



The association of serum vitamin D and calcium level with febrile convulsions

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Febrile convulsions are among the leading public health problems that affect children between 6 months and 5 years of age, and the effect of this condition on their lives and its exact cause are not fully understood. Many risk factors have been underresearched. Among the possible factors are the vitamin D and calcium levels. The aim of this study is to determine the association of febrile convulsion with the level of vitamin D and calcium. The study included 40 children with febrile convulsion as a case group and 40 children with fever ($>38.5^{\circ}\text{C}$) without convulsion as the control group. Blood samples were taken from all the participants, put into gel tubes, then the blood was centrifuged to separate the samples and collect the serum. Then the serum level of vitamin D and calcium level were measured. In the cases group, 75% were male and only 25% were female. There were significant differences between the groups in the serum level of vitamin D and calcium with P-value of $P < 0.0001$, $P < 0.0080$, respectively. The majority of patients in the febrile convulsion group (52.5%) had vitamin D deficiency. There is a significant effect of vitamin D deficiency and low calcium level on the occurrence of febrile convulsion in children.

Keywords: febrile convulsion; vitamin D; calcium; epilepsy.

Introduction

Febrile convulsions (FC), defined as convulsions that are associated with fever higher than 38°C , usually occur in children aged 6 to 60 months without any intracranial reason such as infection, head trauma, epilepsy, or a history of afebrile convulsions (Chungath & Shorvon, 2008; Baradwaj et al., 2024; Kurniawati et al., 2024). They occur in about 2–5% of healthy children around the world (Leung et al., 2018).

There are two types of FCs, the first is simple FCs, which are generalized tonic-clonic convulsions that persist for less than 15 minutes and are not repeated in the next 24 hours. The second type is complex FCs, which may be a generalized or focal convulsions, persist for more than 15 minutes, are repeated within the next 24 hours, and are accompanied by a prior or post-neurological defect (Bhat et al., 2020). Many risk factors may contribute to the etiology of FCs, including the genetic background and the environmental factors that have a major role in their occurrence (Shi et al., 2012).

It is known that many intracellular processes in the brain are influenced by calcium influx (Annapurna et al., 2024). A large amount of research has revealed mixed results regarding the relationship of low serum electrolytes, counting the low calcium level, with the occurrence of convulsions (Sujatha et al., 2025). A significant decrease in calcium level leads to unrestrained epileptic discharges as a result of excitatory postsynaptic transmissions (Banu et al., 2024). Calcium ions bind to the outer surface of the sodium channel's protein in the neuronal plasma membrane, which makes the neuronal membranes more permeable to sodium ions, producing progressive depolarization and increasing the probable action potential. In the absence of calcium ions, the voltage needed to open sodium channels changes considerably (fewer excitations). In hypocalcemia, spontaneous action potentials occur, making peripheral skeletal muscle contract, resulting in convulsions. Throughout acute febrile illness, water and electrolyte disturbances commonly occur. It has been proposed that a variation in serum calcium may raise vulnerability to convulsion (Sarker et al., 2022). Hypocalcemia is a common cause of convulsion, and it can be represented as muscle spasms, convulsions, tetany, and paresthesia (Alkhafaji et al., 2024). The normal range for calcium is 2.15–2.50 mmol/L (Jin et al., 2024). The synthesis of vitamin D depends on the time of day, the part of the body exposed to the sun, and the tone

of the skin. Children with dark skin, higher content of melanin, produce a smaller amount of vitamin D than children with light skin color (Mostafa & Hegazy, 2015). The range of vitamin D is <20 ng/mL deficiency, 20–30 ng/mL insufficient, 30–100 ng/mL sufficient, and >100 vit D toxicity (Holick et al., 2011). Vitamin D is a fat-soluble vitamin, and thyroid hormone is a steroid hormone, and both bind to steroid hormone receptors in a similar manner (Al-Ashou et al., 2020).

