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Risk Factors for Febrile Status Epilepticus: A Case-Control Study

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Abstract

Objective—To identify risk factors for developing a first febrile status epilepticus (FSE) among children with a first febrile seizure (FS).

Study design—Cases were children with a first FS that was FSE drawn from the Consequences of Prolonged Febrile Seizures in Childhood and Columbia cohorts. Controls were children with a

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first simple FS and separately, children with a first complex FS that was not FSE. Identical questionnaires were administered to family members of the 3 cohorts. Magnetic resonance imaging protocol and readings were consistent across cohorts, and seizure phenomenology was assessed by the same physicians. Risk factors were analyzed using logistic regression.

Results—Compared with children with simple FS, FSE was associated with younger age, lower temperature, longer duration (1-24 hours) of recognized temperature before FS, female sex, structural temporal lobe abnormalities, and first-degree family history of FS. Compared with children with other complex FS, FSE was associated with low temperature and longer duration (1-24 hours) of temperature recognition before FS. Risk factors for complex FS that was not FSE were similar in magnitude to those for FSE but only younger age was significant.

Conclusions—Among children with a first FS, FSE appears to be due to a combination of lower seizure threshold (younger age and lower temperatures) and impaired regulation of seizure duration. Clinicians evaluating FS should be aware of these factors as many episodes of FSE go unnoticed. Further work is needed to develop strategies to prevent FSE.

Febrile status epilepticus (FSE), a neurologic emergency, is associated with a marked increased risk for developing epilepsy in population-based studies[1] and with mesial temporal sclerosis and intractable temporal lobe epilepsy.[2] Understanding the risk factors for developing FSE among children who experience febrile seizures (FS) may lead to efforts to prevent FSE.

Although risk factors for FSE are largely unknown, risk factors for first FS are well-established. FS risk factors include prior neurodevelopmental abnormality,[3,4] increased number of febrile illnesses,[5] daycare attendance,[3] temperature greater than 39.4°C,[6,7] maternal smoking,[6,8] and a first-degree family history of FS.[3-6,8] Pre- or perinatal factors, such as low birth weight and preterm birth, are also risk factors for a first FS.[3,4,9-11]

Among children with a first FS, the risk for developing epilepsy is increased. Neurodevelopmental abnormality is the only risk factor that is both associated with developing a first FS[3,4] and with developing epilepsy after a first FS.[4,12-14] Other risk factors for epilepsy after a first FS are complex FS, particularly when they are prolonged or focal,[1,4,12,14] family history of unprovoked seizure,[1,4,12,13] number of episodes of FS,[13] and young age at first FS.[1]

Among children with FS, risk factors for FSE are less well described. Risk factors for FS also may be risk factors for FSE, and some risk factors for developing epilepsy after FS also may be associated with an increased risk for FSE because FSE is closely tied to later epilepsy. Identifying the risk factors for FSE may lead to better understanding and detection of FSE. We examined risk factors for FSE among children with a first FS.

Methods

We combined the Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) cohort of children with FSE and the Columbia University Febrile Seizure Study (Columbia Study) cohort children with FSE to form the case group.[15,16] Briefly, subjects with FSE were recruited from emergency departments of 5 sites for FEBSTAT. Subjects with first FS

in the Columbia Study were recruited from the Emergency Department of the New York Presbyterian Hospital; a proportion of these children were determined to have FSE. The protocols were similar in these studies, identical questionnaires were used, and magnetic resonance imaging (MRI) and phenomenology consensus were performed by the same individuals for both studies.[16] Human herpes virus-6 data were not considered because human herpes virus-6 was measured in the FEBSTAT cohort but not in the Columbia Study. Severe developmental delay was an exclusion criterion in the FEBSTAT cohort but not in the Columbia Study cohort; therefore, this factor was not included in our analysis. The institutional review boards at all sites approved procedures and all parents signed informed consent.

