

Risk Factors for Initial Febrile Seizures in Pediatric Patients at Iranian Tertiary Hospitals (2019-2021): Retrospective Cross-Sectional Study

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ABSTRACT

Objectives: Febrile seizures (FS) are among the most common neurological emergencies in children aged 6 months to 6 years, yet their risk factors remain poorly defined in Iran. This study aimed to identify and analyze the demographic, clinical, and laboratory factors associated with the first episode of febrile convulsion (FC) in children admitted to a major pediatric hospital in Tehran, Iran.

Materials & Methods: This retrospective cross-sectional study was conducted at a large pediatric hospital in Tehran, Iran, from 2019 to 2021. A total of 305 children who met the predefined inclusion criteria were included. Data were extracted from medical records and supplemented by interviews with caregivers. Collected variables included seizure type, perinatal history, family history of febrile seizures, serum biomarkers (e.g., hemoglobin, sodium), cause of fever, and other relevant clinical factors.

Results: Of the seizures, 85.2% were simple and predominantly occurred within the first 24 hours of fever onset. Complex seizures showed a significant association with preterm delivery ($P=0.02$) and a positive family history of febrile seizures ($P=0.01$). Anemia was significantly more common in girls ($P=0.027$), and hemoglobin levels tended to be lower in children with complex seizures, although this difference was not statistically significant ($P=0.06$). Serum sodium levels remained within the normal range in all groups. Routine electroencephalography (EEG) showed abnormal findings in only 0.66% of cases, questioning its routine diagnostic value in first febrile seizures. Antihistamine use was uncommon and showed no association with seizure characteristics. The most frequent underlying causes of fever were upper respiratory tract infections, viral gastroenteritis, and post-vaccination fever.

Conclusion: This study provides novel regional insights into the pathophysiological and epidemiological features of first febrile seizures in Iranian children. The findings highlight specific risk factors for complex seizures (preterm birth and family history) and suggest that targeted screening and preventive strategies could benefit high-risk pediatric populations. The very low yield of routine EEG supports a more selective approach to its use in this setting.

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Introduction

Febrile seizure (FS) is the most common childhood seizure disorder and is diagnosed as seizures in intact children aged 6-60 months with an acute fever without intracranial infection or electrolyte disturbance (1, 2).

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FS with a 2-5% prevalence is an age-related common neurologic complaint categorized into two major subgroups: Complex and simple FC, based on focality in semiology, relapse within the first day of the febrile illness, and prolonged duration of the event (3).



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FS etiology is multifactorial, being dependent on both genetic factors and environmental precipitants (3) (4). A few studies have attempted to find correlations with biochemical measures, such as serum sodium and calcium. However, electrolyte fluctuations in febrile states in general do not seem to be FS-specific (5, 6). Eventful prenatal history, such as prematurity, breastfeeding duration, genetic background, and demographic data, such as gender, are some factors that have been studied as risk factors (7- 9).

Various pathophysiological mechanisms, such as immunization/infections and trace element/nutritional deficiencies, have been identified so far (10). Iron and zinc, two fundamental nutritional elements, play a role as cofactors in neurotransmitter synthesis during normal brain cell development and function. However, deficiency could lead to lowering the FC threshold level (10-12). On the other hand, iron deficiency anemia is considered to have the potential for irreversible brain damage in young children (13, 14).

Despite the severe FS and repeated hospitalization, particularly in the first febrile seizure (FFS) attacks, longitudinal epidemiologic evidence is limited in Iran (15). Limited sample sizes and short follow-up periods have confounded the majority of Iranian studies. Therefore, the present retrospective cross-sectional study aimed to identify demographic, clinical, and laboratory factors associated with FFC risk for pediatric inpatients admitted to Iranian tertiary hospitals in 2019 and 2021, thus providing robust regional evidence for clinical prevention and counseling.

Materials & Methods

This study is a descriptive, cross-sectional, and retrospective investigation aimed at examining risk factors associated with the first episode of FC in children admitted to the Children's Medical Center in Tehran, which has an average annual admission rate of over 10,000 patients. The study sample included all medical records of children aged six months to six years who were diagnosed with their first episode of FC and presented to the hospital between March 20, 2020, and March 19, 2022. Additional inclusion criteria included the absence of underlying conditions or disorders that could explain the seizures, such as epilepsy, metabolic disorders, or severe central nervous system infections, as well as no prior history of seizures. Children with incomplete medical records or whose parents/guardians did not provide consent for participation were excluded from the study. Ultimately, after obtaining formal written consent from parents or guardians, 305 eligible records were included in the study. Parents or guardians were free to withdraw from

