Original Article

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Paediatrics Section

Comparison of Serum Electrolytes among Febrile Children with and without Seizures: A Cross-sectional Study

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ABSTRACT

Introduction: Febrile Seizures (FS) are common in early childhood, and bedside biochemical testing is frequently ordered despite mixed evidence regarding underlying biochemical drivers. Clarifying which analytes truly differ at presentation can help streamline acute care, particularly in resource-constrained settings.

Aim: To compare serum sodium, magnesium, total calcium, ionised calcium, and 25-hydroxyvitamin D levels between children with febrile seizures (FS) and age-matched children with febrile illness without seizures (FI). A secondary objective was to evaluate these analytes across FS subgroups based on seizure type (simple vs. complex).

Materials and Methods: A cross-sectional study was conducted at Max Super Speciality Hospital, Saket, New Delhi, India, from April to November 2016. Children aged six months to five years were enrolled as FS cases (n=64) and febrile illness controls without seizures (FI; n=64). FS cases were included according to the International League Against Epilepsy (ILAE) and American Academy of Paediatrics (AAP) criteria. Serum sodium and total calcium were measured using ion-selective electrodes (indirect potentiometry), magnesium by the calmagite timed endpoint method, ionised calcium by direct potentiometry, and 25-hydroxyvitamin D by chemiluminescent immunoassay. Student's t-test/ANOVA and χ^2 tests were used for statistical analysis.

Results: The FS and FI groups were comparable with respect to age and sex. Within the FS cohort, 19 children (29.7%) had a prior history of febrile seizures, and 8 (12.5%) reported a positive family history. Forty children (62.5%) presented with complex febrile seizures. Mean±SD analyte values in the FS versus FI groups were as follows: sodium 138.17±5.10 vs. 138.61±4.72 mEq/L (p-value=0.615); magnesium 1.85±0.26 vs. 1.79±0.22 mg/dL (p-value=0.179); total calcium 8.88±0.56 vs. 9.27±0.55 mg/dL (p-value<0.0001); ionised calcium 0.97±0.14 vs. 1.01±0.11 mmol/L (p-value≈0.07); and vitamin D 20.02 ±8.08 vs. 20.43±9.77 ng/mL (p-value=0.792). No meaningful inter-relationships were observed among the five biomarkers.

Conclusion: Children with FS had significantly lower total calcium levels and a non significant trend toward lower ionised calcium levels compared with febrile controls, while sodium, magnesium, and vitamin D levels did not differ significantly. In this clinical setting, routine assessment of total and ionised calcium in children with FS appears justified. Vitamin D levels were low in both groups, supporting the need for population-level vitamin D optimisation strategies.

Keywords: Biochemical analytes, Ionised calcium, Neuronal excitability, Neurophysiology, Paediatric emergency

INTRODUCTION

A seizure is a transient clinical event caused by abnormal, excessive, or synchronous neuronal activity [1]. The FS are defined as seizures occurring between six months and six years of age in association with a temperature ≥38°C, without evidence of Central Nervous System (CNS) infection or a prior afebrile seizure. They comprise the majority of childhood seizures and are generally benign [2,3]. Most children recover without sequelae; however, recurrences are common, and a small proportion later develop epilepsy [4,5]. At first presentation, clinicians face practical questions regarding whether biochemical testing alters immediate management, which tests are most informative, and which children should be prioritised for testing.

The pathophysiology of FS is multifactorial. Age-dependent neuronal excitability interacts with genetic susceptibility, including variations in ion channels and synaptic regulators. Pyrogen-driven cytokines, such as interleukin-1β, may lower the seizure threshold by modulating synaptic transmission [4,6]. Fever-associated hyperventilation can result in respiratory alkalosis, which alters ionised calcium levels and neuronal excitability [7]. Additionally, state-dependent factors such as hydration status, nutritional status, and illness severity may transiently shift biochemical homeostasis during febrile episodes and reduce the seizure threshold.

Micronutrient status is a plausible contributor to seizure threshold variability. Sodium disturbances have been linked to seizure recurrence during illness in some cohorts; however, several studies report no clinically significant differences, supporting selective rather than routine testing in typical presentations [8-12]. Calcium and magnesium play critical roles in neurotransmission and membrane stability, but findings in FS remain heterogeneous. These discrepancies likely reflect differences in sampling time, age distribution, pH-related effects on the ionised fraction, and variability in control group selection [10-14]. Vitamin D influences calcium homeostasis and neuroimmune function. Although deficiency or insufficiency is common among Indian children, its direct association with FS remains uncertain and may be obscured by the high background prevalence of low vitamin D levels in the population [15-19].

