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Role of Serum Calcium, Magnesium, Phosphorus, and Vitamin D in Children with Febrile Seizures: A Case-Control Study

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KEYWORDS

Febrile seizures, hypocalcaemia, vitamin D deficiency..

ABSTRACT:

Background: Febrile seizures, the most common paediatric seizure type, are associated with metabolic changes, including electrolyte imbalances and vitamin D deficiency. This study evaluates serum calcium, magnesium, phosphorus, and vitamin D levels in children with febrile seizures compared to febrile children without seizures.

Methods: A hospital-based case-control study was conducted at SMGS Hospital, Jammu, India, from November 2020 to October 2021. The study enrolled 100 children aged 6–60 months with febrile seizures (cases) and 100 age-matched febrile children without seizures (controls). Serum levels of calcium, magnesium, phosphorus, and vitamin D were measured using standardized laboratory methods. Data on age, sex, and nutritional status were collected. Statistical analysis used t-tests for continuous variables and chi-square tests for categorical variables ($p<0.05$ significant).

Results: Mean age was 24.82 months in cases and 22.83 months in controls ($p=0.33$). Males comprised 62% of cases ($p=0.556$). Hypocalcaemia was significantly more prevalent in cases (72%) than controls (42%, $p<0.05$). Mean serum magnesium was higher in cases (2.54 mg/dL) than controls (2.27 mg/dL, $p<0.05$), but hypomagnesemia was rare ($p=0.47$). Phosphorus levels showed no significant difference (3.87 mg/dL vs. 3.77 mg/dL, $p=0.347$). Vitamin D deficiency/insufficiency was more common in cases (47%) than controls (25%, $p=0.001$). No significant differences were found in sodium, potassium, or nutritional status. Upper respiratory tract infection was the primary fever trigger (47% cases).

Conclusion: Hypocalcaemia and vitamin D deficiency/insufficiency are significantly associated with febrile seizures, while magnesium and phosphorus levels show no consistent correlation. These findings suggest a role for calcium and vitamin D in febrile seizure pathogenesis.

Introduction:

Seizures result from abnormal, excessive, or synchronous neuronal activity in the brain. In children, most are provoked by somatic disorders like fever, infections, head injury, hypoxia, or toxins. Epilepsy is defined as two or more unprovoked seizures occurring more than 24 hours apart. Children are more prone to seizures than adults, with 4-10% experiencing at least one seizure by age 16 (1).

The International League Against Epilepsy (ILAE) classifies seizures into: (a) Focal, limited to one cerebral hemisphere, motor or non-motor, with preserved or impaired consciousness; (b) Generalized, involving both hemispheres; (c) Unknown onset, lacking clear data; and

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(d) Unclassified, despite evaluation. Epilepsy involves a predisposition to seizures with neurobiologic, cognitive, psychological, and social consequences. Seizure disorders include epilepsy, febrile seizures, single seizures, and symptomatic seizures from metabolic or infectious causes.

Febrile seizures, the most common paediatric seizure type (2-5% prevalence), occur between 6-60 months with fever ≥38°C (100.4°F), without CNS infection, metabolic imbalance, or prior afebrile seizures (2-3). Simple febrile seizures are generalized, tonic-clonic, lasting ≤15 minutes, non-recurrent within 24 hours, with brief postictal drowsiness. Complex seizures are prolonged (>15 minutes), focal, or recurrent within 24 hours. Febrile status epilepticus exceeds 30 minutes (1).

Febrile seizures are multifactorial, with risk factors including genetics, age, gender, seizure type/duration, family history, and perinatal exposures (4). Pathophysiology includes: (a) Etiology (e.g., tumours, strokes, gene mutations); (b) Epileptogenesis (e.g., kindling via glutamate receptors, BDNF/TrkB, leading to mossy fiber sprouting); (c) Epileptic state (glutamatergic excitation vs. GABAergic inhibition imbalance); and (d) Neuronal injury (apoptosis/necrosis, hippocampal atrophy) (1). Genetic predisposition is significant, with 10% risk in siblings and 50% if parents are affected, involving genes like SCN1A, SCN1B, SCN9A, and CPA6. Cytokine dysregulation (IL-1β, IL-6, IL-8 vs. IL-1RA) is linked to febrile status epilepticus.

