistically different from children with fever and without seizures. Our results are consistent with a previous study in the literature

with a similar methodology. In addition, our study revealed that vitamin D levels were not different between simple and complicated FS and among children with first repetitive FS. More studies with similar methodology are needed to clarify the levels of association.

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