Clarifying which biochemical parameters differ consistently at presentation may guide rational laboratory testing in emergency settings, reduce unnecessary investigations, and identify potentially modifiable risk factors. Therefore, the present study aimed to

compare serum sodium, magnesium, total calcium, ionised calcium, and vitamin D levels between children with FS and age-matched febrile controls without seizures, and to explore subgroup differences based on seizure type (simple vs. complex).

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Paediatrics, Max Super Speciality Hospital, Saket, New Delhi, India, from April to November 2016. Institutional Ethics Committee (IEC) approval was obtained (IEC No. IEC-TS/MSSH/SKT-1/PAED/SC/16-02, dated 16 March 2016). Written informed consent was obtained from parents or legal guardians. All data were de-identified, stored securely, and accessed solely for analysis within the approved protocol.

Inclusion criteria: Children aged six months to five years were enrolled consecutively into two groups. FS cases met the International League Against Epilepsy/American Academy of Paediatrics (ILAE/AAP) criteria for seizures associated with fever, with no evidence of central nervous system infection or other acute symptomatic causes [2,3]. Age- and sex-matched febrile illness (FI) controls without seizures during the same illness episode were recruited during the same period.

Exclusion criteria: Children with unprovoked seizures, CNS infection, developmental delay, or known neurological disorders were excluded from the study.

Sample size: For comparison of two independent means, the sample size was calculated using the formula:

$$n = \{2\sigma^2 (Z_{1-}\alpha_{/2} + Z_{1-}\beta)^2\}/\Delta^2$$

using α=0.05, power 80%, σ=3.5 mEq/L, and Δ=2 mEq/L, yielding a required sample size of 48 participants per group. This was increased to 64 participants per group to account for attrition and to enable subgroup analyses [20,21].

Data collection: Data were collected for all participants on age, sex, seizure semiology, duration and recurrence (FS group only), fever aetiology, prior or family history of FS, nutritional status, socio-economic status (Modified Kuppuswamy scale) [22], and clinical diagnosis in controls. The FS were classified as simple (generalised, ≤15 minutes, no recurrence within 24 hours, and no postictal deficit) or complex (focal features and/or duration >15 minutes and/or ≥2 seizures within 24 hours and/or postictal deficits) [3].

Laboratory measurements: Blood samples were collected within six hours of admission to minimise time-dependent biochemical variations. Two millilitres of serum were collected for electrolyte and total calcium estimation, 1 mL of heparinised whole blood was obtained for ionised calcium measurement using anaerobic collection, and 2 mL of serum were collected for 25-hydroxyvitamin D estimation. Serum sodium and total calcium were measured using ion-selective electrodes (indirect potentiometry). Magnesium was measured by the calmagite timed-endpoint method. Ionised calcium was measured by direct potentiometry. Serum 25-hydroxyvitamin D was measured using a chemiluminescent immunoassay.

Reference ranges: Sodium: 135-145 mEq/L; magnesium: 1.7-2.2 mg/dL; total calcium: 8.5-10.5 mg/dL [23]; ionised calcium: 1.12-1.32 mmol/L [24]. Vitamin D levels were categorised as deficiency (<20 ng/mL), insufficiency (20-29 ng/mL), and sufficiency (≥30 ng/mL). Reference thresholds followed laboratory-validated ranges, and vitamin D categorisation adhered to national and international guidelines [16,17].

Standard preanalytical precautions, including prompt sample processing and use of appropriate anticoagulants where applicable, were followed. Instrument calibration was performed according to laboratory protocol, with internal quality control samples run per shift and participation in external quality assurance programmes as part of routine practice. Children were evaluated in the emergency department and paediatric wards using a uniform clinical pathway to standardise initial assessment, timing of sampling, and documentation.

Outcome measures: The primary outcomes were mean serum sodium, magnesium, total calcium, ionised calcium, and vitamin D levels in FS compared with FI controls. Secondary outcomes included differences in biomarker levels within the FS group based on seizure type (simple vs. complex).

STATISTICAL ANALYSIS

Continuous variables were summarised as mean±standard deviation or median (range), as appropriate, and compared using Student's t-test or one-way Analysis of Variance (ANOVA). Where heterogeneity of variance was present, Welch's correction was applied. Categorical variables were compared using χ^2 tests. A two-sided p-value <0.05 was considered statistically significant. Assumption checks for normality and variance homogeneity guided test selection, and 95% confidence intervals were reported alongside p-values where relevant. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 20.0, with complete-case analysis and no imputation for missing data.

