Evaluation of Risk Factors Associated with First Febrile Seizure: A Hospital Based Case-Control Study

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Abstract

Introduction:
Febrile seizures (FS) are the most prevalent type of seizures seen in paediatric practice, yet the underlying causes remain poorly understood.

Objective:
This study aimed to identify risk factors associated with the first febrile seizure in children aged 6 months to 5 years.

Methods:
This hospital-based case-control study was conducted from January to December 2024 at the Paediatrics Department of Jalalabad Ragib-Rabeya Medical College Hospital in Sylhet including 200 children aged 6 months to 5 years, with 100 cases admitted for their first febrile seizure and 100 controls admitted for fever without a history of seizures. Data were collected using a pre-designed semi-structured questionnaire and statistical analyses, including the Chi-square test, Student's t-test and odds ratio calculations were performed to compare risk factors between the two groups.

Results:
The mean age of children in the case vs control group was insignificant (17.17±8.22 vs 18.89±14.83 months; p=0.3116). However, boys exhibited a significantly higher risk of developing FS, with the odds of boys experiencing FS being twice that of girls (95% CI=1.1578 to 3.6980, p=0.0141). A family history of febrile seizures was notably linked to the occurrence of first febrile seizure, with eight times greater odds for affected children (95% CI=3.355 to 21.209, p<0.0001). There was no significant correlation identified between a family history of epilepsy and the first febrile seizure. Children who were exclusively breastfed had a lower susceptibility to febrile seizures (OR=0.409, 95% CI=0.1924 to 0.8090, p=0.0202). Antenatal and perinatal complications were significantly higher in the case group than the control group (p<0.05). The mean admission temperature for cases was significantly higher at 100.92±1.54^{0}F compared to 100.28±1.46^{0}F in controls (p=0.0029). Upper respiratory tract infections (URTI) emerged as the most common trigger for febrile seizures (p< 0.001) and serum sodium levels were significantly lower while serum calcium and random blood sugar levels were significantly higher in the case group (p<0.05).

Conclusion:
Male gender, positive family history of febrile seizures, inadequate exclusive breastfeeding, elevated body temperature, antenatal and perinatal complications, upper respiratory tract infections as well as abnormal serum sodium, calcium, and blood sugar levels were significant risk factors for the first episode of febrile seizure. Addressing and mitigating these risk factors could significantly reduce the incidence of febrile seizures in children.

Keywords: First febrile seizure, Risk factors, Family history, Upper respiratory tract infection, Children

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Introduction:

A seizure is a brief occurrence of signs or symptoms resulting from abnormal or excessive neuronal activity in the brain. Febrile seizures are the most common type of provoked seizures in children.[1,2] Febrile seizures are defined as seizures

that occur in children between the ages of 6 and 60 months, typically during a fever (with a temperature of 38°C or 100.4°F or higher). They are not caused by infections of the central nervous system or metabolic imbalances and occur in children who have no history of prior afebrile seizures.[3,4] The incidence of febrile seizures ranges from 3% to 10%. Studies in developed countries showing that 2-5% of children between the ages of 6 months and 5 years, experience these seizures.[2,5] Febrile seizures are a common neurological issue in childhood, with an estimated 2-5% of children experiencing at least one seizure during a febrile illness before the age of 5. They account for approximately 30% of all seizures in children.[1,6] Although many paediatricians consider the lower age limit for febrile seizures to be 6 months, both the National Institutes of Health and the International League Against Epilepsy recognize a lower limit of 3 months and 1 month respectively. Most febrile seizures occur between 6 months and 3 years with the highest incidence observed between 12 and 18 months.[3,7] Febrile seizures are more common in boys than in girls, with a male-to-female ratio of around 1.6:1.[8,9] The exact cause of febrile seizures is not fully understood, but it is believed that the developing brain has a low seizure threshold and is particularly sensitive to rapid increases in body temperature. When this is combined with genetic predisposition and environmental factors, increases the likelihood of febrile seizures.[8,10] Several risk factors have been identified for febrile seizures including age, developmental delays, discharge from a neonatal unit after 28 days, daycare attendance, viral infections, a family history of febrile seizures or epilepsy, perinatal factors, maternal smoking and alcohol use during pregnancy, certain vaccinations, and possibly deficiencies in iron, zinc and changes in body electrolytes (e,g sodium, potassium, calcium).[11-13] Viral infections, especially those caused by human herpes virus, are common triggers for febrile seizures.[11] Upper respiratory tract infections (URTI) primarily viral are a frequent cause of febrile seizures in children, along with urinary tract infections (UTI) and acute gastroenteritis.[9,14] Although febrile seizures are usually benign and self-limiting, they often cause significant worry and concern among parents.[8,10] Given the high prevalence of febrile seizures in children, it is crucial to identify the risk factors associated with their occurrence. Understanding these factors is essential for preventing and managing febrile seizures effectively.