Recurrence risk factors include major (age <1 year, fever <24 hours, 38-39°C) and minor (family history, complex seizures, daycare, male gender, low serum sodium), with risks ranging from 12% (no factors) to 73-100% (three or more factors). Electrolyte imbalances play a role in the condition's development.

Fever can trigger metabolic changes like electrolyte disturbances, vitamin B6 deficiency, or reduced GABA levels (5). Changes in electrolytes increase seizure susceptibility (6). Hypocalcaemia, often due to vitamin D deficiency, increases CNS excitability (7). Hypomagnesemia relieves NMDA receptor inhibition, leading to depolarization and epileptiform activity through glutamate, and acts as a calcium channel blocker, boosting nerve excitability when deficient (8-9). Elements such as calcium, phosphorus, and magnesium affect redox reactions and receptor interactions (10).

This study investigates vitamin D status, calcium, phosphorus, and magnesium levels in children aged 6 months to 5 years with febrile seizures, assessing the prevalence of deficiencies.

Material and Methods

This was a hospital-based observational case-control study aimed at comparing serum levels of vitamin D, calcium, phosphorus, and magnesium in children aged 6 months to 5 years with febrile seizures (cases) versus those with febrile illness without seizures (controls).

Study Setting and Duration

The study was conducted in the Paediatric Emergency Department of SMGS Hospital, Jammu, India. Participants were enrolled over one year, from November 1, 2020, to October 31, 2021, with the following inclusion and exclusion criteria:

Inclusion Criteria

- Cases: Children aged 6–60 months with normal neurological development, presenting with febrile seizures and a fever duration ≤3 days.
- Controls: Age-matched children admitted with febrile illness of ≤3 days duration, without seizures.

Exclusion Criteria

Children with afebrile seizures, seizures due to central nervous system (CNS) infections, metabolic causes, head injury, hypoxic-ischemic encephalopathy (HIE), abnormal neurological development, family history of epilepsy, or haematological disorders (e.g., haemolytic anaemias, bleeding/coagulation disorders, malignancies) were excluded.

Sample Size

A total of 200 participants were recruited: 100 cases and 100 controls. Sample size was determined based on anticipated differences in electrolyte and vitamin D levels, ensuring adequate power for statistical comparisons.

Data Collection and Procedure

After obtaining informed written consent from guardians, demographic and clinical data were collected, including age, gender, developmental history, birth

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history, feeding practices, parental consanguinity, and family history of febrile seizures. Under aseptic conditions, 4 mL of venous blood was drawn: 2 mL for 25(OH) vitamin D3 estimation and 2 mL for serum calcium, magnesium, and phosphorus levels. Samples were processed in the Department of Biochemistry, SMGS Hospital.

Laboratory Methods

- **Vitamin D**: Measured by chemiluminescence microparticle immunoassay (CMIA) using Abbott Architect. Deficiency categorized per Indian Academy of Paediatrics (IAP) 2017 guidelines: sufficient (>20 ng/mL), insufficient (12–20 ng/mL), deficient (<12 ng/mL) (Khadilkar A et al., 2017).
- **Calcium:** Analysed via autoanalyzer using CA method on Dimension Clinical Chemistry System (calibrator: CHEM I, DC18B/DC18C; reagent: CA Flex). Normal range: 8.6–10.2 mg/dL; hypocalcemia: <8.8 mg/dL (American Board of Internal Medicine, 2020).
- **Phosphorus**: Assessed by autoanalyzer using PHOS method (modification of phosphomolybdate; calibrator: CHEM 2, DC20; reagent: PHOS Flex, DF61A). Age-dependent normals: 0–5 days (4.8–8.2 mg/dL), 1–3 years (3.8–6.5 mg/dL), 4–11 years (3.7–5.6 mg/dL) (Larry A. Greenbaum, Nelson Textbook of Paediatrics, 21st Ed.).
- **Magnesium**: Determined by autoanalyzer using MG method (calibrator: CHEM II, DC20; reagent: MG Flex, DF57). Normal range: 1.5–2.3 mg/dL.