RESULTS

Baseline characteristics are summarised in [Table/Fig-1]. Sex distribution was identical in both groups, with males comprising 38/64 (59.4%) and females 26/64 (40.6%) in each group (p-value=1.000). Socio-economic status was also comparable; Kuppuswamy classes IV-V predominated equally in the FS and FI groups (44/64, 68.8% each; p-value=1.000), while classes I-III accounted for 20/64 (31.2%) participants in each group. Febrile seizure-specific characteristics (not applicable to controls) included a history of prior febrile seizures in 19/64 children (29.6%), a positive family history in 8/64 (12.5%), and a higher proportion of complex compared with simple febrile seizures (40/64, 62.5% vs. 24/64, 37.5%) [Table/Fig-1].

Characteristic	FS (n=64)	FI (n=64)	p-value
Age 6-24 months, n (%)	48 (75.0)	52 (81.2)	0.392
Age 25-60 months, n (%)	16 (25.0)	12 (18.8)	
Male, n (%)	38 (59.4)	38 (59.4)	1.000
Female, n (%)	26 (40.6)	26 (40.6)	
Past history of FS, n (%)	19 (29.7)	NA	NA
Family history of FS, n (%)	8 (12.5)	NA	NA
FS type: Simple / Complex, n (%)	24 (37.5) / 40 (62.5)	NA	NA
Kuppuswamy I-III, n (%)	20 (31.2)	20 (31.2)	1.000
Kuppuswamy IV-V, n (%)	44 (68.8)	44 (68.8)	

[Table/Fig-1]: Baseline characteristics.
p-values from χ^2 tests comparing FS vs FI distributions for age, sex, and kuppuswamy

Serum sodium and magnesium levels were broadly comparable between children with FS and FI controls, indicating no seizure-specific disturbance in these electrolytes. In contrast, total calcium levels were significantly lower in the FS group, with ionised calcium showing a concordant but less pronounced trend in the same direction. Vitamin D concentrations were low and similar in both

cohorts, suggesting that calcium indices, rather than sodium, magnesium, or vitamin D, provide the greatest biochemical discrimination between FS and FI in this setting [Table/Fig-2].

Biomarker	FS mean±SD	FI mean±SD	p-value
Sodium, mEq/L	138.17±5.10	138.61±4.72	0.615
Magnesium, mg/dL	1.85±0.26	1.79±0.22	0.179
Total calcium, mg/dL	8.881±0.555	9.273±0.554	<0.0001
Ionised calcium, mmol/L	0.97±0.14	1.01±0.11	≈0.07
Vitamin D, ng/mL	20.02±8.08	20.43±9.77	0.792

[Table/Fig-2]: Serum biomarkers in FS vs FI.
Values are presented as mean±SD; p-values are derived from an independent-samples Student's t-test comparing the FS and FI groups

Electrolyte patterns, including sodium, magnesium, total calcium, and ionised calcium, were broadly comparable between simple and complex febrile seizures, and none of these differences reached statistical significance. Vitamin D levels were also similar between simple and complex FS. Overall, these intragroup comparisons indicate that admission biochemistry is largely comparable across febrile seizure phenotypes [Table/Fig-3].

Parameter	Complex group Mean±SD n=40	Simple group Mean±SD n=24	Mean diff	p-value
Sodium	138.58±5.20	137.50±4.80	+1.08	0.419
Magnesium	1.83±0.27	1.87±0.25	-0.04	0.584
Total calcium	8.97±0.58	8.72±0.53	+0.25	0.081
Ionised calcium	0.976±0.15	0.961±0.13	+0.015	0.696
Vitamin D	20.17±8.2	19.93±7.9	+0.24	0.909

[Table/Fig-3]: Subgroup analyses within the Febrile-Seizure (FS) cohort.
Values are presented as mean (SD); p-values are derived from an independent-samples Student's t-test

DISCUSSION

Children with FS demonstrated significantly lower total calcium levels compared with febrile controls without seizures, along with a non significant trend toward lower ionised calcium. Sodium and magnesium levels did not differ between the groups, and vitamin D concentrations were similarly low in both cohorts. Calcium plays a key role in membrane stability and synaptic transmission; even modest reductions in extracellular or ionised calcium can lower the seizure threshold by promoting neuronal hyperexcitability and facilitating synchronous firing [10,13,14]. Fever-related hyperventilation may lead to respiratory alkalosis, increasing albumin-bound calcium and reducing the ionised fraction, thereby amplifying neuronal excitability [7].

In early childhood, limited physiological reserves and higher metabolic demands may accentuate these biochemical shifts, consistent with the more pronounced reduction in total calcium observed in this age group. While total calcium was significantly lower in children with FS, ionised calcium showed only a near-significant trend. Ionised calcium represents the physiologically active fraction and is highly sensitive to pH, protein binding, and sampling conditions. The concordant directional changes in both total and ionised calcium suggest that calcium homeostasis is perturbed at the time of FS presentation, although single time-point ionised calcium measurements may underestimate transient peri-ictal reductions, particularly when acid–base status is not concurrently assessed.