The latest research has demonstrated the key role of vitamin D in the central nervous system's development (Anjum et al., 2018). A great deal of research is being conducted on the effect of vitamin D on convulsions. Both neurons and glial cells contain receptors of vitamin D_3 and enzymes. It has been suggested that vitamin D has an anti-convulsion effect via regulating the gene expression by binding to vitamin D receptors in the nucleus. Vitamin D also helps in absorbing calcium and reducing the excitability of the central nervous system. It also contributes to the regulation of the calcium and chloride currents through neuronal cell membranes (Pendo & DeGiorgio, 2016).

Various studies have demonstrated a correlation between disorders related to vitamin D and epilepsy. Deficiency in vitamin D leads to hypocalcemia, which may lead to seizures as a result of the extreme irritability of neuronal membranes. Convulsions that occur due to low levels of vitamin D and hypocalcemia are usually seen in hereditary or nutritional rickets patients. Studies have also shown that treatment with vitamin D and calcium through reducing hypocalcemia decreases seizures in rickets patients. Furthermore, studies on laboratory animals show direct anticonvulsant effects of 1,25-dihydroxy vitamin D (Abbasi et al., 2021). The hypothesis of the study is that deficiency in vitamin D and low calcium level play a significant role in the incidence of FC in children, and vitamin D supplement decreases the incidence of FC in children.

Material and methods

This case control study was carried out in Al-Mosul General Hospital in Mosul City for five months, June to October 2024. The primary aim of this research was to compare serum levels of vitamin D and calcium levels between two distinct groups of children: children with FC and children who had fever without convulsions. The study enrolled a total of 80 children, with 40 children assigned to each group: Case Group: Children with FC; Control Group: Children with fever

(>38.5 °C) but no history or episode of convulsions. Each group comprised children of 6 months to 60 months of age who were admitted in the hospital during the study period. The control group was matched according to age to the case group so that the results obtained are comparable.

All children had physical examination and their medical history was obtained. Children with any intracranial pathology, including infection, head injury, epilepsy, or febrile seizures or any other neurological developmental abnormality were excluded from the study.

The blood was drawn from each child using a sterile plastic syringe. Blood samples were placed in gel tubes to facilitate clotting and serum separation. The gel tubes were centrifuged so as to form the serum layer of blood. The obtained serum was then portioned for analysis. Of this amount, 200 µL of serum was used in the determination of vitamin D levels. The quantification was done using the VIDS immunoanalyzer device, which is accurate for determining the level of vitamin D.

For calcium measurement, 50 µL of serum were pipetted into cuvettes. The calcium concentration was determined through the use of a ThermoFisher device, which helped in giving accurate measurements.

To analyze the data we used the SPSS software version 26.0 to calculate the percentage, means (\bar{x}) ± standard deviations (SD) of the variables. The independent T-test and chi-square test were used to compare the vitamin D and calcium level between the groups, $P < 0.05$ was considered statistically significant.

Results

This study included 40 patients in the FC group and 40 patients in the fever without convulsion group. This descriptive table presents the mean and standard deviation for key clinical and biochemical parameters in two study groups: children with Febrile Convulsions (FC Group) and children with Fever without Convulsions. The parameters include age, weight, calcium, vitamin D, hemoglobin (Hb), and random blood sugar (RBS) levels.

Table 1
Descriptive table for key clinical and biochemical parameters ($\bar{x} \pm SD$)

Parameter	FC group	Fever group
Age, months	26.1 ± 18.1	24.2 ± 14.3
Weight, kg	11.3 ± 3.5	11.9 ± 2.8
Calcium, mmol/L	2.14 ± 0.13	2.23 ± 0.15
Vitamin D, ng/mL	20.6 ± 12.3	44.9 ± 20.2
Hemoglobin, g/dL	10.8 ± 2.2	10.5 ± 1.0
Random blood sugar, mmol/L	6.6 ± 2.5	5.3 ± 1.1

The results of the study show that there was a different sex distribution between the groups of study. In the FC group, 75% of cases were male patients, and only 25% of cases were female. However, in the fever without convulsion group, 47.5% of cases were male and 52.5% were female (Fig. 1).