Methods

This hospital-based case-control study was conducted from January 2024 to December 2024, at the Department of Paediatrics, Jalalabad Ragib-Rabeya Medical College Hospital on 200 patients aged between 6 months and 60 months through consecutive sampling. The cases were children who were admitted to the paediatric ward with their first episode of febrile seizure, with no evidence of central nervous system infection, metabolic disorders, or a prior history of afebrile seizures or neuro-deficits (N=100). These cases were matched with controls (of similar age and admitted on the same date) who presented with fever but had no history of seizures, either currently or in the past (n=100).Data collection involved trained physicians using a semi-structured questionnaire to record clinical details such as demographics, medical history, and findings related to febrile seizures. Parameters included age, gender, temperature on admission, family history of febrile seizures or epilepsy, history of parental consanguinity, history of exclusive breastfeeding, antenatal, natal, and perinatal factors, the etiology of febrile seizures and clinical and laboratory findings for both groups. Axillary temperature was noted, blood sugar levels measured, and laboratory tests including complete blood count, serum electrolytes and serum calcium were conducted to determine causes of febrile seizures, excluding patients with meningitis. No viral isolation tests or encephalograms were conducted. Informed verbal consent was obtained from guardians for participation. Data analysis was performed using SPSS version 21. Quantitative variables were expressed as means±SD and compared between groups using the student's t-test. Qualitative variables were expressed as frequencies and percentages, with comparisons made using the Chi-square test. The odds ratio (OR) was calculated to assess the risk of febrile seizures in the case group compared to the control group. A significance level of 5% was set, and a p-value of <0.05 was considered statistically significant.

Results:

The mean age was 17.17±8.22 months in the case group and 18.89±14.83 months in the control group (p=0.3116). Most febrile seizures (FS) occurred in the age group of 6 to 24 months, which included 76 children (76%). In contrast, the lowest incidence of FS was found in the age group of 36 to 60 months, comprising only 5 children (5%) (Figure-1).

In children with febrile seizures (FS), 70% of cases were male compared to 30% female. In the control group, males were 53% and females 47%. The risk of developing FS was found to be twice as high in boys as in girls (95% CI=1.16 to 3.69, p=0.014). The male-to-female ratio in the case group was 2.3:1, while it was 1.1:1 in the control group. The case group exhibited a significantly higher mean temperature at admission (100.92±1.54°F) compared to the control group (100.28±1.46°F) (p=0.0029). A notable 35% of cases had a positive family history of febrile seizures, in contrast to only 6% of controls, indicating a higher likelihood of experiencing a first febrile seizure (odds ratio 8.44, 95% CI=3.36 to 21.21, p<0.0001). Although 5% of cases had a family history of epilepsy versus 1% of controls, there was no significant association with febrile seizures (p=0.135). Additionally, the rate of parental consanguinity was 9% in cases and 4% in controls, which was not statistically significant (p=0.1622). 75% of cases and 88% of controls were exclusively breastfed for first six months. Exclusively breastfed children had a lower risk of febrile seizures (OR=0.409, 95% CI=0.192-0.869, p=0.02). No developmental delay was observed in either group. Among the cases studied, 21% had perinatal asphyxia (PNA), compared to 8% in the control group. Children with a history of PNA had a threefold higher risk of febrile seizures than those without it (95% CI=1.283 to 7.283, p<0.006). Additionally, 19% of the cases were admitted to a neonatal unit, while only 4% of controls were, leading to a 5.6 times higher risk of febrile seizures for those admitted (95% CI=1.84 to 17.22, p=0.0025). Preterm births were 6% in cases and 4% in controls, with no significant findings on gestational age. Furthermore, 14% of cases had a history of difficult labor, while 98% of controls did not, resulting in a 7.98 times higher risk of febrile seizures for those with a difficult labor history (95% CI=1.76 to 36.09). (Table-I)

