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Original Article

Serum iron and calcium status in paediatric patients presenting with febrile seizures: A Prospective case-control study.

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Abstract

Background:

Hypocalcemia has been associated with paresthesia, tetany, muscle cramps, convulsions, and seizures. Electrolyte and water balance disturbances are also common during febrile illness. Alterations in serum calcium and iron status can influence seizure vulnerability in young children.

Objectives:

To assess serum iron and calcium status among paediatric patients presenting with febrile seizures and compare these parameters with febrile children without seizures.

Methods:

This prospective case-control study enrolled 400 children aged 6–60 months through consecutive sampling: 200 children with febrile seizures and 200 febrile children without seizures. Demographic and clinical data, complete blood count indices, serum ferritin, and total serum calcium were recorded. Continuous variables were compared using the independent-samples t-test or Mann–Whitney U test, as appropriate; categorical variables were analysed using the Chi-square test or Fisher's exact test.

Results:

Protein-energy malnutrition was observed in 37.0% of controls and 27.0% of cases. Cases had higher red cell distribution width and lower mean corpuscular haemoglobin, mean corpuscular volume, haemoglobin, and serum ferritin than controls (all $p<0.001$). Mean serum calcium was comparable between cases and controls (9.11±0.62 versus 9.03±0.91 mg/dL; $p=0.305$). Iron deficiency anaemia was more frequent among cases (26.0% versus 7.0%; $\chi^2=26.20$, $p<0.001$), whereas hypocalcaemia was comparable (18.0% versus 23.0%; $\chi^2=1.53$, $p=0.216$).

Conclusion:

Iron deficiency was significantly associated with febrile seizures in young children. In contrast, neither mean serum calcium nor the frequency of hypocalcaemia differed significantly between groups.

Recommendations:

Early screening for iron deficiency, prompt nutritional correction, and caregiver counselling should be strengthened in children presenting with febrile illness and febrile seizures.

Keywords: *Anaemia; Children; Febrile seizures; Hypocalcaemia; Iron deficiency; Serum calcium; Serum ferritin.*
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Introduction

Febrile seizures are usually observed in children aged 6 months to 60 months with a temperature of 38°C or above. They occur in the absence of central nervous system infection, metabolic imbalance, or a previous history of afebrile convulsions. The prevalence varies across geographical regions because of differences in case definition, population selection, and genetic or environmental susceptibility. Febrile seizures remain a common reason for paediatric consultation and emergency visits.1,2

Although febrile seizures are generally benign, they create substantial anxiety among caregivers and families. Iron deficiency anaemia is the most common nutritional anaemia worldwide. Iron is essential for haemoglobin synthesis, myelination, neurotransmitter metabolism, and cerebral

oxygen delivery. Neurological manifestations of iron deficiency include behavioural change, delayed motor development, impaired learning, reduced attention, and altered seizure threshold. 3,4

Malnutrition may coexist with iron deficiency and can modify haematological indices in children younger than six years.5 Previous studies have reported both supportive and conflicting relationships between iron deficiency and febrile seizures, indicating the need for additional clinical data that use an appropriate febrile comparison group.6

Hypocalcaemia is a metabolic abnormality that may cause paraesthesia, tetany, muscle cramps, convulsions, and seizures. Acute febrile illness can alter water and electrolyte balance, while reduced calcium concentrations may increase neuronal excitability. However, the value of routine calcium screening in otherwise typical febrile seizures remains uncertain.7,8 Therefore, the present study aimed to assess serum iron and calcium status in paediatric patients presenting with febrile seizures and to compare these parameters with febrile children without seizures.

Methodology

Study design and setting

This prospective case-control study was conducted in the Department of Paediatrics and associated laboratory services of the Department of Paediatrics at JIET Medical College & Hospital, Jodhpur, Rajasthan, India, from October 2025 to March 2026 [6 months]. The department provides paediatric outpatient, emergency, inpatient, and diagnostic laboratory services. Written informed consent was obtained from a parent or legally authorised guardian before enrolment.