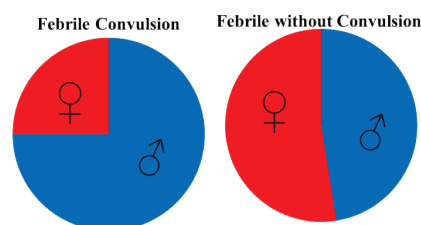


Fig. 1. Sex distribution in febrile with convulsion versus febrile without convulsion

The mean of calcium level in the FC group was 2.14 ± 0.13 mmol/L, which was less than the normal range, while the mean for the fever group was 2.23 ± 0.15 mmol/L. There was a statistically significant difference in the calcium level between the two groups with a $P = 0.008$. Also, the mean value of vitamin D in the FC group was 20.6 ± 12.3 ng/mL, which was an insufficient level, while the mean vitamin D in the fever without convulsion group was 44.9 ± 20.2 ng/mL, which was a sufficient level. There was a statistically sig-

nificant difference in vitamin D level between the FC group and the fever without convulsion group with a $P < 0.0001$ (Table 2). The results also highlight that over half (52.5%) of children in the FC group had low calcium levels, while 70% of children in the fever group had normal calcium levels. These results support the hypothesis that low calcium may be associated with febrile convulsions in children.

Table 2
Comparison of calcium, vitamin D between the febrile convulsion group and fever without convulsion group ($\bar{x} \pm SD$)

Parameters	Febrile convulsion group	Fever without convulsion group	P-value
Calcium, mmol/L	2.14 ± 0.13	2.23 ± 0.15	0.0080
Vitamin D, ng/mL	20.6 ± 12.3	44.9 ± 20.2	0.0001

Table 3
Calcium status in febrile convulsion group and fever without convulsion group

Calcium status	Febrile convulsion group, N (%)	Fever without convulsion group, N (%)
Low calcium level (<2.15 mmol/L)	21 (52.5%)	12 (30.0%)
Normal calcium level (≥2.15 mmol/L)	19 (47.5%)	28 (70.0%)

The chi-square test evaluated the association between vitamin D status (sufficient, insufficient, and deficient) and the grouping (febrile convulsion group vs. fever without convulsion group). There was a difference in the vitamin D state between the groups. The majority of patients in the FC group 21 (52.5%) had vitamin D deficiency, while the majority of the fever without convulsion group had a sufficient vitamin D level of 30 (75%). The test confirms that the differences in vitamin D status between the groups are statistically significant, the P-value is far below the standard significance level ($P < 0.05$), indicating a highly significant association between vitamin D status and the groups, as shown in Table 4.

Table 4
Number of patients according to vitamin D status

Vitamin D Status	Febrile convulsion (n = 40)	Fever without convulsion (n = 40)	Chi-square test	P-value
Sufficient	9 (22.5%)	30 (75.0%)	22.82	0.000011
Insufficient	10 (25.0%)	5 (12.5%)		
Deficient	21 (52.5%)	5 (12.5%)		

There were various causes of fever in the FC group, such as urinary tract infection (UTI), gastroenteritis, bronchiolitis, tonsillitis, chest infection, pneumonia, and viral infection, but the highest percentage was UTI and gastroenteritis, which represent 27.3% and 21.6% of cases, respectively (Fig. 2).

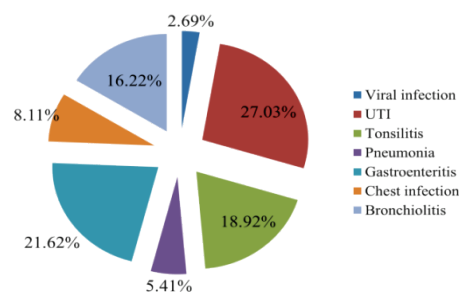


Fig. 2. Distribution of major causes of febrile convulsion

The chi-square test examines the relationship between the febrile convulsion vs fever without convulsion, and two parameters (family history and vitamin D supplementation) were tested. In the febrile convulsion group, 14 patients (35%) had a positive family history, while 26 (65%) did not. In the fever without convulsion group only 4 individuals (10%) had a positive family history, while 36 (90%) did not. A statistically significant association exists between family history and febrile convulsions.