To examine risk factors for FSE, we performed case-control comparisons. Cases were children with FSE that was their first ever FS. Controls were children with a first simple FS from the Columbia Study cohort. To determine if FSE risk factors differed from those for other first complex FS, cases with a first complex FS that was not FSE were compared with controls with a first simple febrile seizure both from the Columbia cohort. Cases of FSE also were compared with other complex FS to elucidate the differences between these 2 groups. Case-control comparisons included children aged 6-60 months, based upon the Columbia Study inclusion criteria.

FS was defined as a seizure provoked by a temperature greater than 38.4°C (101.0°F) without a prior afebrile seizures or acute central nervous system infection or insult.[17] FSE was defined as a seizure lasting 30 minutes or longer without fully regaining consciousness during the interval.[18] Complex FS without FSE was a seizure lasting longer than 15 minutes but less than 30 minutes, or a focal FS, or repeated FS.

MRI was performed within 72 hours after the first FS or very shortly thereafter for cases and controls. Two neuroradiologists (J.B., S.C.) read the MRIs blinded to all clinical details except age.

Description of the FS was obtained through interview with family members and from abstracted medical record data. This information was used to assign FS type by consensus among three pediatric epileptologists (S.S., J.P., D.N.) who were blind to the child's MRI results.

The structured interview included questions about the child's illness, illness history, sociodemographics, gestational exposures, first-degree family history of FS, first-degree family history of epilepsy, and other risk factors. Age at first FS was categorized as <18 months or ≥18months. Temperature in the emergency department was categorized as <104.0°F or ≥104°F. The time that a fever was recognized before the seizure was categorized as <1 hour, 1-24 hours, or ≥24 hours. Daycare was examined as a surrogate for the opportunity to develop a febrile illness. Pregnancy associated factors included prematurity, and smoking or drinking alcoholic drinks during pregnancy.

Pre-existing structural abnormalities on MRI were examined regardless of location and separately in the temporal lobe including hippocampus.[19] Abnormalities included those

classified as suspect and definite. Abnormal T2 signal, which may represent acute abnormality, was not included as a pre-existing abnormality.

Statistical Analyses

We used χ^2 and Fisher exact tests and *t* tests for bivariate analysis, and logistic regression for ORs. Comparisons with FSE were adjusted for insurance, a surrogate for socioeconomic status, which differed between the FEBSTAT and Columbia cohorts.

Results

Among the children with first FS, 169 had FSE, 45 had other complex FS, and 102 had simple FS. Age at first FS was less than 18 months for 63.3% of FSE, 60.0% of complex FS, and 39.2% of simple FS ($P = .004$). There was no difference by sex. Baseline MRI readings were available for 95.2% of FSE, 86.7% of complex FS, and 94.1% of simple FS.

Median age at first FS was 15 months for FSE compared with 19 for simple FS ($P = .0003$) and to 16 for complex FS ($P = .45$). Mean temperature in the emergency department was 102.3°F for FSE compared with 103.6°F for simple FS ($P < .0001$) and to 103.1°F for complex FS ($P = .01$).

FSE vs Simple FS

Univariate analysis (Table I) revealed several statistically significant factors associated with FSE vs simple FS. Children with FSE were younger, had lower temperatures in the emergency department, and longer duration of recognized fever prior to FS. In addition, structural temporal lobe abnormalities, prematurity, female sex, and smoking during pregnancy were associated with an increased risk for FSE. First-degree family history of FS or of epilepsy was not associated with an increased risk of FSE vs simple FS.

In a multivariable model adjusting for insurance status, age, temperature, duration of recognized temperature before FS, female sex, structural temporal lobe abnormalities, and first-degree family history of FS were associated with FSE.

FSE vs Complex FS

In univariate analysis, a lower peak temperature, longer duration of recognized fever, and daycare were associated with an increased risk for FSE vs complex FS (Table II). In a multivariable model adjusting for insurance status, temperature and latency to temperature recognition before FS remained significantly associated with FSE. Age <18 months was no longer a risk factor for FSE.

Complex FS vs Simple FS

In univariate analysis (Table III), younger age was associated with an increased risk of complex FS that was not FSE. The OR for temporal lobe imaging abnormality was 5.1 but did not reach statistical significance. None of the other risk factors for FSE were associated with a statistically significant increased risk for other complex FS.