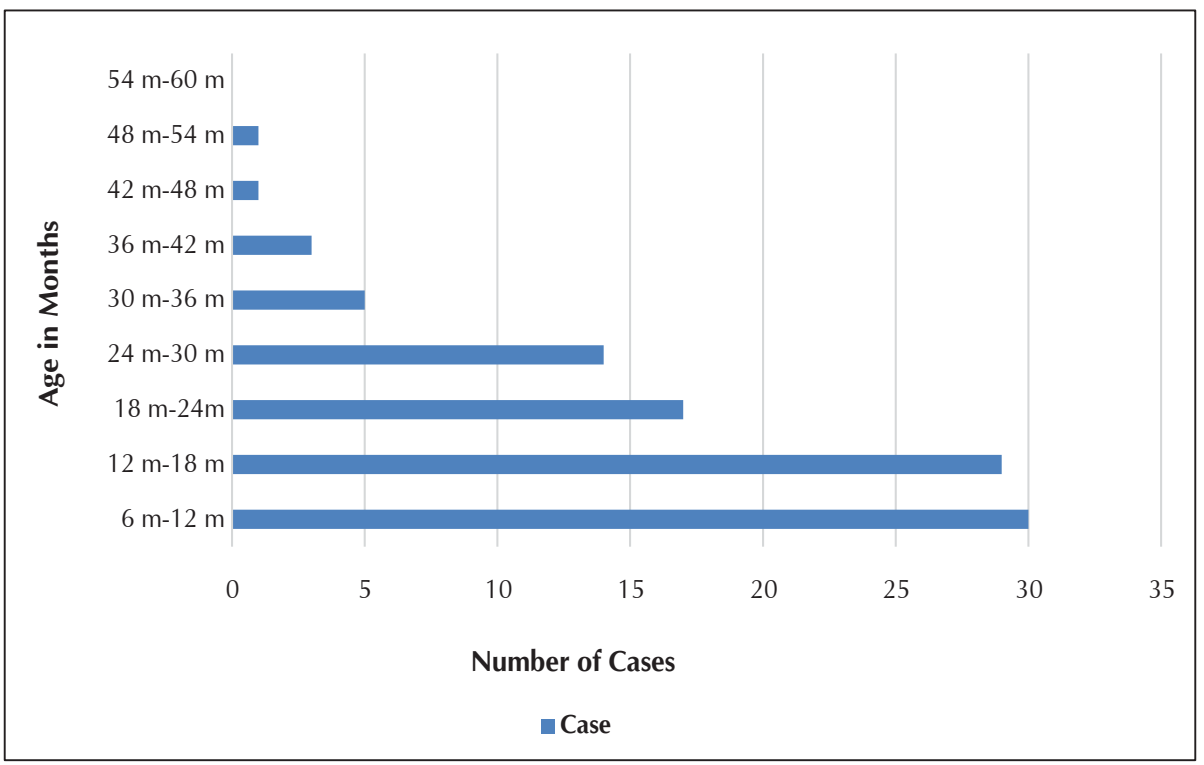

Figure-1: Distribution of febrile seizures incidence versus age groups (n=200)