Participant selection and sampling

Cases were recruited consecutively from children aged 6–60 months who presented with a first febrile seizure. Controls were consecutively recruited febrile children without current or previous seizures who attended the same department during the same study period. Febrile controls were selected rather than healthy controls to reduce confounding from fever, acute illness, and inflammation-related changes in serum ferritin or calcium. Recruitment continued until 200 cases and 200 controls had been enrolled.

Sample size

The sample size was calculated for the comparison of two independent proportions. Based on previous case-control studies, iron deficiency anaemia was anticipated in approximately 25% of cases and 12% of febrile controls.3,4,9,10 Using a two-sided α of 0.05 ($Z\alpha/2=1.96$), 90% power ($Z\beta=1.28$), a 1:1 allocation ratio, P1=0.25, and P2=0.12, the standard two-proportion formula yielded a minimum of approximately 183 participants per group. The target was increased and rounded to 200 participants per group to improve precision and allow for approximately 9% incomplete or unusable observations, resulting in a total sample of 400 children.

Inclusion criteria

Cases were children aged 6–60 months with documented fever of ≥38°C associated with a first febrile seizure, no evidence of central nervous system infection, and parental or guardian consent. Controls were children in the same age range with a fever of ≥38°C for less than three days, no current or previous seizure, and parental or guardian consent.

Exclusion criteria

Children with chronic systemic disease, malignancy, known metabolic disease, renal disease, cardiac disease, acute central nervous system infection, epilepsy, a previous febrile seizure, intravenous calcium therapy, or iron therapy before enrolment were excluded.

Bias control

Consecutive enrolment from the same source population and during the same period was used to reduce selection bias. Febrile controls were chosen to limit confounding by the acute-phase response. Predefined eligibility criteria, uniform clinical proformas, identical anthropometric procedures, common laboratory methods, and prespecified diagnostic cut-offs were applied to both groups. Clinical blinding was not feasible because seizure status defined group allocation; however, participants were not selected on the basis of laboratory results. Residual confounding from diet, infection severity, and inflammatory status remained possible.

Data collection

Baseline data included age, sex, nutritional status, cause of fever, family history of febrile seizures, examination findings at admission, and seizure characteristics among cases. Nutritional assessment followed the Indian Academy of Pediatrics classification of protein-energy malnutrition. Weight was measured using a calibrated digital scale, length was measured using an infantometer in children younger than 12 months, and height was recorded using an age-appropriate stadiometer in older children.

Laboratory assessment

Haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, red cell distribution width, serum ferritin, and total serum calcium were measured using the same laboratory procedures in both groups. Iron deficiency anaemia was defined by serum ferritin <12 µg/L together with supportive microcytic indices, including mean corpuscular haemoglobin <27 pg, mean corpuscular volume

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<70 fL, and haemoglobin <11 g/dL. Hypocalcaemia was defined as total serum calcium <8.5 mg/dL.

Missing data

The final analytical dataset contained complete observations for the primary haematological, ferritin, calcium, and categorical outcome variables in all 400 enrolled children. No statistical imputation was performed. Any unavailable secondary descriptive field was to be handled by complete-case analysis with the applicable denominator reported.