In the febrile convulsion group only 4 individuals (10%) reported taking vitamin D supplements, while 36 (90%) did not. In the fever without convulsion group 17 individuals (42.5%) took vitamin D supplements, while 23 (57.5%) did not. A statistically significant association exists between vitamin D supplementation and febrile convulsions (Table 5).

Table 5
Comparison between the febrile patient group and the fever without convulsion group in the number of patients according to the family history and vitamin D supplement intake

Parameters		Febrile convulsion group (n = 40)	Fever without convulsion group (n = 40)	Chi-square	P-value
Family history	positive	14 (35%)	4 (10.0%)	5.81	0.016
	negative	26 (65%)	36 (90.0%)		
Vitamin D supplement	positive	4 (10%)	17 (42.5%)	9.30	0.002
	negative	36 (90%)	23 (57.5%)		

In the febrile convulsion (FC) group, among those not receiving supplementation (n = 36), nearly 47% (19 children) had a deficient level of vitamin D while only 20% were in the sufficient range. In the supplemented subgroup (n = 4), half (2 children) had sufficient or insufficient levels. Still, 2 children (5%) were deficient despite supplementation as is shown in Table 6.

In the fever without convulsion group, a higher proportion (42.5%) received vitamin D supplementation, among supplemented children (n = 17), 14 children had sufficient vitamin D levels. Only 1 child remained deficient. Among the non-supplemented (n = 23) the majority had sufficient levels and only 4 children were deficient as is shown in Table 7.

Table 6
Vitamin D status in febrile convulsion (FC) group

Vitamin D Status	Supplement intake (Yes), N (%)	Supplement intake (No), N (%)
Sufficient	1 (2.5%)	8 (20.0%)
Insufficient	1 (2.5%)	9 (22.5%)
Deficient	2 (5.0%)	19 (47.5%)

Table 7
Vitamin D status in fever without convulsion group

Vitamin D status	Supplement intake (Yes)	Supplement intake (No)
Sufficient	14 (35.0%)	16 (40.0%)
Insufficient	2 (5.0%)	3 (7.5%)
Deficient	1 (2.5%)	4 (10.0%)

Discussion

Febrile convulsion is one of the leading public health issues around the world that affect children. This makes the researcher seek to find the causes of this condition. There is growing evidence that the etiology of FCs may include vitamin D. We aimed to explore vitamin D and calcium status in children with convulsions. In this study, the percentage of males and females with FC was 75% and 25%, respectively. This result is similar to the studies by Nawaz et al. (2023), which found that 70% of cases of FC in the study were male; Mahyar et al. (2010) indicated that gender is an important factor in FC, with 66% of patients being male. Similarly, Sunitha et al. (2023) found that 64% of cases of FC were boys.

The mean level of calcium for the case group was 2.14 ± 0.13 mmol/L, which was less than the normal level of calcium (hypocalcaemia), while the mean level of calcium for the control group was within the normal level (2.23 ± 0.15 mmol/L), and there was a statistically significant difference between the groups with a $P = 0.008$. Namakin et al. (2016) also found that there was a significant difference in serum calcium level between children with simple FC in comparison with febrile children without convulsion, also Sharma et al. (2018) in his study found that ionized calcium level was highly significantly different between the study groups with a $P < 0.001$. Sarker et al. (2022) in their cross sectional study, which took 100 patients as

cases and control group, found that there was a statistically significant difference in calcium mean \pm SD level with a $P < 0.001$, which is similar to our result.

