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Epilepsy in children with a history of febrile seizures

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Purpose: Febrile seizure, the most common type of pediatric convulsive disorder, is a benign seizure syndrome distinct from epilepsy. However, as epilepsy is also common during childhood, we aimed to identify the prognostic factors that can predict epilepsy in children with febrile seizures.
Methods: The study comprised 249 children at the Korea University Ansan Hospital who presented with febrile seizures. The relationship between the subsequent occurrence of epilepsy and clinical factors including seizure and fever-related variables were analyzed by multivariate analysis.
Results: Twenty-five patients (10.0%) had additional afebrile seizures later and were diagnosed with epilepsy. The subsequent occurrence of epilepsy in patients with a history of febrile seizures was associated with a seizure frequency of more than 10 times during the first 2 years after seizure onset (P<0.001). Factors that were associated with subsequent occurrence of epilepsy were developmental delay (P<0.001), preterm birth (P=0.001), multiple seizures during a febrile seizure attack (P=0.005), and epileptiform discharges on electroencephalography (EEG) (P=0.008). Other factors such as the age at onset of first seizure, seizure duration, and family history of epilepsy were not associated with subsequent occurrence of epilepsy in this study.
Conclusion: Febrile seizures are common and mostly benign. However, careful observation is needed, particularly for prediction of subsequent epileptic episodes in patients with frequent febrile seizures with known risk factors, such as developmental delay, history of preterm birth, several attacks during a febrile episode, and epileptiform discharges on EEG.

Key words: Febrile seizure, Epilepsy, Child

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Introduction

Febrile seizures are defined as seizures which occur in childhood that are accompanied by a temperature of 38°C or higher without evidence of an intracranial infection or defined seizure cause. The International League Against Epilepsy defines a febrile seizure as "a seizure occurring in childhood after 1 month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures"[1]. Epilepsy is defined as the occurrence of at least 2 episodes of unprovoked seizures on 2 different days[2,3]. Febrile seizures are common and have a good prognosis, except for the risk of subsequent occurrence of epilepsy.

Association studies between febrile seizures and epilepsy have largely focused on the link between prolonged febrile seizures and the subsequent development of temporal lobe epilepsy, using epidemiological studies and investigations of the underlying mechanisms of epileptogenesis with animal models[4]. However, epilepsy may be considered to be febrile seizures when the first attack occurs in a state of systemic febrile illness. Also, a number of

patients who experience febrile seizures may develop epilepsy. In this study, we analyzed the demographic, clinical, and electroencephalographic data of children with febrile seizures to determine any prognostic factors that can predispose children with febrile seizures to epilepsy[5-8].

Materials and methods

1. Subjects

Study participants were children below 12 years old who had a diagnostic history of febrile seizures and presented at the Korea University Ansan Hospital between March 2005 and February 2007. Among 261 patients who visited hospital, we excluded 12 patients who were not revisited after emergency management. We retrospectively reviewed the medical records of 249 hospital patients whose first febrile seizures developed between 3 months and 5 years of age. The data obtained from these records included demographic variables, seizure semiology, family history, birth history, electroencephalography (EEG) findings, and brain imaging. We excluded patients who had evidence of a central nervous system infection, acute electrolyte imbalance, or afebrile seizures that had developed before the occurrence of febrile seizures. Of this population, patients with at least 5 years of follow-up history were evaluated for prognostic indicators.

Epilepsy was defined as the occurrence of at least 2 episodes of unprovoked seizures on 2 different days[2,3]. Seizure semiology, seizure number during the attack, and seizure duration were evaluated, along with clinical variables, such as peak fever temperature and focal neurologic deficits. EEG and brain imaging were performed when necessary. EEG was performed for 183 patients, while brain imaging was performed for 50 patients. Clear focal spikes, repetitive sharp waves, or generalized spikes and waves were classified as epileptiform discharges. The development of epilepsy was evaluated. We compared the likelihood of subsequent epilepsy between patients with simple and complex febrile seizures. We also attempted to assess the relative importance of each criterion that defined complex febrile seizures. Abnormalities in EEG and brain imaging were compared between patients with or without subsequent epilepsy.

