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RESEARCH ARTICLE
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FACTORS ASSOCIATED WITH SUBSEQUENT EPILEPSY IN CHILDREN WITH FEBRILE SEIZURES

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ABSTRACT
This study was conducted to evaluate the risk factors of recurrence and development of epilepsy in children with febrile seizures at Pediatrics Department of Ibn-e Sina Hospital, Multan from January 2023 to January 2025.A total of 100 children with febrile seizures being follow-up for at least 1 year were included in the study. All patients whose guardians reported more two occurrences of febrile seizures, complex febrile seizures and an episode of febrile seizure with neurodevelopmental delay underwent electroencephalogram. Children with ≥2 unprovoked seizures after febrile seizure occurrence and those with an unprovoked seizure showing epileptiform discharges as detected on an EEG were suspected for development of epilepsy. Results showed that FS recurrence was significantly associated with type of seizure($p<0.001$) and family history of epilepsy ($p=0.030$). Logistic regression analysis revealed that patients who suffered from a seizure after one hour of developing a fever had a 7 times greater chance of recurrence and those with longer episodes had 3 times more risk. Patients who had a FS onset at younger than 1 year were 18 folds more likely to develop epilepsy and 10 folds in those with longer seizure duration. In conclusion, younger than 1-year, complex seizures, seizures within 1 hour of fever, low fever before FS onset and family history are significant risk factors of FS recurrence in children with febrile seizures. Development of epilepsy in such patients is significantly associated with FS onset at younger than 12 months of age, longer seizure duration, clonic seizures, neurodevelopmental delay, abnormal EEG, recurrent FS and complex FS.

Keywords: Children, Epilepsy, Febrile seizures, Pediatrics

INTRODUCTION
Febrile seizures are a frequent condition in children aged 6 months to 5 years, characterized by seizures with fever without any underlying health issue. It is not fatal but is the most common cause

of pediatric hospital visits. They occur in healthy children with normal development due to burst of electrical brain activity. In Pakistan, almost 2-5% of children suffer from it with those aged 2-2.5 years at most risk.[1]

Most of the febrile seizures are simple febrile seizures constituting 80% of the cases.[2] They last <15 minutes and do not have a recurrent episode within next 24 hours. They do not impact the intellectual ability or cause neurological damage. Prolonged, consistently recurrent and focal episodes are complex febrile seizures.[3] Usually, they resolve on its own and are localized, however, they can be complicated by risk factors and epilepsy diagnosis.[4]
This study was conducted to evaluate the risk factors of recurrence and development of epilepsy in children with febrile seizures.

METHODOLOGY

A retrospective study was conducted in the Pediatrics Department of Ibn-e Sina Hospital, Multan from January 2023 to January 2025.A total of 100 children with febrile seizures being follow-up for at least 1 year were included in the study. Consent was obtained from all patients' guardians and were briefed about study. The ethical review board approved the study.
All patients whose guardians reported more two occurrences of febrile seizures, complex febrile seizures and an episode of febrile seizure with neurodevelopmental delay underwent electroencephalogram. Children with ≥2 unprovoked seizures after febrile seizure occurrence and those with an unprovoked seizure showing epileptiform discharges as detected on an EEG were suspected for development of epilepsy.
Patients' data including age, gender, gestation age at birth, birth weight, type of delivery, neonatal data, relationship between parents, family history of febrile seizures and epilepsy, age of FS onset, neuromotor development, fever etiology, duration between fever and seizure onset, body temperature, type and duration of seizure, recurrent episodes, epileptic occurrences and radiological findings were recorded. Children with slower motor skills as compared to other children were regarded to have neurodevelopmental delay except patients with only speech delay.
All data was evaluated by SPSS version 21. Number and percentages were used to calculate categorical parameters and compared by Mann-Whitney U test. Variables within the groups were compared by Chi-squared test and Fisher's test. Risk factors for development of epilepsy were determined by logistic regression analysis.

RESULTS

A total of 100 pediatric patients with FS with mean age 20.63 months were included in analysis. 56 (56%) children were male and 44 (44%) were female. Most FS onset occurred in 2 years or older children (34%), followed by subsequent risk in 12-17 months olds (26%). 18 (18% were born premature and 20% had a parental consanguinity. Half of the patients had a family history of FS and 25 (25%) had a family history of epilepsy. Almost all patients (88%) first developed fever preceding FS was due to upper respiratory tract infection with high fever in 64 children (64%). 73 patients (73%) had simple FS and 17 (17%) patients had complex FS. Patients did not differ significantly with respect to gender, gestation age, birth weight, delivery route, type of FS and relationship between parents. The neonatal data and seizure details are shown in Table I and II.
Electroencephalogram was performed in 66 (66%) patients among which 6 patients had abnormal findings, with majority of patients with complex seizures (20%) ($p<0.001$). 12% patients with multiple seizure had an abnormal EEG and all findings were normal in patients with single seizure activity ($p=0.003$). 2 patients with neurodevelopmental delay had an abnormal EEG which was statistically higher than those with no neurodevelopmental delay ($p<0.001$). 20 (20%) patients underwent neuroimaging among which 5 patients (5%) had abnormal results and was significantly related to neurodevelopmental delay ($p<0.001$).
58 patients (58%) experienced recurrent seizures among which 25% had two episodes and 18 patients (18%) had four or more episodes. Recurrence was significantly associated with type of seizure with a lower risk in patients with simple FS ($p<0.001$). Similarly, complex FS patients were