the study at any time without any consequences. Data were extracted from the patients' medical records. In cases where records were incomplete, supplementary information was collected through telephone contact with families, with accuracy verified by cross-referencing medical reports. The collected data included demographic information, such as age, gender, gestational age (weeks), delivery type, residence, parental education, parental job, family history of FS, and family history of epilepsy, seizure characteristics, including type of seizure simple or complex, duration, and frequency of seizures during the febrile episode, causes of fever, and physical examination findings, as well as diagnostic tests and treatment measures. A simple FC was defined as a seizure lasting less than 15 minutes, of a generalized nature, and occurring only once during the febrile episode. A complex febrile seizure was defined as a seizure lasting more than 15 minutes, focal in nature, or occurring more than once during the febrile episode. Statistical analysis was performed using SPSS version 22.0. Descriptive statistics were presented as frequencies and percentages for categorical variables and as mean \pm standard deviation for continuous variables. Categorical variables were evaluated using Pearson's chi-square test. For all tests, a p-value of less than 0.05 was considered statistically significant.

Results

To explore possible factors linked to FC, the researchers collected detailed data on perinatal and sociodemographic characteristics and analyzed this data closely. The goal of this study was to identify any significant connections that could enhance understanding of the risk factors influencing seizure occurrence and their potential impact on seizure classification.

Analysis showed that preterm birth was more common in children with complex FC (27.7%) than in those with simple seizures (14.2%). This difference was statistically significant ($P = 0.02$). While female children and those with mothers who had lower educational levels showed a trend towards higher seizure frequency, these connections did not reach statistical significance. No notable associations were found regarding place of residence or delivery method.

Association of Demographic Factors with Seizure Type

Children born prematurely showed a significant increase in the likelihood of having complex FC. This suggests that being born early might be a risk factor for more complex seizures. However, there was no significant link between the type of seizure and where the family lived or how the child was delivered. Interestingly, a positive family history of FC was much

more common in the complex seizure group ($P = 0.01$). Although lower levels of parental education appeared

to be relate to increased seizure complexity, this finding was not statistically significant.

Table 1. Demographic and perinatal characteristics

Variable	Category / Value	n (%)	P-value (Simple vs. Complex FS)
Age (months)	Mean ± SD	21.2 ± 13.46	
Sex	Male	160 (52.5%)	0.027
	Female	145 (47.5%)	
Gestational Age (weeks)	Mean ± SD	38.1 ± 2.4	—
	Preterm (<37 wks)	49 (16.1%)	0.02
Delivery Type	Vaginal Delivery (NVD)	180 (59%)	0.31
	Cesarean Section	125 (41%)	
Residence	Urban	233 (76.4%)	0.48
	Rural	72 (23.6%)	
Parental Education (Mother)	Below High School	86 (28.2%)	0.14
	High School Diploma	130 (42.6%)	
	University Degree	89 (29.2%)	
Parental Education (Father)	Below High School	69 (22.6%)	0.08
	High School Diploma	120 (39.4%)	
	Bachelor and higher	116 (38.0%)	
Parental Job (Mother)	Housewife	206 (67.5%)	—
	Employed	99 (32.5%)	
Parental Job (Father)	Employed/Self-employed	272 (89.2%)	—
	Unemployed/Other	33 (10.8%)	
Family History of FS	Positive	42 (13.8%)	0.01
	Negative	263 (86.2%)	
Family History of Epilepsy	Positive	8 (2.6%)	0.33
	Negative	297 (97.4%)	

The majority of seizures, 84.4%, occurred within the first 24 hours after fever began. Most of these were simple FC, making up 85.2%, and lasted less than five minutes. Furthermore, most children had only one seizure during their febrile episode, at 88.5%. This highlights that these events are usually brief.

Table 2. Characteristics of FC

Parameter	Value	Percentage (%)
Seizure onset within 24 hours	257 children	84.4%
Simple FC	260 children	85.2%
Duration less than 5 minutes	260 children	85.2%
Occurred only once during febrile illness	270 children	88.5%

The leading cause of fever in the group was a non-COVID upper respiratory tract infection. This was followed by viral gastroenteritis and febrile responses related to vaccines. These findings reveal the range of infections that can cause fever and trigger seizures.

Family History

Most children lacked a familial predisposition to FC (86.1%) or epilepsy (97.5%), suggesting a limited genetic contribution within this cohort. The data

indicate that genetic predisposition may not play a predominant role in this sample population.