Discussion

Our study identified low temperature, short duration of recognized fever, female sex, and structural temporal lobe abnormalities as associated with FSE compared with first simple FS. These findings suggest that children prone to FSE have a lower seizure threshold manifest in particular by lower temperatures at their first FS and younger age compared with children with simple FS. The increased risk for FSE associated with lower temperature may both explain the propensity of these children to develop a first FS and their propensity to have a greatly increased risk for epilepsy (eg, Annegers et al).[1] Animal models of fever-induced seizures suggest a role of genetic factors that modify the occurrence and the consequence of FS.[20] This also is reflected in the familial tendency to experience febrile and afebrile seizures in patients with generalized epilepsy with FS plus.[21] We also found that structural temporal lobe abnormalities may interact with indicators of low seizure threshold to increase FSE risk. Others also have found young age to be associated with complex FS and with FSE compared with controls without FS.[22]

Daycare attendance, prematurity, and smoking during pregnancy were associated with FSE in univariate analysis only. In studies comparing FS cases with controls without FS, risk factors include daycare attendance, prematurity, and smoking during pregnancy.[22] Interestingly, pubescent rats exposed to nicotine during gestation show increased glial fibrillary acidic protein in the CA1 area of the hippocampus,[23] an area prone to injury in FSE.[19]

Only young age at FS was a risk factor for complex FS that was not FSE. Even though this is a marker of lower seizure threshold, low temperature and short latency for seizure recognition did not emerge as significant risk factors for this subtype of complex FS. In a post-hoc power analysis comparing risk factors in simple vs complex FS, there was 80% or greater power to detect ORs of 2.9 when the prevalence of the exposure is 50% and ORs of 4.4 when the prevalence of exposure is 7%. Thus, lack of significance may be due to small sample size, although the effect sizes were similar to those seen for FSE.

A major limitation of this analysis is that we could not examine developmental delays as risk factors for FSE. This was because enrollment criteria differed in the FEBSTAT and Columbia Study cohorts. FEBSTAT excluded children with severe developmental delay, but the Columbia Study cohort included all children with a first FS, and thus, the full range of developmental delay in FS. In prior work restricted to the Columbia Study cohort, we showed that developmental delay is associated with prolonged FS.[24]

Our study suggests that, compared with children with simple FS, children who experience FSE as their first FS have a lower seizure threshold in addition to an inability to extinguish a seizure once it has begun. This information may assist physicians in classifying FSE, as more than one-third of cases are unrecognized at presentation.[16] Further consideration of why a child would experience FSE rather than a short FS in the setting of a low fever and young age may lead to interventions to prevent prolonged FS.

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Appendix

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Glossary

Columbia Study	Columbia University Febrile Seizure Study
FEBSTAT	Consequences of Prolonged Febrile Seizures in Childhood
FSE	Febrile status epilepticus
FS	Febrile seizure
MRI	Magnetic resonance imaging

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Table I
Risk factors for developing FSE compared with simple FS