Statistical Analysis

Data were analysed using SPSS version 23. Continuous variables were compared with an independent samples t-test, and categorical variables with a chi-square test. A p-value <0.05 was considered statistically significant.

Results and Observations:

The study included 200 patients divided into case and control groups. The case group had 100 children aged 6 months to 5 years with febrile seizures, while the control group had 100 age-matched children with fever but no seizures from the same setting. The mean age was 24.82 months (median 24.0, SD 13.20) in cases and 22.83 months (SD 15.54) in controls, with no significant difference (p=0.33). In the case group, nearly 45% were aged 1-2 years, 22% were 2-3 years, 21% under 1 year, and 12% between 3-5 years. The majority (1-2 years) was statistically more common in cases than controls (p=0.006). Males comprised 62%, females 38%, with no gender difference between groups (P=0.556), indicating males are more prone to febrile seizures.

Table 1: Association of Serum mean sodium levels in cases and controls.

Na (mmol/L)	Group		t	p
	Cases	Controls		
Mean	139.23±4.01	139.97±4.50	-1.22	0.221`
K (mmol/L)				
Mean	4.25±.46	4.18±.48	1.18	0.236 (ns)
Ca				
Mean	7.98±0.81	8.93±.83	-8.17	<0.05 (s)

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Table-1 depicts the association of serum mean sodium levels in cases and controls. In the study, the mean serum sodium level was 139.23 mmol/L in the case group and 139.97 mmol/L in the control group, showing no significant difference (p=0.221). The mean serum potassium levels were 4.25 mmol/L in the case group and 4.18 mmol/L in the control group, also insignificant (p=0.236). However, the mean serum calcium level was 7.98 mg/dL in the case group and 8.93 mg/dL in the control group, indicating a significant correlation with febrile seizures (p<0.05).

Table 2: Serum Electrolytes and Vitamin D Levels in Cases and Controls

Parameter	**Cases**	**Controls**	**Statistical Significance**
Serum Calcium			
Hypocalcemia (<8.8 mg/dL)	72% (n=72)	42% (n=41)	χ^2=22.62, p<0.05 (s)
Normal (8.6-10.2 mg/dL)	24% (n=24)	57% (n=57)	
Hypercalcemia (>10.2 mg/dL)	4% (n=4)	2% (n=2)	
Serum Magnesium			
Mean ± SD (mg/dL)	2.54 ± 0.54	2.27 ± 0.53	t=3.56, p<0.05 (s)
Hypomagnesemia	3% (n=3)	5% (n=5)	χ^2=0.52, p=0.47 (ns)
Normal	97% (n=97)	95% (n=95)	
Serum Phosphorus			
Mean ± SD (mg/dL)	3.87 ± 0.78	3.77 ± 0.67	t=0.942, p=0.347 (ns)
Low (age-specific)	45% (n=45)	57% (n=57)	χ^2=2.88, p=0.09 (ns)
Normal (age-specific)	55% (n=55)	43% (n=43)	
Serum Vitamin D			
Mean ± SD (mg/dL)	23.17 ± 16.28	24.70 ± 9.65	t=-0.812, p=0.42 (ns)
Deficiency	6% (n=6)	0% (n=0)	χ^2=13.66, p=0.001 (s)
Insufficient	41% (n=41)	25% (n=25)	
Sufficient	53% (n=53)	75% (n=75)	

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(s) = statistically significant, (ns) = not significant

Table-2 depicts the Serum electrolytes and vitamin D levels in cases and controls. The study shows a strong link between hypocalcaemia and febrile seizures, with 72% of cases having low serum calcium levels (<8.8 mg/dL), compared to 42% of controls ($p<0.05$). Serum magnesium levels are higher in cases (2.54 mg/dL) than controls (2.27 mg/dL, $p<0.05$), but hypomagnesemia prevalence is low (3% in cases, 5% in controls) and not significant ($p=0.47$). Serum phosphorus levels show no meaningful relationship with febrile seizures (mean: 3.87 mg/dL in cases vs. 3.77 mg/dL in controls, $p=0.347$), with 45% of cases and 57% of controls having low levels ($p=0.09$). Vitamin D deficiency or insufficiency is more common in cases (47%) than controls (25%), with a significant association ($p=0.001$), especially in males (40%, $p=0.039$) and females (58%, $p=0.019$).