Statistical analysis

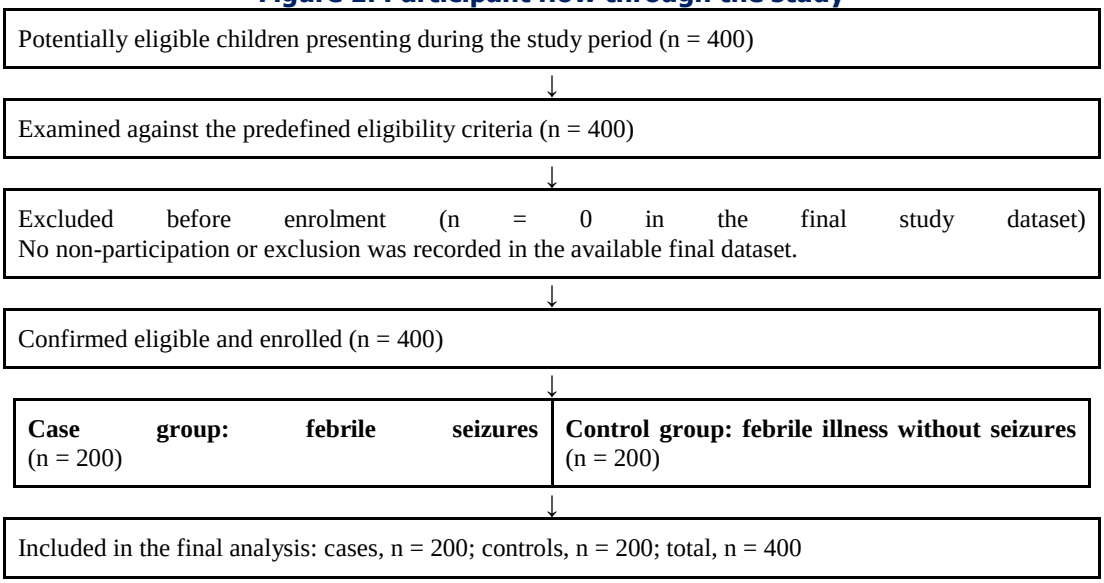
Data were analysed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarised as mean±standard deviation. Normality was assessed before group comparison. The independent-samples Student's t-test was applied to normally distributed continuous variables, including anthropometric measurements, temperature, haematological indices, serum ferritin, and serum calcium; the Mann–Whitney U test was reserved for non-normally distributed continuous data. Categorical variables, including sex, age category, protein-energy malnutrition, cause of fever, iron deficiency anaemia, and hypocalcaemia, were compared using the Chi-square test. Fisher's exact test was used when an expected cell count was <5, including a family history of febrile seizures. One-way analysis of variance was not required for the primary two-group comparisons. All tests were two-sided, and $p<0.05$ was considered statistically significant.

Ethical considerations

The study protocol was approved by the Institutional Ethics Committee of JIET Medical College and Hospital, Jodhpur, Rajasthan India.Written informed consent was obtained from parents or legally authorised guardians. Participant confidentiality was maintained, and study procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Results

Figure 1. Participant flow through the study



The final dataset comprised 400 eligible children. Two hundred children with febrile seizures were included as cases, and 200 febrile children without seizures were included as controls. All enrolled participants contributed data to the primary analysis (Figure 1).

Table 1. Baseline demographic and clinical characteristics of cases and controls

Characteristic	Controls (n=200)	Cases (n=200)	Test statistic	p-value
Age 6–11 months, n (%)	56 (28.0)	42 (21.0)	χ^2=2.65	0.104
Age 12–60 months, n (%)	144 (72.0)	158 (79.0)	—	—
Male sex, n (%)	116 (58.0)	130 (65.0)	χ^2=2.07	0.150
Female sex, n (%)	84 (42.0)	70 (35.0)	—	—
Head circumference, cm	46.81±3.70	46.35±2.77	t=1.41	0.160
Height/length, cm	85.41±15.53	79.64±11.06	t=4.28	<0.001
Weight, kg	10.61±3.32	9.71±2.49	t=3.07	0.002
Admission temperature, °F	101.71±0.54	102.11±0.84	t=5.66	<0.001
Protein-energy malnutrition, n (%)	74 (37.0)	54 (27.0)	χ^2=4.60	0.032
No protein-energy malnutrition, n (%)	126 (63.0)	146 (73.0)	—	—
Positive family history, n (%)	0 (0.0)	18 (9.0)	Fisher exact	<0.001
Upper respiratory tract infection, n (%)	104 (52.0)	126 (63.0)	χ^2=4.95	0.026
Other febrile illnesses, n (%)	96 (48.0)	74 (37.0)	—	—

Note. Values are presented as n (%) or mean±standard deviation. Student's t-test was used for continuous variables, the Chi-square test for categorical variables, and Fisher's exact test for family history.