significantly more likely to have three or more recurrences (p<0.001). A family history of epilepsy also significantly increased the risks of recurrence (p=0.030). Logistic regression analysis revealed that patients who suffered from a seizure after one hour of developing a fever had a 7 times greater chance of recurrence and those with longer episodes had 3 times more risk.

A total of 7 patients were diagnosed with epilepsy at an average age of 40 months. Epilepsy was not associated with gender, gestation age, birth weight, delivery route, relationship between parents and history of FS and epilepsy in 1st and 2nd degree relatives. Six patients (13%) with a low body temperature and 2 (3%) patients with high fever developed epilepsy (p<0.001). 6 patients (13.3%) who suffered from a seizure after one hour of developing a fever developed epilepsy as compared to 1 (2%) patient who had a seizure after 1 hour or more developed epilepsy (p<0.001). Epilepsy was also significantly associated with FS onset at younger than 12 months of age (p=0.006), longer seizure duration (p<0.001), clonic seizures (p<0.001), neurodevelopmental delay (p<0.001), abnormal EEG (p<0.001), recurrent FS (p<0.001) and complex FS (p<0.001). Patients who had a FS onset at younger than 1 year were 18 folds more likely to develop epilepsy and 10 folds in those with longer seizure duration. The logistic analysis of risk factors of recurrence and epilepsy is shown in Table III.

Table I: Neonatal and demographic data

Variables	**N (%)**
Gender	
Male	56 (56%)
Female	44 (44%)
Gestation age at birth	
Less than 37 weeks	18 (18%)
37-42 weeks	80 (80%)
More than 42 weeks	2 (2%)
Birth weight	
Less than 2500 g	10 (10%)
More than 2500 g	90 (90%)
Delivery route	
Cesarean section	45 (45%)
Vaginal	55 (55%)
Consanguinity between parents	20 (20%)
Family history of FS	50 (50%)
Family history of epilepsy	25 (25%)
EEG findings	
Normal	60 (60%)
Abnormal	6 (6%)
Neuroimaging	
Normal	15 (15%)
Abnormal	5 (5%)
Neurodevelopmental delay	5 (5%)
Anti-epileptic treatment	22 (22%)

Table II: Febrile seizures details

Variables	**N (%)**
Age of FS onset	
6-11 months	20 (20%)
12-17 months	26 (26%)
18-23 months	20 (20%)
24 or more months	34 (34%)

Fever etiology	
Upper respiratory tract infection	88 (88%)
Viral rash disease	5 (5%)
Acute gastroenteritis	4 (4%)
Lower respiratory tract infection	3 (3%)
Acute otitis media	9 (9%)
Urinary tract infection	1 (1%)
Body temperature before seizure	
Less than 39°C	46 (46%)
39°C or more	64 (64%)
Duration of fever before FS	
Less than 1 hour	45 (45%)
1 hour or more	55 (55%)
Type of FS	
Simple	73 (73%)
Complex	27 (27%)
Number of FS episodes	
1	42 (42%)
2	25 (25%)
3	15 (15%)
4 or more	18 (18%)
Characteristic of seizure	
Focal	4 (4%)
Generalized	96 (96%)
Type of seizure	
Tonic	46 (46%)
Tonic-clonic	35 (35%)
Atonic	14 (14%)
Clonic	5 (5%)
Duration of seizure	
Less than 15 minutes	88 (88%)
15 minutes or more	12 (12%)

Table III: Risk factors of recurrence and development of epilepsy

	FS recurrence	**P value**	**Development of epilepsy**	**P value**
Gender				
Male	23 (41.2%)	0.781	5 (9%)	0.548
Female	18 (41%)		3 (7%)	
Gestation age at birth				
Less than 37 weeks	8 (44.5%)	0.538	3 (17%)	0.095
37-42 weeks	32 (40%)		5 (6.3%)	
More than 42 weeks	1 (50%)		1 (50%)	
Birth weight				
Less than 2500 g	4 (40%)	0.879	1 (10%)	0.723
More than 2500 g	36 (40%)		7 (7.8%)	
Delivery route				
Cesarean section	18 (40%)	0.847	4 (9%)	0.648
Vaginal	22 (40%)		4 (7.4%)	
Consanguinity between parents	8 (40%)	0.861	2 (10%)	0.274