Through the acute phase of febrile disease, there are frequent disturbances in water and electrolyte balance, which suggests that a change in the serum calcium may lead to an increase in the vulnerability to convulsion (Chhapparwal et al., 1971). The mean value of vitamin D in this study was 20.6 ± 12.3 ng/mL for the FC group, which is insufficient, and there was a statistically significant difference when compared with the fever without convulsion group with a $P < 0.0001$. In the cross-sectional study of Shariatpanahi et al. (2018), they also found insufficient vitamin D levels for the FC children with a mean value of 24.4 ± 11.2 ng/mL. Aydin et al. (2021) also found significant differences in vitamin D between cases and controls with a $P \leq 0.017$. Adnan et al. (2023) found a statistically significant difference in vitamin D level between two groups ($P < 0.05$) and revealed that the level of vitamin D was significantly low in children with simple FC when compared with children with fever without convulsion.

In our study, the majority (52.5%) of FC children had a deficiency in vitamin D, 25% had insufficient vitamin D, and only 22.5% of FC children had a sufficient vitamin D level, while another study by Bhat et al. (2020) shows that FC patients had vitamin D deficiency in 30.95% of cases, insufficiency in 43.7%, and a normal level of vitamin D in 25.6% of cases. Motlaghzadeh et al. (2016) and Singh et al. (2019) also reported a high percentage of vitamin D insufficiency in children with FC.

In this study, causes such as bronchiolitis (16.2%), chest infection (8.11%), tonsillitis (18.9%), and pneumonia (5.4%) that related to respiratory tract infection represented about 50% of the causes of fever in the FC group. This is similar to the study of Hossain et al. and Shrestha et al. (2014), who found that the major cause of fever in the FC children was upper respiratory tract infection, which occurred in 56.3% of children (Adnan et al., 2023). A study by Millichap & Millichap (2006), showed that the most common causes of FC were respiratory tract infections and gastroenteritis, which is comparable to our finding.

In this study, 35% of the febrile convulsion group had a family history of epilepsy as compared to 4% of the fever group and there was a significant difference ($P = 0.016$). This result is similar to the finding of Adnan et al. (2023), who found that the 39% of febrile convulsion patients had a family history which significantly differed from the control group with ($P = 0.001$). Studies of Shariatpanahi et al. (2018) and Tosun et al. found that 60%, and 57% of febrile convulsion children respectively had a positive family history of febrile convulsion, which corresponds with the finding of this study (Tosun et al., 2010; Shariatpanahi et al., 2018).

In this study, the chi-square value (9.30) and $P = 0.002$ indicate a highly significant association of febrile convulsion with vitamin D supplement, suggesting that vitamin D supplementation may have a protective effect against febrile convulsions. This result is comparable to the result of Thoppil et al. (2024), whose findings indicated that while mean vitamin D levels were not significantly different between children with and without febrile seizures, children who received vitamin D supplementation had a significantly lower recurrence of seizures. The study suggested that vitamin D supplementation could play a protective role against recurrent febrile seizures.

It is well recognized that vitamin D plays a role in calcium homeostasis, neuromodulation, and neuroprotection – all of which are essential in reducing neuronal excitability, which could result in seizures (Holick, 2007). Increased inflammatory cytokines and changed calcium metabolism have been associated with vitamin D deficiency, and these changes may enhance the risk of seizures (Shariatpanahi et al., 2018).

Conclusion

Under the limitation of the study, we can conclude that vitamin D insufficiency and low calcium levels significantly affect the occurrence of febrile convulsions in children, which may suggest that they are risk factors for the development of febrile convulsions. Maintaining

adequate vitamin D levels in children is crucial, as seen by the strong correlation found between vitamin D status and febrile convulsions. Children taking vitamin D supplement have a lower risk of febrile convulsions. The short period of time, the reliance on just a single health center and the small sample size are the limitations of this study. It could be helpful to do more research in multiple centers, with larger sample sizes and longer time frames to confirm or correct the results reported here.

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This study received ethical approval from the Collegiate Committee for Medical Research Ethics/University of Mosul, date: 27/6/2024 with code: CCMRE-phA-24-5.

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