Table-I: Risk factors associated with first episode of febrile seizures (N=200)

Variables	Case (n=100) no. (%)	Control (n=100) no. (%)	Odds Ratio (95% CI)	p-value
Mean age (months)	17.17±8.22	18.89±14.83		0.3116
Gender				
Male	70 (70)	53 (53)	2.06(1.16-3.69)	0.014
Female	30 (30)	47 (47)		
Mean temperature on admission	100.92±1.54^{0}F	100.28±1.46^{0}F		0.0029
Family history of febrile seizure				
Present	35 (35)	6 (6)	8.44(3.36-21.21)	<0.0001
Absent	65 (65)	94 (94)		
Family history of epilepsy				
Present	5 (5)	1 (1)	5.20(0.59-45.43)	0.135
Absent	95 (95)	99 (99)		
History of Consanguinity				
Present	9 (9)	4 (4)	2.40(0.71-7.79)	0.1622
Absent	91 (91)	96 (96)		
Exclusive breast feeding				
Yes	75 (75)	88 (88)	0.409(0.192-0.869)	0.0202
No	25 (25)	12 (12)		
History of perinatal asphyxia				
Present	21 (21)	8 (8)	3.057(1.283-7.283)	0.0116
Absent	79 (79)	92 (92)		
History of admission in neonatal unit				
Yes	19 (19)	4 (4)	5.63(1.84-17.22)	0.0025
No	81(81)	96 (96)		
Gestational age				
Preterm	6 (6)	4 (4)	1.53(0.42-5.60)	0.519
Term	94 (94)	96 (96)		
History of difficult labour				
Present	14 (14)	2 (2)	7.98(1.76-36.09)	0.007
Absent	86 (86)	98 (98)		

Student's t-Test was used for differences in mean. Data were analyzed using Chi-square(x^2) Test, Odds Ratio was used for estimation of significance in risk factors between numbers. CI: Confidence Interval

Among the children presenting with FS, 39% had an upper respiratory tract infection (URTI), whereas 28% of the controls had URTI. The incidences of lower respiratory tract infection, viral fever, UTI and unclassified fever in the case group were 18%, 25%, 10% and 8%, respectively, compared to 48%, 8%, 8% and 8% in the control group. URTI triggered the development of febrile seizures much more frequently than any other diseases presented in the table (p=0.00003). (Table-II)

Table-II: Etiology of febrile seizure (N=200)

Etiology	Case (n=100) no. (%)	Control (n=100) no. (%)	x^2	p-value
Upper respiratory tract infection	39(39)	28(28)		
Lower respiratory tract infection	18 (18)	48 (48)	20.4	0.00007
Viral fever	25 (25)	08 (08)		
Urinary tract infection	10 (10)	08 (08)		
Unclassified	08 (08)	08 (08)		

Data were analyzed using Chi-square Test.

Biochemical parameters of children with FS showed that the levels of blood glucose and calcium were significantly higher than those of the control group (p=0.0116, p=0.0002). Conversely, the sodium level was significantly lower in the case group compared to the control group (p=0.0001). There was no significant statistical difference between the study groups in terms of mean hemoglobin level (p=0.599). (Table-III)

Table-III: Baseline laboratory findings (N=200)

Mean value	Cases	Controls	p-value
Mean Haemoglobin (gm/dl)	10.51±1.06	10.42±1.34	0.5990
Serum Sodium) (meq/L)	137.6±2.88	139.99±5.39	0.0001
Serum total calcium (mg/dl)	9.89±1.13	9.33±0.94	0.0002
Random Blood sugar (mmol/L)	7.06±1.65	6.52±1.33	0.0116

Data were analyzed using Student's t-Test.

