6세 이상 소아에서 발열을 동반한 첫 경련의 예후

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Prognosis in Late-Onset Febrile Seizure

Purpose: There is a paucity of evidence about prognosis after a first febrile seizure in older children. We investigated the prognosis and potential risk factors associated with subsequent unprovoked seizures in children who had experienced a first febrile seizure over 6 years of age, which we termed as late-onset febrile seizure.

Methods: We included all patients six years or older who presented to the emergency department with a febrile seizure between 2009 and 2015. Clinical data was collected by chart review and parents were contacted for information on seizure progress. We used the Cox proportional-hazards model and Kaplan-Meier analysis for evaluating the risk factors for subsequent unprovoked seizures.

Results: Of 247 patients, we excluded 168 children who had a history of epilepsy, unprovoked, or febrile seizure and who were followed-up for period less than six months. Overall, 79 patients were classified as having had a first late-onset febrile seizure. During follow-up of 34.9 ± 25.7 (mean $\pm$ SD) months, unprovoked seizure recurred in 7 of 79 patients (9%). The cumulative probability of seizure recurrence was 4% at 6 months, 6% at 1 year and 9% at 2 years. Clinical variables predictive of subsequent unprovoked seizures were not proved.

Conclusion: This is the first multicenter study focusing on prognosis after a late-onset febrile seizure in children six years or older. The percentage of subsequent unprovoked seizure in patients with late-onset febrile seizure was 9% at 2 years of follow-up. Prospective follow-up study with longer duration is warranted.

Key Words: Febrile seizure, Seizure, Epilepsy, Child

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Introduction

Febrile seizures is a common disorder among younger children mainly from 6 months to 5 years of age and the incidence in the general pediatric population ranges between 2 to 5%¹⁻⁴. Unprovoked seizures subsequently develop in 2 to 7% of them^{1,2,5}. There are a few literatures comparing outcome between younger and older children. Verrotti et al. reported that children with febrile seizures after five years of age may have a 2–3-fold higher risk of subsequent unprovoked seizures compared to children with febrile seizures under the age of five years⁶. Kim SH et al. reported that when the first seizure with fever occurred after 6 years of age this group was at significant risk of subsequent afebrile seizure⁷.

However, there is limited data available focusing on the prognosis of late-onset febrile seizures with smaller patient population in older ages. Hence, we evaluated the prognosis and risk factors for subsequent unprovoked seizures in children who had experienced a first febrile seizure over 6 years of age, which we termed 'late-onset febrile seizure'.

Materials and Methods

We included all patients between 6 and 19 years of age who presented to the emergency department at the Korea University Guro, Anam, and Ansan Hospital with a febrile seizure from January 2009 to December 2015. Patients with acute encephalopathy, lasting longer than 24 hours, were assumed as not being in a postictal state, and were not eligible. As shown in Fig. 1, of 247 patients who were eligible, we excluded 140 patients with a history of epilepsy, unprovoked, or febrile seizure before the age of six years. Patients who were followed-up for less than six months and whose parents did not respond when we attempted to contact them, were excluded (28 patients). Overall, the study sample consisted of 79 patients who had a late-onset febrile seizure.

1. Definitions

We defined a first febrile seizure that occurred at age six years or older that met the aforementioned inclusion and exclusion criteria, as a late-onset febrile seizure. Fever was defined as body temperature higher than 38°C. The criteria for diagnosing a febrile seizure as complex are the following: focal seizure,

multiple seizure episodes within the same febrile illness, or seizure lasting more than 15 minutes⁸⁾. Status epilepticus was defined as seizures lasting more than 30 minutes or a series of epileptic seizures during which consciousness is not regained between episodes.

2. Data collection

We retrospectively reviewed patients' information based on medical records. For patients who had been followed-up for less than six months, we attempted to contact their parents by phone to inquire seizure outcome including the presence of recurrent seizure, seizure manifestation and medical history since the first febrile seizure. Viral studies and electroencephalography (EEG) were performed in patients who had a late-onset febrile seizure. Viral studies of nasopharyngeal aspirates were performed using polymerase chain reaction including fourteen viruses (influenza A, influenza B, respiratory syncytial virus A, B, parainfluenza virus 1,2,3,4, coronavirus, enterovirus, rhinovirus, adenovirus, bocavirus, metapneumovirus). EEG was tested through waking and sleep phase with 18 channels. Development was assessed with the Bayley scale or Korean Wechsler Preschool and Primary Scale of Intelligence when a child had delayed milestones or abnormal results of the Korean Developmental Screening Test.