In our study, the Gender-specific analysis indicates that 69.4% of male cases and 76.3% of female cases have hypocalcaemia, both statistically significant ($p=0.007$ and $p=0.001$, respectively). Similarly, there are no significant gender differences in magnesium levels.

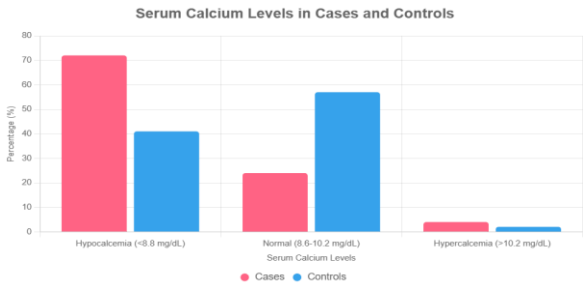

Figure 1: Serum Calcium Levels in Cases and Controls

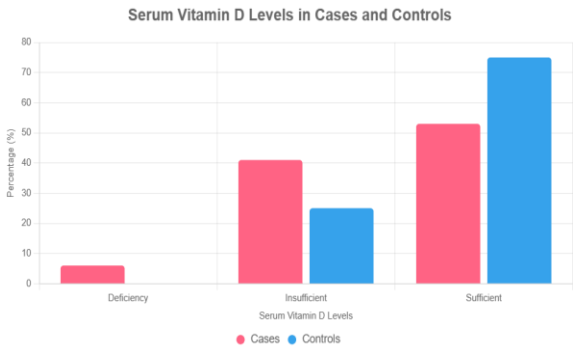

Figure 2: Serum Vitamin D Levels in Cases and Controls

Table 3: Clinical Characteristics and Gender Differences

Parameter	**Cases**	**Controls**	**Statistical Significance**
Duration of Fever			
Mean ± SD (hours)	25.96 ± 18.60	43.68 ± 16.49	t=-7.13, $p<0.05$ (s)
Mean time to seizure (hours)	18.19 ± 13.53	-	-
Occipitofrontal Circumference			
Mean ± SD (cm)	46.99 ± 2.35	46.79 ± 2.56	t=0.581, p=0.56 (ns)
Seizure Type (Cases)			
GTC Simple	65% (n=65)	-	-
GTC Atypical	32% (n=32)	-	-
Focal	3% (n=3)	-	-
Family History of Seizures			
Yes	17% (n=17)	-	-

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No	83% (n=83)	-	-
Focus of Fever			
URTI	47% (n=47)	21% (n=21)	-
AGE	16% (n=16)	5% (n=5)	-
LRTI	6% (n=6)	71% (n=71)	-
No Focus	18% (n=18)	0% (n=0)	-
Nutritional Status			
Moderate Acute Malnutrition	12% (n=12)	12% (n=12)	-
No Malnutrition	88% (n=88)	88% (n=88)	-

(s) = statistically significant, (ns) = not significant

Table-3 represents the clinical characteristics of study participants. The mean duration of fever is significantly shorter in cases (25.96 hours) than controls (43.68 hours, $p<0.05$), and seizures typically occur after 18.19 hours of fever in cases. No significant difference is found in OFC between groups ($p=0.56$). Among cases, 97% have generalized tonic-clonic (GTC) seizures (65% simple, 32% atypical), and 17% report a family history of seizures. Upper respiratory tract infection (URTI, 47%) and acute gastroenteritis (AGE, 16%) are common fever foci in cases, while lower respiratory tract infection (LRTI, 71%) predominates in controls. Nutritional status shows no association with febrile seizures, with 12% of both groups having moderate acute malnutrition.

