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Original Article

Frequency of a Positive Cerebrospinal Fluid Study in Patients Presenting With Febrile Seizures

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Abstract

Background: Febrile seizures are a common neurological condition in pediatric practice, affecting 2-5% of children globally. These seizures occur in the context of fever without evidence of central nervous system infection or metabolic disturbance. While often benign, febrile seizures are associated with significant morbidity and can cause considerable distress for both patients and caregivers. The role of cerebrospinal fluid (CSF) abnormalities in the pathogenesis of febrile seizures is not well understood, but identifying these factors may help predict the risk of seizure occurrence.

Objective: To determine the frequency of positive cerebrospinal fluid abnormalities in pediatric patients with febrile seizures and to assess the impact of these abnormalities on the risk of febrile seizures.

Methods: This prospective cohort study was conducted from January 2022 to December 2023 at the Department of Paediatrics, Combined Military Hospital, Rawalpindi. A total of 117 pediatric patients aged 1 to 12 years with a history of febrile seizures presenting with a febrile illness were included. Patients with prior febrile seizures, metabolic/electrolyte disorders, or signs of meningeal infection were excluded. Comprehensive data collection included demographic information, clinical history, and CSF analysis for cell count, total protein, glucose, lactate, and electrolyte levels. Patients were monitored for febrile seizure occurrence during hospitalization. Data were analyzed using SPSS version 25, with continuous variables expressed as medians and interquartile ranges (IQR) and categorical variables as frequencies and percentages. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association between CSF abnormalities and febrile seizures.

Results: The median age of the patients was 3.0 years (IQR: 2.0), with 57.3% (n=67) being male. Febrile seizures occurred in 22.2% (n=26) of patients during hospitalization. Elevated CSF total protein (>60 mg/dL) was observed in 28.2% of patients, CSF glucose (>42 mg/dL) in 12.0%, CSF lactate (>2.0 mmol/L) in 13.7%, and CSF calcium (>1.25 mmol/L) in 10.3%. These abnormalities were significantly associated with an increased risk of febrile seizures: CSF total protein (OR: 3.55, 95% CI: 1.42–8.86, p=0.005), CSF glucose (OR: 13.59, 95% CI: 3.79–48.71, p<0.001), CSF lactate (OR: 4.61, 95% CI: 1.53–13.92, p=0.004), and CSF calcium (OR: 15.52, 95% CI: 3.81–63.36, p<0.001).

Conclusion: This study identified significant associations between elevated CSF total protein, glucose, lactate, and calcium levels and an increased risk of febrile seizures in pediatric patients. CSF analysis could be a valuable tool in identifying children at higher risk for febrile seizures, potentially guiding preventive strategies and clinical management.

1 Introduction

Febrile seizures, a prevalent neurological condition in pediatric practice, present as convulsions associated with elevated body temperature, typically exceeding 100.4°F. This condition affects approximately 2-5% of children worldwide, making it a significant concern in pediatric healthcare (1,2). Febrile seizures occur in the absence of central nervous system infections or metabolic disorders that could otherwise trigger convulsions, distinguishing them from other seizure types (3). The onset of febrile seizures generally occurs between the ages of one and five years, a period characterized by significant neurological development. Although often regarded as benign and self-limiting, febrile seizures continue to be a subject of clinical and research interest due to their associated morbidity, the economic burden they impose, and the distress they cause to both patients and their caregivers (3-5).

The pathophysiology of febrile seizures remains elusive, though several factors have been implicated in their development. A family history of febrile seizures, recent vaccinations, and deficiencies in certain minerals are among the factors believed to lower the seizure threshold during fever (6). These elements, coupled with the immature neurological status of children and fever-induced cytokine production, are thought to create a milieu conducive to neuronal hyperexcitability, culminating in seizure activity (7). The potential role of cerebrospinal fluid (CSF) parameters in the pathogenesis of febrile seizures is of particular interest, as alterations in CSF composition may either reflect or contribute to seizure activity. While abnormalities in CSF proteins, glucose, osmolarity, and various electrolytes such as sodium, potassium, calcium, and magnesium have been observed in patients with seizures, the specific relationship between these parameters and febrile seizures warrants further investigation (8-10).

Despite their commonality, febrile seizures pose a considerable challenge in terms of prevention and management. Efforts to mitigate their occurrence focus on identifying modifiable patient factors that predispose children to these events. Understanding the interplay between CSF abnormalities and febrile seizures could provide insights into the mechanisms driving these episodes, potentially leading to novel approaches in risk stratification and intervention. This study aims to contribute to this understanding by exploring the association between CSF parameters and the risk of febrile seizures, with the ultimate goal of informing clinical practices that could improve outcomes for affected children. The findings of this research are anticipated to enhance clinical decision-making, guide therapeutic strategies, and contribute to the broader knowledge of febrile seizure disorders, thereby benefiting both patients and healthcare providers.