3. Statistical analysis

We used the Kaplan–Meier method for displaying the time-based probability of recurrence of an unprovoked seizure. The prognostic factors were analyzed using the Cox proportional hazards model with a 95% confidence interval (SPSS version

Fig. 1. Patient inclusion and exclusion.

Table 1. Baseline Characteristics of Patients with the First Febrile Seizure at Six Years or Older (n=79)

Variable	Value
Age (years)	8.1±2.5
Temperature (°C)	38.8±0.6
Duration of recognized fever, hour	15.4±33.0
Male/Female	49 (62.0)/30 (38.0)
Complex seizure	25 (32)
Focal seizure	20 (25)
Seizure duration, minute	7.2±12.8
≥ 15 minutes	8 (10.1)
≥ 30 minutes	7 (8.9)
Multiple seizure episodes	6 (8)
Family history of febrile seizure/epilepsy	16 (20)/0
Developmental delay	8 (10)
Abnormal EEG / MRI	40 (51)/5 (6)
Influenza infection	29 (37)
Admission to the intensive care unit	2 (3)

Data are mean±standard deviation or number of patients (%). EEG, electroencephalography; MRI, magnetic resonance imaging.

22.0, IMB SPSS Inc., Armonk, NY). The prognostic factors included the duration of recognized fever, type of febrile seizure, the presence of more than two complex seizure features, developmental delay, family history of febrile seizures, abnormal EEG and influenza infection. Statistical significance was set at $P < 0.05$. Numerical data were described by mean $\pm$ standard deviation (SD) and categorical data by percentage.

4. Ethical Approval

This study was approved by the Institutional Review Board at Korea University College of Medicine (KUGH16329-002).

Results

1. Patient characteristics

The median onset age of first febrile seizure was 7.6 ± 2.5 years; there were 49 boys and 30 girls (Table 1).

2. Seizure characteristics

Fifty-four patients (68%) had a simple and 25 (32%) had a

complex febrile seizure. Among patients with complex seizures, 20 (25%) had a focal type of seizure. The median duration of the seizure was 3.0 ± 12.8 minutes and 8 patients had seizures that lasted longer than 15 minutes. Six patients (8%) had multiple episodes during the same febrile illness (Table 1).

3. Medical history and neurological findings

Of the 79 patients with late-onset febrile seizure, no patient had a family history of epilepsy, while 16 (20%) had a family history of febrile seizures. Eight patients had a history of developmental delay (10%): 6 had language delay and 2 motor delay (Table 1).

4. Diagnostic results

Half of the patients had electroencephalographic abnormalities ($n=40/79$, 51%): twenty-five patients had focal epileptiform discharges, 2 displayed generalized spike-and-wave discharges and 13 displayed diffuse or focal slowing. There were abnormalities on the brain magnetic resonance imaging of 5 (6%) patients: these were 1 periventricular leukomalacia, 1 diffuse brain atrophy, 1 callosal dysgenesis with pericallosal

Table 2. Univariate Associations between Variables and the Risk of Unprovoked Seizures

Variable	N	Unprovoked seizure, n (%)	Hazard ratio (95% CI)	P-value
Temperature				
≤ 39°C	60	6 (10)	1.62 (0.19-13.56)	0.66
> 39°C	19	1 (5)	1	
Duration of recognized fever				
≤ 24 hour	27	0 (0)	1	
> 24 hour	52	7 (14)	36.68 (0.04-34553.28)	0.30
Type of febrile seizure				
Simple	54	4 (7)	1	
Complex	25	3 (12)	1.94 (0.42-8.94)	0.40
Focal seizure	20	3 (15)	2.17 (0.48-9.89)	0.32
Multiple episodes	6	1 (17)	1.39 (0.16-11.80)	0.76
Number of complex features				
< 2	72	5 (7)	1	
≥ 2	7	2 (29)	4.740 (0.87-25.91)	0.07
Developmental delay				
Yes	8	1 (13)	2.11 (0.24-18.37)	0.50
No	71	6 (9)	1	
Family history of febrile seizures				
Yes	16	1 (6)	1	
No	63	6 (10)	1.89 (0.23-15.75)	0.56
Abnormal EEG				
Yes	40	4 (57)	2.33 (0.43-12.73)	0.33
No	39	3 (43)	1	
Influenza infection				
Yes	29	1 (3)	1	
No	50	6 (12)	3.62 (0.43-30.12)	0.24