History Type	Negative (n)	Percentage (%)
Febrile Seizures	263	86.1
Epilepsy	297	97.5

Electroencephalographic (EEG) Findings

Parameter	Value	Percentage (%)
EEG performed	150 children	49.0%
Complex-to-simple seizure ratio	4:1	N/A
Abnormal EEG findings	1 child	0.66%

A routine EEG was performed in nearly half of the patients. The findings reveal a very low yield of abnormal results, with only a single case demonstrating EEG abnormality, emphasizing the limited utility of routine EEG in evaluating uncomplicated FC.

Etiology of Fever

Etiology	Frequency	Percentage (%)
Non-COVID Upper Respiratory Tract Infection	142	46.7%
Viral Gastroenteritis	55	18.0%
Vaccine-Related Fever	35	11.5%
COVID-19	33	10.7%
Shigellosis	17	5.7%
Urinary Tract Infection (UTI)	10	3.3%

Hematologic and Serum Parameters

Anemia: Hemoglobin levels were below normal for anemia in 12.3% of the children, with a significantly higher rate in females (19.3%) compared to males (6.2%) ($P = 0.027$). Although hemoglobin was lower in children with complex seizures (11.43 ± 1.51 g/dL) compared with children with simple seizures (11.93 ± 0.95 g/dL), this was not a statistically significant difference ($P = 0.06$). The other hematologic values did not show significant differences between seizure types.

Parameter	Simple FS	Complex FS	P-value
Hemoglobin (g/dL)	11.93 ± 0.95	11.43 ± 1.51	0.06
Female anemia (%)	19.3	—	0.027
Male anemia (%)	6.2	—	

Serum Sodium: Average serum sodium concentration was within normal limits (136.31 ± 3.3 mmol/L), with no significant variability observed between seizure classifications or anemia status.

Group	Mean Sodium (mmol/L)	P-Value
Simple FS	136.45	0.29
Complex FS	135.55	-
With anemia	137.33	0.2
Without anemia	136.17	-

Use of Antihistamines

Antihistamines were administered to a small proportion of children (5.7%) for their febrile illnesses. Antihistamine administration was not associated with seizure type ($P = 0.97$) or anemia status ($P = 0.86$), suggesting that antihistamine administration did not significantly influence seizure characteristics in the study population.

Discussion

The research examined the characteristics of FFS in children at a specialized tertiary center over a two-year span. Data from 305 participants indicated an average age exceeding 12 months (21.2 months, SD: 13.4), with no significant gender disparity (male/female ratio: 1.1). While Sartori et al. studied 118 patients with their FFC over one year and found no gender difference (16), other research reports a male predominance ranging from 1.5 to 1.8 times that of females (17-19). Since FC are age-specific, the ages of patients across various studies are comparable (20, 21), typically occurring within the first two years of life (22, 23).

The average fever temperature in the current research was $38.2 \pm 0.4^\circ\text{C}$, which is below the threshold considered a risk factor for initial FC, set at temperatures exceeding 40.5°C as per Sawires' study (4). The occurrence of seizures during febrile episodes

was similar in both the present study (88.5%) and Tosun et al.'s research (90%). Additionally, the proportion of patients experiencing FC on the first day of illness (84.4%) aligns with findings from Liang's study (24).

In the present survey, simple FC were more common than complex ones, with rates of 85% and 15%, respectively. This distribution is supported by recent large-scale cohort studies (25) and the latest national research (2).

Respiratory infections not related to COVID-19, viral gastroenteritis, and post-vaccination responses account for over two-thirds of fever causes in the study. While viral respiratory and gastrointestinal infections are recognized as risk factors for initial FC, the connection between fever, vaccination, and seizures remains complex (4). Although approximately 10% of FC may occur within two weeks following vaccination, immunization can ultimately reduce the risk of viral infections that lead to febrile seizures (4, 25).

Family history of febrile and afebrile seizures or epilepsy is recognized as a risk factor (4), with nearly half of cases exhibiting this background (27). In the current research, only 14% and 2.5% of participants had a family history of febrile and afebrile seizures/epilepsy, respectively, aligning more closely with the findings of Romanovska, reporting a 9.6% family history of seizures (28, 29).