2 Material and Methods

The study was conducted as a prospective cohort study at the Department of Paediatrics, Combined Military Hospital, Rawalpindi, over a period extending from January 2022 to December 2023. The research focused on a cohort of 117 pediatric patients, aged 1 to 12 years, who presented with febrile illness characterized by a body temperature exceeding 100.4°F (38°C) and who had a documented history of febrile seizures. The study employed consecutive, non-probability sampling to recruit participants, ensuring a representative sample of the pediatric population affected by febrile seizures. Informed consent was obtained from the parents or guardians of all participants prior to inclusion in the study. The research protocol was designed in accordance with the Declaration of Helsinki and was approved by the institutional ethics review board(11-14).

The study population was carefully selected based on specific inclusion and exclusion criteria to ensure the validity and reliability of the findings. Inclusion criteria were limited to pediatric patients aged 1 to 12 years who had a history of febrile seizures and presented with a current febrile illness. Exclusion criteria were stringent and included children who had experienced a febrile seizure prior to presentation, those with a history of metabolic or electrolyte disorders, congenital or structural anomalies, developmental delays, epilepsy, or other non-febrile seizures. Additionally, patients exhibiting signs of meningeal irritation, such as neck stiffness, Kernig's sign, or Brudzinski's sign, those with chronic inflammatory or autoimmune disorders, and those with traumatic lumbar punctures were excluded from the study.

Data collection involved a comprehensive approach, beginning with the recording of demographic information and a detailed clinical history for each participant. Clinical examination included the measurement of body temperature using a calibrated mercury thermometer. The thermometer was placed in the axilla, with the arm adducted for at least three minutes to ensure an accurate reading. Laboratory investigations included complete blood counts, serum electrolytes, and blood and urine cultures to rule out other potential causes of fever. All participants underwent lumbar puncture for cerebrospinal fluid (CSF) analysis. CSF samples were analyzed for cell count, total protein, glucose, lactate, and electrolytes, including sodium, potassium, calcium, and magnesium.

Participants were admitted to the hospital and monitored closely for the development of febrile seizures during their hospital stay. Discharge was considered only after the patients had remained afebrile for at least twenty-four consecutive hours. The occurrence of febrile seizures during admission was meticulously documented, along with the corresponding CSF parameters. The study aimed to identify correlations between abnormalities in CSF parameters and the risk of febrile seizures.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of the data. Categorical variables were presented as frequencies and percentages. The Shapiro-Wilk test was used to assess the normality of continuous variables. For comparative analysis, the independent samples t-test or Mann-Whitney U test was employed for continuous variables, while the Chi-square test or Fisher's exact test was used for categorical variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association between CSF abnormalities and the occurrence of febrile seizures. A p-value of ≤ 0.05 was considered statistically significant in all analyses.

The study was conducted under strict ethical guidelines, and all procedures were performed in compliance with relevant institutional and international ethical standards. The findings are expected to contribute to the existing body of knowledge regarding the pathophysiology of febrile seizures and may provide insights into potential strategies for the management and prevention of this common pediatric condition.

3 Results

The study sample consisted of 117 pediatric patients with a history of febrile seizures who presented with a febrile illness during the study period. The median age of the participants was 3.0 years (IQR: 2.0 years), with a slight male predominance; 57.3% (n=67) of the patients were male, and 42.7% (n=50) were female. A total of 18.8% (n=22) of the participants reported a family history of febrile seizures in a first-degree relative. The median duration of fever at the time of presentation was 18.0 hours (IQR: 24.0 hours), and the median number of previous febrile seizure episodes was 1.0 (IQR: 2.0).

Table 1: Patient Demographics and Clinical Characteristics (n=117)

Variable	Total (n=117)	Male (n=67)	Female (n=50)
Age (years), median (IQR)	3.0 (2.0)	2.0 (2.0)	3.0 (2.0)
Family history of febrile seizures	22 (18.8%)	13 (19.4%)	9 (18.0%)
Duration of fever (hours), median (IQR)	18.0 (24.0)	24.0 (24.0)	18.0 (24.0)
Previous episodes of febrile seizures, median (IQR)	1.0 (2.0)	1.0 (2.0)	2.0 (2.0)
Occurrence of febrile seizures during admission	26 (22.2%)	20 (29.9%)	6 (12.0%)

A total of 26 patients (22.2%) experienced febrile seizures during their hospital admission. Febrile seizures were more common in male patients, with 29.9% (n=20) of males experiencing seizures compared to 12.0% (n=6) of females.