The present findings are consistent with previous studies reporting modest reductions in calcium levels in FS [10,13,14] and help reconcile heterogeneity in the literature by underscoring the importance of timing, age, and physiological context. The absence of differences in serum sodium between cases and febrile controls aligns with existing recommendations that discourage routine electrolyte testing in typical simple febrile seizures, instead supporting a targeted approach in the presence of dehydration, prolonged or focal seizures, altered sensorium, or other clinical red flags [2,3,11,12]. Magnesium levels did not differ between groups, consistent with evidence suggesting that hypomagnesaemia is not a primary contributor at presentation [10,11]. Vitamin D levels, which clustered around 20 ng/mL in both groups, reflect the high prevalence of vitamin D insufficiency among Indian children and do not suggest a specific acute association with FS at admission [15-17].

Routine assessment of total calcium and, where available, ionised calcium is reasonable in children presenting with FS, particularly in infants and toddlers and in cases where seizures are prolonged or recur within the same illness episode. Electrolyte testing beyond calcium should be ordered selectively, guided by clinical assessment and in accordance with ILAE/AAP recommendations [2,3,12]. Given the low vitamin D status observed across both groups, prioritising population-level optimisation through food fortification and supplementation policies is more appropriate than febrile seizure-specific testing during acute care [15-17].

Strengths of the present study include a clearly defined case–control design, uniform laboratory assays performed within six hours of admission, and prespecified subgroup analyses. Future prospective multicentre studies should incorporate serial measurements of total and ionised calcium, alongside blood gas analysis, hydration indices, and inflammatory markers, to characterise calcium dynamics across the febrile course and in relation to seizure timing. Interventional trials could evaluate whether protocolised detection and correction of clinically relevant hypocalcaemia in high-risk FS presentations reduce short-term recurrence or hospital length of stay. Given the pervasive vitamin D insufficiency, programme-level evaluations linking fortification or supplementation strategies to seizure-related outcomes would further inform public health action.

Based on the present findings, total calcium- and ionised calcium where available- should be measured at presentation in children with FS, with prioritisation of infants and those with prolonged or recurrent events. Sodium and magnesium testing should be reserved for children with dehydration, altered mental status, focal neurological features, prolonged seizures, or other clinical red flags, in line with current guideline recommendations [2,3,12]. Vitamin D optimisation programmes should be supported in accordance with national guidance [15-17].

Limitation(s)

This single-centre study conducted in a tertiary emergency care setting over an eight-month period may not be generalisable to community or primary care presentations. The observational comparative design limits causal inference. Biochemical measurements were obtained at a single time point within six hours of admission; without serial sampling or blood gas and pH data, transient peri-ictal biochemical shifts- particularly in ionised calcium- may have been underestimated. Pre-hospital fluid administration, hydration status, nutritional factors, illness severity, and antipyretic use were not standardised or adjusted for, and febrile controls had heterogeneous diagnosis, introducing the possibility of residual confounding.

Total calcium levels were not corrected for serum albumin, and albumin and phosphate concentrations were not measured.

Assay-related limitations, including the use of indirect ion-selective electrodes for sodium and chemiluminescent immunoassay for vitamin D, may have introduced measurement bias despite adherence to routine quality control procedures. Subgroup analyses were modestly powered, and incomplete recording of some subgroup means reduced precision for within-FS comparisons. The high proportion of complex FS suggests potential referral bias. Complete-case analysis was used, and the effects of seasonality on vitamin D levels and infection patterns were not assessed.

CONCLUSION(S)

Children with FS exhibited significantly lower total calcium levels and a non significant trend toward lower ionised calcium compared with febrile controls, while sodium, magnesium, and vitamin D levels did not differ. These findings are physiologically plausible and suggest that transient disturbances in calcium homeostasis may contribute to a reduced seizure threshold during febrile illness. Routine measurement of total and ionised calcium should therefore be considered at the time of FS presentation, particularly in infants and in cases involving prolonged or recurrent seizures, with selective testing of other electrolytes guided by clinical features. Vitamin D insufficiency was common in both groups and warrants a public health response focused on population-level optimisation rather than episode-specific testing. Future multicentre studies incorporating serial biochemical sampling and acid–base assessment may further elucidate the temporal dynamics of calcium during febrile seizures and inform targeted correction strategies.

Availability of data: De-identified data are available upon reasonable request, subject to institutional policies.

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