No clear consensus exists regarding the use of EEG or neuroimaging as diagnostic tools for FC. While EEG is generally not recommended for simple FC by most authorities, its role in complex FC remains debated (30, 31). In this study, an EEG was conducted on approximately half of the patients, with a ratio of 4:1 for complex to simple FC. Only one study within the complex febrile convulsion group showed abnormal EEG findings, accounting for 1.6% of the total. Conversely, Aslan et al. reported a higher abnormal EEG rate of 7.3%, resulting in half of the patients receiving anti-seizure medication (21). The significance of EEG abnormalities remains uncertain. Although an abnormal EEG has been considered an independent risk factor for FC recurrence according to Cappellari, the FEBSTAT study emphasized localized slowing as a key feature associated with acute hippocampal abnormalities observed in imaging studies (32, 33).

Low serum iron levels are recognized as a potential risk factor for initial FC. The study observed hemoglobin concentrations ranging from 7 to 14 g/dl among participants, with 12.3% diagnosed with anemia based on age-specific reference values, and a female-to-male ratio of 3:1. Hemoglobin levels appeared to be slightly higher in children experiencing simple FC compared to those with complex seizures. However,

this difference was not statistically significant ($P = 0.06$). No other hematological parameters showed significant differences related to anemia. Research indicates that anemia and iron deficiency may increase the likelihood of FC, possibly through effects on neurotransmitter function (29, 34). One study reported significant differences in hemoglobin, hematocrit, mean platelet volume, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio between simple and complex FC groups (35). Another investigation of ferritin levels in children with their FFC suggested that iron deficiency could be a contributing factor (36). Conversely, some studies found no hematological differences between children with FC and healthy controls. Nonetheless, research involving larger sample sizes has supported the association between iron deficiency and the risk of FC, including simple cases (37, 38).

The study found that the average serum sodium level was within the normal range, averaging 136.31 mmol/L with a standard deviation of 3.3. No significant differences were observed between simple and complex FC, nor between patients with or without anemia (39). An inverse relationship was identified between serum sodium levels and body temperature, suggesting that sodium levels may be affected during febrile illnesses. Navaeifar's research indicated that although serum sodium tends to be lower in children with FC compared to controls, it does not predict the likelihood of seizure recurrence within 24 hours of a febrile episode (40).

Since respiratory infections are a common cause of fever, antihistamines are frequently prescribed, raising concerns about their potential impact on seizure risk. Some studies suggest that antihistamines may shorten the interval between fever onset and seizure or extend seizure duration, while other research reports conflicting results (41-43). In the current study, only 5.7% of participants received antihistamines, and statistical analysis showed no association between medication use and other risk factors.

Considering the limitations of this research, including its short duration, small sample size, and the scope of laboratory assessments, further comprehensive studies are recommended to better understand these relationships.

In Conclusion

Research examining the initial FC in children highlights that most episodes occur in those under two years old, typically presenting as simple and brief seizures within the first 24 hours of fever onset. Common causes include upper respiratory infections and viral gastroenteritis, while a family history of

seizures appears less frequently compared to other studies. EEG results suggest that this test is generally unnecessary for simple seizures, and even in complex cases, abnormal findings are rare. Blood tests revealed higher hemoglobin levels in children with simple seizures compared to those with complex seizures, though the difference was not statistically significant. Serum sodium levels remained within normal limits across all groups, aligning with research that links iron deficiency to FC. The use of antihistamines was limited among participants, with no significant association found between their use and seizure risk factors.

This study, conducted over two years at a specialized pediatric center, focused on children aged six months to six years and provided comprehensive data on causes of fever and their relationship to seizures. It clarified the roles of viral infections and post-vaccination fever in the occurrence of seizure. By analyzing risk factors such as family history, anemia, and serum sodium levels, the research offered new insights into the mechanisms underlying FC, filling gaps in existing knowledge. These findings can inform the development of targeted treatment and prevention strategies, especially for high-risk groups, and may help reduce disease burden. Future research should involve larger, multicenter studies to deepen understanding of seizure mechanisms and explore genetic and environmental influences, as well as the impact of early interventions. Such efforts could enhance clinical management and decrease the incidence of FC in children.

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Authors' Contribution

Mahya Sadat Mohammadi: Study planning, data collection.

Mahsa Soti Khiabani: Study planning, data collection.

Roghayeh Nemati: Data collection, writing the article.

Baram Yarali: Study planning, supervising.

Zahra Rezaei: Supervising, writing the article.

Amir Hossein Dehghan: Data collection, writing the article.

Golnar Ghane: final review of the manuscript,

Matineh Sadat Tabatabaei was responsible for data analysis.

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Conflicts of Interest

The authors declared no financial or non-financial conflicts of interest that would influence the judgment or writing of this article.

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