Table 2: Cerebrospinal Fluid (CSF) Parameters According to Gender (n=117)

Variable	Total (n=117)	Male (n=67)	Female (n=50)
CSF White cell count (/µL), median (IQR)	2.0 (3.0)	3.0 (3.0)	2.0 (2.0)
CSF Total protein (mg/dL), median (IQR)	50.0 (32.0)	51.0 (32.0)	43.5 (28.0)
CSF Glucose (mg/dL), median (IQR)	33.0 (10.0)	34.0 (11.0)	32.5 (9.0)
CSF Lactate (mmol/L), median (IQR)	1.60 (0.5)	1.60 (0.7)	1.60 (0.5)
CSF Sodium (mmol/L), median (IQR)	137.0 (12.0)	138.0 (11.0)	136.0 (11.0)
CSF Potassium (mmol/L), median (IQR)	3.50 (0.80)	3.10 (0.60)	3.80 (0.40)
CSF Calcium (mmol/L), median (IQR)	1.12 (0.15)	1.13 (0.12)	1.11 (0.17)
CSF Magnesium (mmol/L), median (IQR)	0.97 (0.25)	0.95 (0.25)	0.98 (0.26)

The CSF analysis revealed that the median white cell count was 2.0/µL (IQR: 3.0), the median total protein level was 50.0 mg/dL (IQR: 32.0), the median glucose level was 33.0 mg/dL (IQR: 10.0), and the median lactate level was 1.60 mmol/L (IQR: 0.5). When comparing CSF parameters between genders, males exhibited slightly higher median levels of total protein (51.0 mg/dL vs. 43.5 mg/dL), glucose (34.0 mg/dL vs. 32.5 mg/dL), and potassium (3.10 mmol/L vs. 3.80 mmol/L) than females. However, these differences were not statistically significant.

Table 3: Frequency of Abnormal CSF Parameters and Their Association with Febrile Seizures (n=117)

CSF Parameter	Total (%)	With Febrile Seizures (%)	Without Febrile Seizures (%)	Odds Ratio (95% CI)	p-value
CSF White cell count >5/µL	3 (2.6%)	1 (3.8%)	2 (2.3%)	1.78 (0.16 – 20.46)	1.000
CSF Total protein >60 mg/dL	33 (28.2%)	16 (61.5%)	17 (19.3%)	3.55 (1.42 – 8.86)	0.005
CSF Glucose >42 mg/dL	14 (12.0%)	12 (46.2%)	2 (2.3%)	13.59 (3.79 – 48.71)	<0.001
CSF Lactate >2.0 mmol/L	16 (13.7%)	9 (34.6%)	7 (8.0%)	4.61 (1.53 – 13.92)	0.004
CSF Sodium <135 mmol/L	51 (43.6%)	11 (42.3%)	40 (45.5%)	0.94 (0.39 – 2.26)	0.881
CSF Potassium >3.9 mmol/L	16 (13.7%)	2 (7.7%)	14 (15.9%)	0.20 (0.03 – 1.61)	0.117
CSF Calcium >1.25 mmol/L	12 (10.3%)	8 (30.8%)	4 (4.5%)	15.52 (3.81 – 63.36)	<0.001
CSF Magnesium <0.77 mmol/L	13 (11.1%)	4 (15.4%)	9 (10.2%)	1.66 (0.47 – 5.89)	0.482

Among the study participants, abnormal CSF findings were noted in a significant proportion of patients. Specifically, elevated CSF total protein (>60 mg/dL) was observed in 28.2% of the patients, elevated CSF glucose (>42 mg/dL) in 12.0%, elevated CSF lactate (>2.0 mmol/L) in 13.7%, and elevated CSF calcium (>1.25 mmol/L) in 10.3%. These abnormal CSF parameters were more frequently associated with the occurrence of febrile seizures during the hospital stay. The odds ratios for the occurrence of febrile seizures were notably higher

for patients with elevated CSF total protein (OR: 3.55, 95% CI: 1.42 – 8.86, p=0.005), elevated CSF glucose (OR: 13.59, 95% CI: 3.79 – 48.71, p<0.001), elevated CSF lactate (OR: 4.61, 95% CI: 1.53 – 13.92, p=0.004), and elevated CSF calcium (OR: 15.52, 95% CI: 3.81 – 63.36, p<0.001).