2. Statistical analysis

Statistical analysis was performed using a *t* test for continuous variables, and a Pearson chi-square and Fisher exact test for dichotomous variables. Multivariate logistic regression was performed for the variables with a *P* value of less than 0.05 in the univariate analysis. Odds ratios and 95% confidence intervals were also calculated. The statistics package PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used.

Results

1. Patient demographics

In our study, 249 patients with a history of febrile seizures were analyzed. The age at onset of febrile seizures ranged between 3 months and 8 years (mean age, 21.8±13.8 months). Of the total patient population, there were 137 boys (55.0%) and 112 girls (45.0%). For the associated factor of temperature, 100 patients (40.2%) had a peak fever temperature of up to 39°C, while 149 patients (59.8%) had a peak fever temperature greater than 39°C. The mean number of seizures was 2.7±2.7, while the number of patients who experienced multiple seizures (≥2 seizures/episode) during 1 attack was 112 (45.0%). 17 children (6.8%) had a seizure duration below 30 seconds, 211 (84.7%) had a seizure duration of 30 seconds to 15 minutes, and 21 (8.4%) had a seizure duration of over 15 minutes. 16 children (6.4%) had focal seizures, which included unilateral clonic seizures, asymmetric tonic seizures, and head version. 17 children (6.8%) exhibited developmental delay, 10 (4.0%) had a preterm birth, 72 (28.9%) had a family history of febrile seizures, while 10 (4.0%) had a family history of epilepsy. EEG was performed on 183 patients. Of them, epileptiform discharges were seen in 52 (28.4%). Of these 52 patients, focal slowing was seen in 23 patients (44.2%), spike and sharp waves in 27 patients (51.9%), and generalized spikes in 2 patients (3.8%). Brain imaging studies were performed on 50 patients; abnormal findings were seen in 9 of them (18.0%).

2. Comparison of febrile seizures and subsequent epilepsy

Among the 249 children in this study, 25 (10.0%) had recurrent, unprovoked seizures and were diagnosed with epilepsy 2–119 months later. Clinical characteristics of the febrile seizures-only group and the subsequent epilepsy group are shown in Table 1. The age at onset of febrile seizure was 21.3±12.5 months in the febrile seizures-only group and 26.3±22.9 months in the subsequent epilepsy group, which was not significantly different (P=0.172). There was no significant difference in gender distribution between the 2 groups (P=0.757). However, the number of seizures during an individual seizure attack was significantly different between the 2 groups. The total number of seizures during the first 2 years after a febrile seizure attack was 2.2±2.2 in the febrile seizures-only group, and 6.9±3.1 in the subsequent epilepsy group, which was significantly different (P<0.001). The subsequent epilepsy group exhibited multiple repetitive seizure attacks. The number of seizures during 1 episode in the febrile seizures-only group was 42.0%, and 72.0% for the subsequent epilepsy group (P=0.005). Seizure duration was divided into 3 groups: less than 30 seconds, 30 seconds to 15 minutes, and ≥15 minutes. There were no significant differences in seizure durations between the febrile seizures-only group and the subsequent epilepsy group. Peak fever was divided into 2 groups, either the low fever group

(<39°C) or the high fever group (≥39°C). Peak fever also did not significantly differ between the febrile seizures-only group and the subsequent epilepsy group.

Seizure semiology was assessed, although this assessment was limited because this measure was based on parent report for most patients. In the febrile seizures-only group, 15 patients (6.7%) had focal seizures, such as unilateral clonic seizures (4 patients), asymmetric tonic seizures (3 patients) and atonic seizures (8 patients). 1 patient (4.0%) exhibited head version in the epilepsy group (*P*=1.000). In the febrile seizures-only group, 61 patients (27.2%) had a family history of febrile seizures, while 11 patients (44.0%) had a family history of febrile seizures in the subsequent epilepsy group (*P*=0.102). In the febrile seizures-only group, 5 had a family history of epilepsy, while 2 patients had a family history of epilepsy in the subsequent epilepsy group (*P*=0.162).