Derived from the proportional-hazard model.
EEG, electroencephalography.

lipoma, 1 suspicious gyral thickening in the right frontal gyrus, and 1 possible hippocampal sclerosis (Table 1).

5. Associated viral infection

Influenza infection was diagnosed in 29 patients (37%) through polymerase chain reaction using nasopharyngeal aspirates. There were 18 instances of influenza A infection and 11 of influenza B infection. Other minor viral pathogens were 5 instances of rhinovirus, 4 of adenovirus, 3 of enterovirus and 1 of metapneumovirus (Table 1). CSF examination was performed in 16 of 79 patients who had no symptom of encephalitis and test for CNS infection was negative.

Follow-up period (yr)	0.5	1	2.0	3.0	4.0	5.0
Follow-up number of patients	79	74	60	42	29	21
% Seizure recurrence	4	6	9	9	9	9
Cumulative number of unprovoked seizure	3	5	7	7	7	7

Fig. 2. Kaplan-Meier curves for the risk of a subsequent unprovoked seizure after a late-onset febrile seizure.

6. Recurrence of unprovoked seizure

Of 79 the patients, 7 children (9%) had unprovoked seizures after 1.1 to 21.7 months of follow-up (34.9 ± 25.7 , months) (Fig. 1). As seen in Fig. 2, the cumulative risk of subsequent unprovoked seizures was calculated using the Kaplan-Meier method. The cumulative probability of seizure recurrence was 4% at 6 months, 6% at 1 year and 9% at 2 years.

7. Risk factors for subsequent unprovoked seizure

We analyzed risk factors for subsequent unprovoked seizures in patients with late-onset febrile seizure. As shown by the proportional-hazard model, no variable showed a statistically significant association with subsequent unprovoked seizures (Table 2). Although not significant, the duration of recognized fever lasting longer than 24 hours had a 36-fold higher risk (7 of 52 patients, $P=0.30$) and the presence of more than two complex seizure features had a 5-fold higher risk for subsequent seizures (2 of 7 patients, $P=0.07$). In addition, 1 of 29 (3%) patients with an influenza infection had a subsequent unprovoked seizure, contrary to 6 of 50 (12%) patients without an influenza infection ($P=0.24$). Detailed clinical features of seven patients who experienced subsequent unprovoked seizures were described on Table 3.

Discussion

As there is limited data about late-onset febrile seizures, we investigated the recurrence rate and potential risk factors for subsequent unprovoked seizures in children six years or older who had a first late-onset febrile seizure. Our study revealed that an unprovoked seizure recurred in seven of 79 patients (9%) following a first late-onset febrile seizure. We also reviewed previous studies regarding the prognosis of either first

Table 3. Clinical Features of Seven Patients who Experienced Subsequent Unprovoked Seizures

No.	Age at first febrile seizure (years)	Type of seizure	Number of episodes	Developmental delay	EEG finding	MRI finding	Follow-up duration (months)	Latency to the subsequent seizure (years)
1	7	GTCs	1	no	Focal slowing on left occipital area and frequent sharp waves on left centro-temporal area	Normal	6.3	0.3
2	6	GT	1	no	Occasional high voltage spike and wave complexes on left frontal area	Normal	8.9	0.7
3	6	Atonic, focal motor	2	yes	Frequent sharp waves on right occipital area	NA	9.4	0.3
4	10	Atonic	1	no	High voltage spike and waves on left parieto-occipital area	Normal	22.1	0.7
5	15	Focal motor	1	no	Normal	Normal	30.7	0.1
6	6	GTCs	1	no	Normal	Normal	47.7	1.8
7	9	GT	1	no	Normal	Normal	90.1	1.8

None of above patients were diagnosed with epilepsy syndromes.

EEG, electroencephalography; MRI, magnetic resonance imaging; GTCs, Generalized tonic-clonic seizure; GT, Generalized tonic seizure; NA, not available.