Factor	FSE N (%)	Simple FS N (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age				
<18 mo	107 (63.3%)	40 (39.2%)	2.7 (1.6, 4.4)	2.8 (1.47, 5.43)
≥18 mo	62 (36.7%)	62 (60.8%)	1.0 (Referent)	1.0 (Referent)
Daycare attendance				
Daycare	32 (19.5%)	15 (15.3%)	1.3 (0.7, 2.6)	
No daycare	132 (80.5%)	83 (84.7%)	1.0 (Referent)	
Drinking during pregnancy				
At least 1 drink in pregnancy	10 (6.3%)	1 (1.0%)	6.5 (0.8, 51.7)	
No drink in pregnancy	149 (93.7%)	97 (99.0%)	1.0 (Referent)	
First-degree family history of FS				
Positive family history	42 (25.0%)	20 (20.2%)	1.3 (0.7, 2.4)	3.0 (1.28, 6.88)
No family history	126 (75.0%)	79 (79.8%)	1.0 (Referent)	1.0 (Referent)
First-degree family history of epilepsy				
Positive family history	22 (13.1%)	8 (8.1%)	1.7 (0.7, 4.0)	
No family history Cpv	146 (86.9%)	91 (91.9%)	1.0 (Referent)	
Sex				
Female	87 (51.5%)	43 (42.2%)	1.5 (0.9, 2.4)	2.2 (1.14, 4.43)
Male	82 (48.5%)	59 (57.8%)	1.0 (Referent)	1.0 (Referent)
Premature birth				
≤ 37 wk	46 (29.1%)	15 (15.5%)	2.2 (1.2, 4.3)	1.8 (0.82, 3.90)
>37 wk	112 (70.9%)	82 (84.5%)	1.0 (Referent)	1.0 (Referent)
Smoking during pregnancy				
No	139 (82.2%)	94 (94.0%)	1.0 (Referent)	1.0 (Referent)
Yes	30 (17.8%)	6 (6.0%)	3.4 (1.4, 8.4)	2.4 (0.77, 7.77)
Any temporal lobe abnormality other than increased T2 signal				
Abnormal	21 (13.0%)	3 (3.1%)	4.6 (1.3,16.0)	4.6 (1.17,18.33)
No abnormality	140 (87.0%)	93 (96.9%)	1.0 (Referent)	1.0 (Referent)
Any structural abnormality on MRI				
Abnormal	60 (37.3%)	34 (35.4%)	1.1 (0.6, 1.8)	
No abnormality	101 (62.7%)	62 (64.6%)	1.0 (Referent)	
Temperature				
<104.0°F	136 (81.0%)	57 (55.9%)	3.4 (1.9, 5.8)	3.7 (1.80, 7.50)
≥104.0°F	32 (19.0%)	45 (44.1%)	1.0 (Referent)	1.0 (Referent)
Time temperature was recognized before seizure				
1-24 h	139 (82.2%)	53 (53.0%)	2.2 (1.2, 4.2)	2.4 (1.10, 5.33)
<1 h	28 (16.6%)	24 (24.0%)	1.0 (Referent)	1.0 (Referent)
>24 h	2 (1.2%)	23 (23.0%)	0.1 (0.0, 0.3)	0.1 (0.01,0.56)

Table II
Risk factors for developing FSE compared with complex FS

Factor	FSE N (%)	Complex FS N (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age				
<18 mo	107 (63.31%)	27 (60.00%)	1.15 (0.6,2.3)	
≥18 mo	62 (36.69%)	18 (40.00%)	1.0 (Referent)	
Daycare attendance				
Daycare	32 (19.51%)	3 (6.82%)	3.31 (1.0,11.4)	3.0 (0.7,13.4)
No daycare	132 (80.49%)	41 (93.18%)	1.0 (Referent)	1.0 (Referent)
Drinking during pregnancy				
At least 1 drink in pregnancy	10 (6.29%)	0 (0%)	NA	
No drink in pregnancy	149 (93.71%)	45 (100.00%)	1.0 (Referent)	
First-degree family history of FS				
Positive family history	42 (25.00%)	9 (20.00%)	1.33 (0.6,3.0)	
No family history	126 (75.00%)	36 (80.00%)	1.0 (Referent)	
First-degree family history of epilepsy				
Positive family history	22 (13.10%)	1 (2.22%)	6.63 (0.9,50.6)	
No family history Cpv	146 (86.90%)	44 (97.78%)	1.0 (Referent)	
Sex				
Female	87 (51.48%)	22 (48.89%)	1.11 (0.6,2.1)	
Male	82 (48.52%)	23 (51.11%)	1.0 (Referent)	
Premature birth				
≤ 37 wk	46 (29.11%)	8 (17.78%)	1.90 (0.8,4.4)	
>37 wk	112 (70.89%)	37 (82.22%)	1.0 (Referent)	
Smoking during pregnancy				
No	139 (82.25%)	38 (84.44%)	1.0 (Referent)	
Yes	30 (17.75%)	7 (15.56%)	1.17 (0.5,2.9)	
Any temporal lobe abnormality other than increased T2 signal				
Abnormal	21 (13.04%)	5 (12.82%)	1.02 (0.4, 2.9)	
No abnormality	140 (86.96%)	34 (87.18%)	1.0 (Referent)	
Any structural abnormality on MRI				
Abnormal	60 (37.27%)	16 (41.03%)	0.85 (0.4,1.7)	1.3 (0.5, 3.1)
No abnormality	101 (62.73%)	23 (58.97%)	1.0 (Referent)	1.0 (Referent)
Temperature				
<104.0°F	136 (80.95%)	27 (60.00%)	2.83 (1.4, 5.8)	3.6 (1.5, 8.5)
≥104.0°F	32 (19.05%)	18 (40.00%)	1.0 (Referent)	1.0 (Referent)
Time temperature was recognized before seizure				
1-24 h	139 (82.25%)	21 (46.67%)	3.07 (1.4, 6.9)	3.4 (1.4, 8.4)
<1 h	28 (16.57%)	13 (28.89%)	1.0 (Referent)	1.0 (Referent)
>24 h	2 (1.18%)	11 (24.44%)	0.08 (0.0, 0.4)	0.1 (0.0, 0.5)