Developmental delay was seen in 8 patients (3.6%) in the febrile seizures-only group, compared to 9 patients (36.0%) in the subsequent epilepsy group (*P*<0.001). Five patients had a history of preterm birth in the febrile seizures-only and in the subsequent epilepsy group; however, this represented 2.2% of the febrile seizures-only group and 20.0% of the subsequent epilepsy group (*P*=0.001).

EEG epileptiform discharges were seen in 39 patients (24.7%) in the febrile seizures-only group, and 13 patients (52.0%) in the subsequent epilepsy group (*P*=0.008). Brain MRI abnormalities were identified in 4 patients (14.8%) in the febrile seizures-only group and 5 patients (21.7%) in the subsequent epilepsy group (*P*=0.715).

Table 1. Prognostic factors for subsequent epilepsy

Clinical factor	Total (n=249)	Febrile seizure only (n=224)	Subsequent epilepsy (n=25)	*P* value†
Age at onset of febrile seizure (mo)				0.172
Mean±SD	21.8±13.8	21.3±12.5	26.3±22.9	
Range	3–95	3–95	5–93	
Gender				0.757
Male	137 (55.0)	124 (90.5)	13 (52.0)	
Female	112 (45.0)	100 (90.1)	12 (48.0)	
No. of total seizures‡	2.7±2.7	2.2±2.2	6.9±3.1	0.000*
Multiple seizures (≥2/episode) in one attack	112 (45.0)	94 (42.0)	18 (72.0)	0.005*
Duration				0.064
<30 sec	17 (6.8)	15 (6.7)	2 (8.0)	
30 sec–15 min	211 (84.7)	193 (86.2)	18 (72.0)	
≥15 min	21 (8.4)	16 (7.1)	5 (20.0)	
Peak temperature				0.079
<39°C	100 (40.2)	86 (38.4)	14 (56.0)	
≥39°C	149 (59.8)	138 (61.6)	11 (44.0)	
Focal seizure	16 (6.4)	15 (6.7)	1 (4.0)	1.000
Unilateral clonic	4 (26.7)	4 (26.7)	-	
Asymmetric tonic	3 (20.0)	3 (20.0)	-	
Hypokinetic	8 (53.3)	8 (53.3)	-	
Versive	1 (4.0)	-	1 (4.0)	
Developmental delay	17 (6.8)	8 (3.6)	9 (36.0)	0.000*
Preterm birth	10 (4.0)	5 (2.2)	5 (20.0)	0.001*
Family history of febrile seizure	72 (28.9)	61 (27.2)	11 (44.0)	0.102
Family history of epilepsy	10 (4.0)	5 (2.2)	2 (8.0)	0.162
Abnormal EEG	52/183 (28.4)	39/158 (24.7)	13/25 (52.0)	0.008*
Focal slowing	23/52 (44.2)	17/39 (43.6)	6/13 (46.1)	
Spike/sharp wave	27/52 (51.9)	21/39 (53.8)	6/13 (46.1)	
Generalized	2/52 (3.8)	1/39 (2.6)	1/13 (7.7)	
Abnormal brain MRI	9/50 (18.0)	4/27 (14.8)	5/23 (21.7)	0.715

Values are presented as mean±standard deviation (SD) or number (%) unless otherwise indicated.
EEG, electroencephalography; MRI, magnetic resonance imaging.
*$P<0.05$, statistical significance. †*P* values were calculated using the Pearson chi-square or Fisher exact test for categorical variables. ‡During first 2 years after febrile seizure onset.