Cases and controls were broadly similar in sex distribution and the proportion aged 6–11 months. Cases had lower mean height/length and weight but a higher admission temperature. Protein-energy malnutrition was present in 74 controls (37.0%) and 54 cases (27.0%). A positive family history occurred in 18 cases (9.0%), and no controls. Upper respiratory tract infection was the most frequent febrile illness, affecting 126 cases (63.0%) and 104 controls (52.0%) (Table 1).

Among the 200 cases, seizure duration was ≤5 minutes in 162 children (81.0%) and >5 minutes in 38 (19.0%). Generalised tonic-clonic seizures occurred in 182 cases (91.0%), whereas focal seizures occurred in 18 (9.0%).

Table 2. Comparison of haematological parameters between controls and cases

Parameter	Controls (n=200)	Cases (n=200)	t statistic	p-value
RDW (%)	16.42±1.74	18.71±1.75	13.12	<0.001
MCH (pg)	28.48±3.58	25.38±3.45	8.82	<0.001
MCV (fL)	78.57±9.80	68.81±8.84	10.46	<0.001
Haemoglobin (g/dL)	10.76±1.58	9.21±1.28	10.78	<0.001

Note. Values are mean±standard deviation. Between-group comparisons used the independent-samples Student's t-test. Absolute t values are presented.

The primary iron-related haematological indices differed significantly between groups. Cases had a higher mean red cell distribution width and lower mean corpuscular haemoglobin, mean corpuscular volume, and haemoglobin than controls (all p<0.001), indicating a predominantly microcytic, hypochromic pattern (Table 2).

Table 3. Comparison of serum ferritin and total serum calcium between controls and cases

Parameter	Controls (n=200)	Cases (n=200)	t statistic	p-value
Serum ferritin (µg/L)	79.00±22.35	39.04±16.21	20.47	<0.001
Serum calcium (mg/dL)	9.03±0.91	9.11±0.62	1.03	0.305

Note. Values are mean±standard deviation. p-values were calculated from the displayed group means, standard deviations, and sample sizes using the independent-samples Student's t-test; absolute t values are shown.

Mean serum ferritin was markedly lower among cases than controls (39.04±16.21 versus 79.00±22.35 µg/L; p<0.001). In contrast, mean serum calcium did not differ significantly between cases and controls (9.11±0.62 versus 9.03±0.91 mg/dL; p=0.305) (Table 3).

Table 4. Frequency of iron deficiency anaemia and hypocalcaemia in controls and cases

Outcome	Controls (n=200)	Cases (n=200)	χ^2	p-value
Iron deficiency anaemia, n (%)	14 (7.0)	52 (26.0)	26.20	<0.001
Hypocalcaemia, n (%)	46 (23.0)	36 (18.0)	1.53	0.216

Note. Percentages were calculated using 200 participants as the denominator in each group. Pearson's Chi-square test was used for both comparisons.

Iron deficiency anaemia occurred in 52 cases (26.0%) and 14 controls (7.0%), demonstrating a significant association with febrile seizures (χ^2=26.20, p<0.001). Hypocalcaemia occurred in 36 cases (18.0%) and 46 controls (23.0%); this difference was not statistically significant (χ^2=1.53, p=0.216) (Table 4).

Discussion

The study objectives were to compare iron status and serum calcium between children with febrile seizures and febrile controls. The baseline findings showed that brief generalised seizures predominated among cases, while admission temperature and the frequency of upper respiratory tract infection were higher in the case group (Table 1). These features are consistent with the recognised clinical presentation of febrile seizures in early childhood, although the case-control design does not establish that fever intensity independently caused seizure occurrence.