Family history of FS	23 (46%)	0.048	4 (8%)	0.522
Family history of epilepsy	13 (52%)	0.032	2 (8%)	0.030
Body temperature before seizure				
Less than 39°C	21 (45.7%)	0.030	6 (13.2%)	<0.001
39°C or more	23 (36%)		2 (3.2%)	
Duration of fever before FS				
Less than 1 hour	30 (66.8%)	<0.001	7 (15.6%)	<0.001
1 hour or more	11 (20%)		1 (1.9%)	
Age of FS onset				
Younger than 12 months	12 (60%)	<0.001	3 (15%)	0.006
12 months or older	28 (35%)		4 (5%)	
Type of FS				
Simple	22 (30.2%)	<0.001	2 (2.8%)	<0.001
Complex	17 (63%)		2 (7.7%)	
Characteristic of seizure				
Focal	2 (50%)	0.722	1 (25%)	0.099
Generalized	39 (40.7%)		7 (7.3%)	
Type of seizure				
Tonic	18 (39.2%)	0.052	2 (4.5%)	<0.001
Tonic-clonic	14 (40%)		2 (6%)	
Atonic	7 (50%)		2 (14.5%)	
Clonic	4 (80%)		4 (80%)	
Duration of seizure				
Less than 15 minutes	31 (35.3%)	<0.001	5 (5.7%)	<0.001
15 minutes or more	8 (66.7%)		4 (34%)	
Neurodevelopmental delay	4 (80%)	<0.001	3 (60%)	<0.001
Anti-epileptic treatment	18 (82%)	<0.001	7 (32%)	<0.001
EEG findings				
Normal	40 (45%)	<0.001	4 (4.5%)	<0.001
Abnormal	9 (90%)		8 (80%)	

DISCUSSION

This study was conducted to evaluate factors associated with development of epilepsy and recurrent seizures in children with febrile seizures. The results showed that neurodevelopmental delay and abnormal EEG were significant predictor of FS recurrence and epilepsy, respectively. In addition, a family history of FS contributes greatly to onset of FS. Our findings comply with previous studies.[5, 6]

In our study, 50% children had a history of FS in 1st and 2nd degree relatives among due to which 46% of these children had recurrent FS and 8% developed an epilepsy. In Gunes et al, 25% of the FS patients had a family history.[7]Kim et al also reported family history of FS (55%), epilepsy (6%) and neurodevelopmental delay (6%) as significant determinants of FS onset.[8]Premature birth has also been reported as major risk factor.[9]Family history of epilepsy in 2-9% children leads to development of epilepsy proceeding FS.[10] In current study, 18% were premature, 20% had familial relationship between parents, 5% had a neurodevelopmental delay, and 25% had family history of epilepsy.

Upper respiratory tract infection was the most common cause of fever in 88% patients. This is

different from majority of literature where acute gastroenteritis was the major cause but only 4% had AGE in our study. Age of patient and duration between fever and FS onset are also important factors to watch for. In this study, 45.7% patients had a low fever and FS occurred within 1 hour of developing fever. Husodo et al also reported that 20% patients had a seizure within the first hour and 58% after one hour.[11]

Most of children in our study had tonic (46%), generalized (88%), simple (73%) and short-lived (88%) seizures. These findings are similar to other studies.[12]The rate of single seizures 42% in our study and 33% had three or more recurrences which is significantly higher than 10% previously reported. The rate of recurrence was 58% in our study which is same as 28%-56% as reported before.[5, 13]Younger than 1-year (60%), complex seizures (63%), seizures within 1 hour of fever (66.8%), low fever before FS onset (45.7%) and family history (46%) were risk factors of FS recurrence. Kuruva et al reported a 40% recurrence in patients younger than 1 year and 46% in patients with duration between fever and FS as 1 hour.[14]

The development of epilepsy was observed in 7% patients which is compliant to 2-7% rate found in patients with FS.[15] Simple FS poses a significantly lower risk with only 2.8% developing epilepsy as compared to 7.7% with complex FS. Recent research also shows 1-4% risk of epilepsy in simple FS and 4-15% in complex FS patients.[16, 17]Epilepsy was significantly associated with FS onset at younger than 12 months of age ($p=0.006$), longer seizure duration ($p<0.001$), clonic seizures ($p<0.001$), neurodevelopmental delay ($p<0.001$), abnormal EEG ($p<0.001$), recurrent FS ($p<0.001$) and complex FS ($p<0.001$). Other studies agree with our results.[18]

CONCLUSION

Younger than 1-year, complex seizures, seizures within 1 hour of fever, low fever before FS onset and family history are significant risk factors of FS recurrence in children with febrile seizures. Development of epilepsy in such patients is significantly associated with FS onset at younger than 12 months of age, longer seizure duration, clonic seizures, neurodevelopmental delay, abnormal EEG, recurrent FSand complex FS.

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