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In this study, 25 patients (10.0%) were diagnosed as having epilepsy. Variables that significantly differed between the groups were the number of seizures within the first 2 years after febrile seizure onset (P=0.000), developmental delay (P=0.000), history of preterm birth (P=0.001), multiple seizures per febrile episode (P=0.005), and abnormal EEG findings (P=0.008). Meanwhile, variables such as gender distribution, seizure duration, peak temperature, focality of seizure semiology, family history of febrile seizure, and family history of epilepsy, were not significant prognostic factors for a subsequent epilepsy diagnosis.

In the multivariate analysis, more than 4 times seizures within the first 2 years after febrile seizure onset (odds ratio, 28.5), developmental delay (odds ratio, 8.5), history of preterm birth (odds ratio, 14.3) multiple seizures per febrile seizure episode (odds ratio, 3.1) and abnormal EEG findings (odds ratio, 4.4) were risk factors for epilepsy.

3. Classification and treatment of subsequent epilepsy

The subsequent epilepsy group consisted of 9 cases (38.0%) of idiopathic generalized epilepsy, 7 cases (28.0%) of symptomatic focal epilepsy, 4 cases (16.0%) of cryptogenic focal epilepsy, and 3 cases (12.0%) of febrile seizure plus. Two patients (8.0 %) were undetermined (Table 2)

Discussion

The present study sought to determine the prognostic factors in children with febrile seizures for risk of subsequent epilepsy. Our results demonstrate that the frequency of febrile seizures during the first 2 years after initial seizure onset was associated with subsequent occurrence of epilepsy. Other factors predictive of a subsequent occurrence of epilepsy were developmental delay, history of preterm birth, several seizure attacks during one febrile illness, and EEG epileptiform discharges.

Febrile seizures are the most common form of childhood seizure. Over the past 25 years, as more information on febrile seizures has accumulated, the prognosis for febrile seizures is generally found to be good. However, the first seizure in patients with epilepsy can be accompanied by fever. The overall risk of epilepsy following febrile seizures is 2%–5%, which is double the risk for the general child population[5,7,9]. Approximately 15%–20% of children who develop epilepsy have previously had febrile seizures[10-12].

Table 2. Classification of later epilepsy

Classification	No. (%)
Cryptogenic focal epilepsy	4 (16.0)
Symptomatic focal epilepsy	7 (28.0)
Idiopathic generalized epilepsy	9 (36.0)
Febrile seizure plus	3 (12.0)
Undetermined	2 (8.0)
Total	25 (100)

Our study revealed that the incidence of subsequent epilepsy after febrile seizures was 10% in individuals that had febrile seizures. This is similar to the results in a prospective cohort study by Neligan et al.[13], which demonstrated that the risk of developing epilepsy following febrile seizures was 2%–10%.

Previous studies have shown that the risk factors for unprovoked seizures after febrile seizures include the onset of febrile seizures at an early age, complex febrile seizures, neurodevelopmental abnormalities, abnormal EEG, and a family history of epilepsy[5-8,14,15]. The risk factor for epilepsy in patients with no previous risk factors is only 0.9%. With 2 or more risk factors, that incidence increases to 2%[5,16]. If febrile seizures are prolonged, approximately 9.4% of children may develop epilepsy[7,17]. However, all children with a history of febrile seizures do not have the same risk for developing subsequent epilepsy.

Generally, childhood febrile seizures are benign and self-limiting. In most cases, it is recommended that health care providers should have reduced anxiety through decreasing uncertainty[18]. However, complex febrile seizures, particularly prolonged febrile seizures or febrile status epilepticus (defined as seizures lasting more than 30 minutes), have been associated with subsequent limbic epilepsy in both prospective and retrospective clinical studies[19]. In particular, prolonged or focal febrile seizures have been associated with a significantly increased risk for temporal lobe epilepsy[20,21].

In this study, the prognostic factors associated with later epilepsy included total relapse number of seizures, developmental delay, preterm birth, multiple seizures per febrile seizure attack, and abnormal EEG findings. However, gender, seizure duration, peak temperature, focal seizures, family history of febrile seizures, and family history of epilepsy were not associated with subsequent epilepsy.