Discussion:

Febrile seizures can distress parents, leading them to seek emergency care. The exact cause is unclear, but several risk factors exist for first febrile seizure. In the current study, age did not correlate with febrile seizures similar to the result of Sharawat IK et al[10] and Nahid et al[11] However, a significant majority (76%) of first febrile seizures occurred in children under the age of 2, which aligned with findings of Sharawat IK et al[10] and Nahid et al,[11] where 60% and 56% of first febrile seizures were observed in the same age group, respectively. Research showed that, boys being twice as likely to have febrile seizures than girls, supporting the findings of Nahid et al.[11] The risk for boys is 3.5 times higher.The male-to-female ratio in our study was 2.3:1, comparable to the ratio of 2:1 reported by Pabani GD and Khanna PPC.[1]

A positive family history of febrile seizures emerged as a strong risk factor, with an odds ratio of 8 (95% CI=3.355-21.209, P<0.0001). Nahid et al[11] identified a 36.4-fold increase in risk for those with a family history of FS. In our findings, 5% of patients had a family history of epilepsy, but this was not classified as a risk factor consistent with those of Sharawat IK et al[10] and Nahid et al.[11] The mean admission temperature for cases was 100.92±1.54°F, compared to 100.28±1.46°F in controls. This is inconsistent with the results of Shrestha BD et al,[15] who reported lower mean temperatures in their cases.

Upper respiratory tract infections (URTI) were identified as the most common trigger for febrile seizures in our study, echoing findings from Sharawat IK et al[10] but differing from Nahid et al,[11] who highlighted viral fever as the predominant cause.

Our analysis found that children who were exclusively breastfed for the first six months had a lower incidence of febrile seizures (OR=0.4091, P=0.0202), supporting the conclusions of Nahid et al[11] (OR=0.149, P<0.001).

Perinatal asphyxia was linked to first febrile seizures in our study, corroborating previous research that identified it as a significant risk factor.[11] We also noted that antenatal factors, such as difficult labor, were significant in predicting the first episode of febrile seizures, aligning with Sharawat IK et al,[10] which identified antepartum hemorrhage and difficult labor as related risk factors. While the study by Nahid et al[11] suggested a strong association between prematurity and febrile seizures with nearly three times the risk, our findings revealed no significant link between prematurity and first febrile seizures (P=0.5).

Additionally, serum sodium levels were significantly lower in children with FS than in controls (P=0.0001), consistent with findings of Zakaria et al,[13] Namakin et al[16] who reported lower sodium levels in children experiencing febrile seizures. Conversely, we found a significantly higher serum calcium level in the febrile seizure group compared to controls (P=0.0002), which aligned with Shrestha BD et al,[15] although some studies suggest a link between low calcium levels and febrile seizures.[10,17]

Stressful events such as seizures can lead to temporary hyperglycemia due to increased levels of cortisol, glucagon, growth hormone and other cytokines.[13] We found that random blood glucose levels were significantly elevated in children with FS compared to those without seizures (p=0.0116). This agreed with research by Zakaria et al[13] and Costea et al[18] who also reported higher blood glucose levels in children with FS. Conversely, another study suggested that low blood sugar may be associated with FS.[10]

Notably, there was no significant difference in hemoglobin levels between the study groups, which is consistent with Gunes A et al.[19] However, many studies had indicated that blood indices, including hemoglobin, hematocrit, MCV, MCH, and MCHC values, tend to be lower in the febrile seizure group compared to the control group.[10,20]

Limitation:

We did not include follow-up to evaluate risk factors related to the recurrence of febrile seizures and long-term outcomes, including the potential development of epilepsy.

Conclusion:

Several factors contributed to the onset of the first episode of febrile seizures. These included male gender, a family history of febrile seizures, exclusive breastfeeding for less than six months, elevated body temperature, antenatal and perinatal complications. Additionally, upper respiratory tract infections, low serum sodium levels, high serum calcium levels and elevated random blood sugar levels were identified as triggers. Addressing these risk factors may help reduce the incidence of febrile seizures.

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