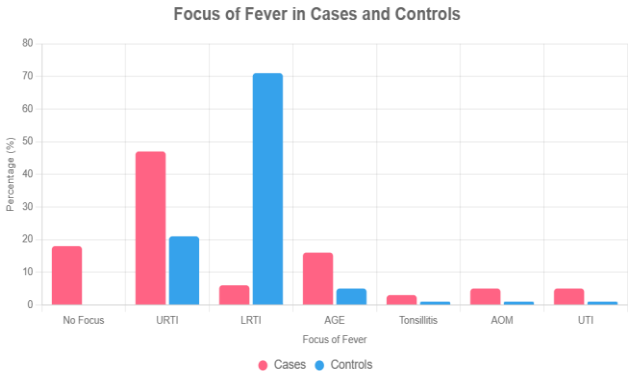

Figure 3: Focus of Fever in Cases and Controls

Discussion:

This study investigates the role of serum calcium, magnesium, phosphorus, and vitamin D levels in children with febrile seizures compared to febrile children without seizures. The groups were also compared for age, sex, and nutritional status.

The mean age of febrile seizure onset was 24.82 months, consistent with ***Namakin et al.*** and other studies reporting 20–27 months (11). Febrile seizures were most common (67%) in children aged 1–2 years, followed by 2–3 years, aligning with ***Talebian et al.***, though their study reported a lower prevalence (48%). Males were more affected (62%) than females (38%), consistent with ***Namakin et al.,*** but ***Talebian et al.*** found no significant sex differences (11-12).

Family history of seizures was present in 17% of cases, comparable to ***Usha Kiran et al.*** (14%) and ***Sherlin et al.*** (20%), indicating a genetic predisposition (13-14). Upper respiratory tract infection (URTI) was the primary fever trigger (50%), followed by acute gastroenteritis (16%) and urinary tract infections (5%), with 18% showing no fever focus, consistent *with* ***Rutter et al.*** **(15).**

No significant differences were found in mean serum sodium or potassium levels between groups, aligning with ***Nadkarni et al.,*** though ***Hawas et al.*** reported differences (16-17). Mean serum calcium was significantly lower in cases (7.98 ± 0.81 mg/dL) than in controls (8.93 ± 0.83 mg/dL, $p<0.05$), indicating a significant correlation with hypocalcemia, consistent

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with ***Namakin et al.*** and ***Usha Kiran et al.,*** but not ***Rutter et al.*** **(**11,13,15**)**. Mean serum magnesium levels were higher in cases (2.54 mg/dL) than in controls (2.27 mg/dL, p<0.05), similar *to* ***Sreekrishna et al.*** and ***Khosroshahi et al.*** **(18-19).** However, hypomagnesemia was rare (3% cases, 5% controls, p=0.47), and no correlation was found with age, sex, or fever-seizure interval, consistent with prior studies. ***Talebian et al.*** and others reported lower magnesium levels, possibly due to smaller sample sizes (e.g., 49 cases vs. 100 in this study) (12).

Mean serum phosphorus levels were 3.87 mg/dL in cases and 3.77 mg/dL in controls (p=0.347), showing no significant correlation, consistent with the literature. Mean serum vitamin D was 23.17 ng/mL in cases and 24.70 ng/mL in controls, with deficiency in 6% and insufficiency in 41% of cases (p=0.001), aligning with ***Bhat et al.*** (20) (43.5% insufficiency, 30.85% deficiency).

Conclusion

No significant association was found between hyponatremia, hypophosphatemia, or serum magnesium levels and febrile seizures. However, hypocalcemia and vitamin D deficiency/insufficiency showed significant correlations with febrile seizures, suggesting their role in pathogenesis.

Limitations of the study:

The study, conducted in a tertiary care center, included mostly urban children, potentially unrepresentative of the broader population. Some cases were lost to follow-up, and recurrent febrile seizures were not studied.

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