Different results were reported by Kanemura et al.[22], such that fever duration increased the risk of unprovoked seizures. However, most studies differ from ours in that fever duration and peak temperature had no relationship with subsequent epilepsy[14]. Most data demonstrate that persistent febrile seizures were related to hippocampal damage, which developed into temporal lobe epilepsy [23,24]. However, in this study, fever and seizure duration were not related to a later presentation of recurrent unprovoked seizures. Brief, recurrent and frequent febrile seizures during the first 2 years after seizure onset were related to later epilepsy in this study, which differs from previous studies. Most of later diagnoses of epilepsy were not temporal lobe epilepsy. Moreover, patients diagnosed with symptomatic frontal epilepsy with cortical dysplasia during adolescence only presented with recurrent, febrile, and generalized tonic-clonic seizures, without definitive focal symptoms during childhood. Therefore, we hypothesize that fever in those patients

may be a provocative factor for a first presentation of seizure in patients with epileptic potential.

Focal semiology of febrile seizures increases the risk for subsequent epilepsy[15,25]. Ictal motor manifestations, such as version, clonic and tonic activity, unilateral epileptic spasms, dystonic posturing and unilateral automatisms, automatisms with preserved responsiveness, ictal spitting and vomiting, unilateral eye blinking, ictal nystagmus, and akinesia, have lateralizing value. Ictal language manifestations and postictal features, such as Todd's paralysis, postictal aphasia, postictal nose wiping, postictal memory dysfunction, as well as peri-ictal water drinking, peri-ictal headache, and ipsilateral tongue biting, are semiological lateralizing signs[26]. In this study, unilateral clonic seizures, asymmetric tonic seizures, or atonic seizures were not related to later epilepsy, while patients with head version were later diagnosed with epilepsy.

For seizure semiology, this study was limited because it relied on parent recall. Parents with anxiety could not recall the exact description of focal signs and seizure shape[27]. Therefore, there should be allowances made for any discrepancies regarding their observations of video EEG monitoring for seizure semiology. This may be one of the reasons why the number of patients who showed obvious focal signs was relatively small, and why this was not a significant association factor for later epilepsy.

The role of EEG in the work-up of febrile seizures is controversial. However, recent studies show the localizations of EEG paroxysmal discharges, such as spikes, sharp waves, or spike-wave complexes, are predictors for subsequent epilepsy[28]. In particular, frontal paroxysmal EEG abnormalities are related to subsequent diagnoses of epilepsy. In this study, abnormal EEG findings were seen in 39 patients (24.7%) in the febrile seizures-only group and 13 patients (52.0%) in the subsequent epilepsy group. However, not all the patients who experienced febrile seizures had EEG. Abnormal EEG findings were significant in our data set. Therefore, serial EEG in patients with localized paroxysmal discharges during the first EEG should be performed, even though it may not contribute to treatment.