Table III
Risk factors for developing complex FS compared with simple FS

Factor	Complex FS N (%)	Simple FS N (%)	Univariate OR (95% CI)
Age			
<18 mo	27 (60.0%)	40 (39.2%)	2.3 (1.1,4.8)
≥18 mo	18 (40.0%)	62 (60.8%)	1.0 (Referent)
Daycare attendance			
Daycare	3 (6.8%)	15 (15.3%)	0.4 (0.1,1.5)
No daycare	41 (93.2%)	83 (84.7%)	1.0 (Referent)
Drinking during pregnancy			
At least 1 drink in pregnancy	0 (0%)	1 (1.0%)	NA
No drink in pregnancy	45 (100.0%)	97 (99.0%)	1.0 (Referent)
First-degree family history of FS			
Positive family history	9 (20.0%)	20 (20.2%)	1.0 (0.4, 2.4)
No family history	36 (80.0%)	79 (79.8%)	1.0 (Referent)
First-degree family history of epilepsy			
Positive family history	1 (2.2%)	8 (8.1%)	0.3 (0.0, 2.1)
No family history	44 (97.8%)	91 (91.9%)	1.0 (Referent)
Sex			
Female	22 (48.9%)	43 (42.2%)	1.3 (0.6, 2.7)
Male	23 (51.1%)	59 (57.8%)	1.0 (Referent)
Premature birth			
≤ 37 wk	8 (17.8%)	15 (15.5%)	1.2 (0.5, 3.0)
>37 wk	37 (82.2%)	82 (84.5%)	1.0 (Referent)
Smoking during pregnancy			
No	38 (84.4%)	94 (94.0%)	1.0 (Referent)
Yes	7 (15.6%)	6 (6.0%)	2.9 (0.9, 9.1)
Any temporal lobe abnormality other than increased T2 signal			
Abnormal	2 (5.1%)	1 (1.0%)	5.1 (0.5, 58.3)
No abnormality	37 (94.9%)	95 (99.0%)	1.0 (Referent)
Any structural abnormality on MRI			
Abnormal	16 (41.0%)	34 (35.4%)	1.3 (0.6, 2.7)
No abnormality	23 (59.0%)	62 (64.6%)	1.0 (Referent)
Temperature			
<104.0°F	27 (60.0%)	57 (55.9%)	1.2 (0.6, 2.4)
≥ 104.0°F	18 (40.0%)	45 (44.1%)	1.0 (Referent)
Time temperature was recognized before seizure			
1-24 h	21 (46.7%)	53 (53.0%)	0.7 (0.3,1.7)
<1 h	13 (28.9%)	24 (24.0%)	1.0 (Referent)
>24 h	11 (24.4%)	23 (23.0%)	0.9 (0.3, 2.4)