With respect to the first objective, the case group had significantly lower haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, and serum ferritin, together with higher red cell distribution width (Tables 2 and 3). Iron deficiency anaemia was nearly four times as frequent among cases as controls (26.0% versus 7.0%; Table 4). These findings agree with previous case-control studies reporting depleted iron stores or anaemia among children with febrile seizures.9–13

The association is biologically plausible. Iron contributes to monoamine and gamma-aminobutyric acid metabolism, myelination, mitochondrial function, and cerebral oxygen transport. Deficiency may therefore reduce seizure threshold during fever. Nevertheless, serum ferritin is an acute-phase reactant and may rise during infection. The use of febrile rather than healthy controls partly addressed this concern because both groups were exposed to acute illness, but inflammatory markers were not measured, and residual confounding cannot be excluded.

Regarding the second objective, neither the mean total serum calcium nor the frequency of hypocalcaemia differed significantly between groups (Tables 3 and 4). Thus, the data do not support hypocalcaemia as a major explanatory factor for febrile seizures in this population. This interpretation is consistent with studies questioning the routine diagnostic yield of calcium screening in otherwise typical febrile seizures, although calcium estimation remains appropriate when clinical features or risk factors suggest a metabolic disturbance.6–8

Clinically, the results support targeted assessment of anaemia and iron deficiency in children presenting with febrile seizures, particularly where nutritional vulnerability is common. Documented deficiency should be treated according to paediatric guidelines, accompanied by dietary counselling and follow-up. The findings do not justify routine calcium supplementation in the absence of confirmed hypocalcaemia. Because the study assessed association rather than temporality, it cannot determine whether iron correction prevents recurrent febrile seizures.

Generalizability

The findings are mainly applicable to children aged 6–60 months attending comparable hospital-based paediatric services for acute febrile illness. The use of febrile controls improves clinical comparability, but the single-centre setting, referral pattern, and local nutritional context may differ from community populations or other regions. Broader multicentre studies are therefore needed before extrapolating the observed magnitude of association.

Conclusion

Children with febrile seizures had significantly lower haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, and serum ferritin than febrile controls, and iron deficiency anaemia was substantially more frequent among cases. By contrast, mean serum calcium and the frequency of hypocalcaemia were comparable between groups. These findings indicate an association between iron deficiency and febrile seizures but do not establish causality. Clinical evaluation should therefore include attention to nutritional and haematological status, while calcium testing should be guided by individual clinical suspicion rather than routine etiological assumption.

Limitations

The hospital-based design may have preferentially included children with more severe fever or greater caregiver concern, thereby limiting community generalisability. Dietary iron intake, socioeconomic factors, infection severity, and inflammatory markers were not measured; these unmeasured variables may have confounded the association. Because ferritin increases during inflammation, iron deficiency may have been underestimated, potentially biasing the observed association toward the null. The case-control design cannot determine temporality or causality. Finally, the absence of longitudinal follow-up prevented assessment of seizure recurrence or response to iron treatment.

Recommendations

Children presenting with febrile seizures should undergo clinical screening for anaemia and iron deficiency where feasible. Paediatric departments should strengthen caregiver counselling on iron-rich foods, a balanced diet, and timely supplementation. Children with documented iron deficiency require appropriate treatment and follow-up. Calcium testing should be reserved for children with clinical suspicion or risk factors for hypocalcaemia rather than used as a routine etiological assumption.

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Abbreviations

CNS: Central nervous system
MCH: Mean corpuscular haemoglobin
MCV: Mean corpuscular volume
RDW: Red cell distribution width
SPSS: Statistical Package for the Social Sciences.

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The study received no external or institutional funding.

Conflict of interest

The authors declare no conflict of interest.

Data availability

Data are available from the corresponding author upon reasonable request.

Author Contributions

Rakesh Balamkar contributed to study conception, clinical data collection, interpretation of paediatric findings, manuscript drafting, and final approval of the manuscript.

Dr Minal Ambade contributed to study design, clinical supervision, data interpretation, literature review, and critical revision of the manuscript.

Dr Rajesh Kumar Nain contributed to manuscript coordination, data interpretation, correspondence, drafting, revision, and final approval of the manuscript.

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