In conclusion, prognostic factors, such as total relapse number of seizures, developmental delay, preterm birth, multiple seizures per febrile seizure, and abnormal EEG findings, can assist with the early recognition of increased risk for developing epilepsy after febrile seizures. Prospective studies are recommended, with particular attention to seizure semiology, peak fever temperature, fever onset, and family history of epilepsy.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 1993;34:592-6.
2. Camfield PR, Camfield CS, Dooley JM, Tibbles JA, Fung T, Garner B. Epilepsy after a first unprovoked seizure in childhood. Neurology 1985;35:1657-60.
3. Shinnar S, Berg AT, O'Dell C, Newstein D, Moshe SL, Hauser WA. Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure. Ann Neurol 2000;48:140-7.
4. Dubé CM, Brewster AL, Baram TZ. Febrile seizures: mechanisms and relationship to epilepsy. Brain Dev 2009;31:366-71.
5. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med 1987;316:493-8.
6. Berg AT, Shinnar S. Unprovoked seizures in children with febrile seizures: short-term outcome. Neurology 1996;47:562-8.
7. Verity CM, Golding J. Risk of epilepsy after febrile convulsions: a national cohort study. BMJ 1991;303:1373-6.
8. Sapir D, Leitner Y, Harel S, Kramer U. Unprovoked seizures after complex febrile convulsions. Brain Dev 2000;22:484-6.
9. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med 1976;295:1029-33.
10. Berg AT, Shinnar S, Levy SR, Testa FM. Childhood-onset epilepsy with and without preceding febrile seizures. Neurology 1999;53:1742-8.
11. Camfield P, Camfield C, Gordon K, Dooley J. What types of epilepsy are preceded by febrile seizures? A population-based study of children. Dev Med Child Neurol 1994;36:887-92.
12. Hamati-Haddad A, Abou-Khalil B. Epilepsy diagnosis and localization in patients with antecedent childhood febrile convulsions. Neurology 1998;50:917-22.
13. Neligan A, Bell GS, Giavasi C, Johnson AL, Goodridge DM, Shorvon SD, et al. Long-term risk of developing epilepsy after febrile seizures: a prospective cohort study. Neurology 2012;78:1166-70.
14. Hwang G, Kang HS, Park SY, Han KH, Kim SH. Predictors of unprovoked seizure after febrile seizure: short-term outcomes. Brain Dev 2015;37:315-21.
15. Pavlidou E, Panteliadis C. Prognostic factors for subsequent epilepsy in children with febrile seizures. Epilepsia 2013;54:2101-7.
16. Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. Pediatrics 1978;61:720-7.
17. Vestergaard M, Pedersen CB, Sidenius P, Olsen J, Christensen J. The long-term risk of epilepsy after febrile seizures in susceptible subgroups. Am J Epidemiol 2007;165:911-8.
18. Ju HO, McElmurry BJ, Park CG, McCreary L, Kim M, Kim EJ. Anxiety and uncertainty in Korean mothers of children with febrile convulsion: cross-sectional survey. J Clin Nurs 2011;20:1490-7.
19. Loddenkemper T. Febrile status epilepticus: time is of the essence. Epilepsy Curr 2014;14:345-7.
20. Patterson KP, Baram TZ, Shinnar S. Origins of temporal lobe epilepsy: febrile seizures and febrile status epilepticus. Neurotherapeutics 2014;11:242-50.
21. Nishiyama M, Nagase H, Tanaka T, Fujita K, Maruyama A, Toyoshima D, et al. Demographics and outcomes of patients with pediatric febrile convulsive status epilepticus. Pediatr Neurol 2015;52:499-503.
22. Kanemura H, Sano F, Mizorogi S, Aoyagi K, Sugita K, Aihara M. Duration of recognized fever in febrile seizure predicts later de-

velopment of epilepsy. Pediatr Int 2012;54:520-3.
23. Nordli DR Jr, Moshé SL, Shinnar S, Hesdorffer DC, Sogawa Y, Pellock JM, et al. Acute EEG findings in children with febrile status epilepticus: results of the FEBSTAT study. Neurology 2012;79:2180-6.
24. Scott RC, King MD, Gadian DG, Neville BG, Connelly A. Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study. Brain 2003;126(Pt 11):2551-7.
25. Rocca WA, Sharbrough FW, Hauser WA, Annegers JF, Schoenberg BS. Risk factors for complex partial seizures: a population-based case-control study. Ann Neurol 1987;21:22-31.
26. Blume WT, Luders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel J Jr. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. Epilepsia 2001;42:1212-8.
27. van Stuijvenberg M, de Vos S, Tjiang GC, Steyerberg EW, Derksen-Lubsen G, Moll HA. Parents' fear regarding fever and febrile seizures. Acta Paediatr 1999;88:618-22.
28. Kanemura H, Mizorogi S, Aoyagi K, Sugita K, Aihara M. EEG characteristics predict subsequent epilepsy in children with febrile seizure. Brain Dev 2012;34:302-7.