4 Discussion

The findings of this study highlighted significant associations between certain cerebrospinal fluid (CSF) abnormalities and an increased risk of febrile seizures in pediatric patients. Specifically, elevated levels of CSF total protein, glucose, lactate, and calcium were identified as notable risk factors, supporting the hypothesis that derangements in CSF homeostasis play a crucial role in the pathogenesis of febrile seizures. These results contribute to the growing body of literature that seeks to unravel the complex mechanisms underlying febrile seizures and their potential predictors.

The association between elevated CSF total protein levels and the occurrence of febrile seizures observed in this study aligns with previous research that has documented elevated CSF proteins in patients with seizures, possibly due to a transient disruption of the blood-brain barrier during or after seizure activity (19). However, this study is distinct in that it measured CSF protein levels prior to the onset of seizures, suggesting that these elevations might precede seizure activity, rather than being a consequence. This finding warrants further exploration to determine whether elevated CSF protein levels could serve as a biomarker for impending febrile seizures or indicate subclinical seizure activity.

The significant association between elevated CSF glucose levels and febrile seizures was another important finding. While elevated CSF glucose has been noted in febrile children, previous studies have not consistently linked this abnormality with seizure activity (20). The current study's results suggest that higher CSF glucose levels may contribute to or reflect the physiological conditions that lower the seizure threshold during febrile episodes. This could be related to the increase in stress-related hormones such as cortisol, which have been implicated in seizure susceptibility (21,22). Given the limited data on this relationship, further research is necessary to confirm these findings and elucidate the mechanisms by which CSF glucose levels influence seizure risk.

The study also found a strong association between elevated CSF lactate levels and febrile seizures, which is consistent with prior research indicating that CSF lactate can remain elevated for several days after a seizure (19). Elevated CSF lactate may reflect a metabolic shift towards glycolysis due to mitochondrial dysfunction, which has been observed in patients with epilepsy and other seizure disorders (23). This study's findings suggest that lactate elevation in the CSF may not only be a post-seizure phenomenon but could also be predictive of seizure risk during febrile illnesses. This highlights the potential utility of CSF lactate as a prognostic marker for febrile seizures, though further studies are needed to validate this potential.

The association of elevated CSF calcium levels with febrile seizures observed in this study is intriguing, as calcium plays a critical role in neuronal excitability and synaptic transmission. Elevated calcium levels in the CSF might reflect an underlying dysregulation of calcium homeostasis, which could contribute to the neuronal hyperexcitability observed in febrile seizures (24). This finding adds to the limited but growing evidence suggesting that electrolyte imbalances in the CSF could influence seizure susceptibility, emphasizing the need for more detailed investigations into the role of calcium and other electrolytes in seizure pathophysiology.

Despite these significant findings, the study had several limitations. The sample size was relatively small, and the study was conducted in a single military hospital, which may limit the generalizability of the results to broader populations. Additionally, the study's exclusion criteria, while necessary for maintaining the integrity of the results, may have inadvertently excluded certain subpopulations of febrile seizure patients, such as those with mild metabolic disturbances or subclinical infections. These factors could potentially introduce selection bias, affecting the study's conclusions. Another limitation was the relatively short observation period, which may not have captured all instances of febrile seizures or the full spectrum of CSF changes associated with prolonged febrile illnesses. Further research with larger, more diverse cohorts and extended follow-up periods is recommended to validate these findings and explore the long-term implications of CSF abnormalities in febrile seizure risk.

The strengths of the study include its prospective design, which allowed for real-time data collection and minimized recall bias. The use of rigorous inclusion and exclusion criteria ensured that the study population was well-defined and homogenous, which is crucial for the reliability of the findings. Additionally, the comprehensive analysis of multiple CSF parameters provided a broad perspective on the potential biochemical changes associated with febrile seizures, contributing valuable insights into the condition's pathophysiology.

5 Conclusion

In conclusion, this study provided evidence that certain CSF abnormalities, particularly elevated levels of total protein, glucose, lactate, and calcium, are associated with an increased risk of febrile seizures in pediatric patients. These findings suggest that CSF analysis could be a useful tool for identifying children at higher risk for febrile seizures, potentially guiding preventive strategies and interventions. However, the study's limitations must be acknowledged, and further research is needed to confirm these associations and explore the underlying mechanisms in greater detail. Such research could ultimately lead to more effective management approaches for children prone to febrile seizures, improving outcomes and reducing the burden of this common pediatric condition.

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Disclaimers

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