Table 4. Available Outcome Data among Previous Reports for Patients who had a First Febrile Seizure in Older Ages

Authors (published year)	Onset age of first febrile seizure, years	Total number of patients	Subsequent unprovoked seizures, Patient No. (%)
Webb et al. ¹⁶⁾ (1999)	≥ 5	12	0
Verrotti A et al. ¹²⁾ (2000)	≥ 5	20	4 (20)
Kim SH et al. ¹⁴⁾ (2010)	≥ 6	15	2 (13)
Baek JH et al. (Present study)	≥ 6	79	7 (9)

or recurrent febrile seizures in older ages and extracted the available data about late-onset febrile seizures (Table 4)^{6,9-13)}. Summarizing the available prognostic data, the percentage of subsequent unprovoked seizures in patients older than 5 years was 13% (4 of 32)^{6,10)} and in patients older than 6 years was 9% (9 of 94) including our results¹²⁾.

In younger patients, the predicting factors for subsequent unprovoked seizures after the first febrile seizure have been reported as family history of epilepsy, neurodevelopmental abnormalities, complex features of febrile seizure^{1,13-16)}, the age at the time of the first febrile seizure¹⁷⁾, and status epilepticus at the first febrile seizure^{7,16)}. We found, though, no significant variables predictive of subsequent unprovoked seizures in older ages. Other smaller studies also failed to find the risk factors in older patients^{11,12)}.

Several variables with a relatively high hazard ratio should be discussed in our study. Duration of recognized fever lasting longer than 24 hours before seizure onset showed a high hazard ratio (37 times) in our study, which is not significant. For younger children, no association between the duration of precedent fever and a recurrence rate of unprovoked seizures has been found^{9,14,17)}. Our study also showed a high hazard ratio (5 times) for the presence of more than two complex features; focal seizure (2.2 times) and multiple episodes (1.4 times) (Table 2). On literatures, the recurrence rate of unprovoked seizure after a first febrile seizure has been reported as 4–27% for complex febrile seizures^{9,14,15,17,18)} and up to 49% for those with all three features of complex febrile seizures in children younger than five years¹⁷⁾.

Regarding a viral association with febrile seizures, our study showed that the recurrence rate of unprovoked seizures was four times higher in patients without an influenza infection (6 of 50, 12%) as compare to them with an influenza infection (1 of 29, 3%), though not significant ($P=0.24$). Febrile seizures associated with influenza infection has been commonly reported and the incidence rate ranges from 18.8–88.0% in children¹⁹⁻²⁵⁾. The influenza virus may be more neurotropic than the other respiratory viruses. It has been speculated that the

influenza virus causes seizures directly²⁰⁾, particularly in patients having a lower seizure threshold²¹⁾ or via an exaggerated cytokine response²⁶⁾. It may be possible that influenza-associated febrile seizure is more likely of one-time event rather than recurrent. The prognostic significance of the influenza virus for subsequent unprovoked seizures warrants further study in larger populations.

Febrile seizures persisting beyond age 6 years need to be distinguished from the syndrome of generalized epilepsy with febrile seizures plus (GEFS+). The GEFS+ is an autosomal dominant disorder with relation of several sodium channel subunit genes characterized by febrile seizures that comprised childhood onset (median 1 year)^{27,28)} and persist beyond age 6 years. Although we did not routinely perform genetic screening of GEFS+, we only included the patients who experienced a first febrile seizure over 6 years of age.

Limitation of our study is small number of patients. We collected all patients for 7 years in three major hospitals but found only 79 patients with late-onset febrile seizure.

In conclusions, this is the first multicenter study to focus on prognosis after late-onset febrile seizure. The percentage of subsequent unprovoked seizure in patients with late-onset febrile seizure was 9% at 2 years of follow-up. Prospective follow-up study with longer duration is warranted.

요약

목적: 열성경련은 6개월에서 5세 사이의 소아에서 가장 흔하게 발생하는 경련 질환으로, 추후 비열성 경련의 발생률은 2-7%로 알려져 있다. 하지만 6세 이상의 비교적 나이가 많은 환자에서 발생한 첫 열성경련에 대한 연구들은 거의 없는 실정으로, 추후의 비열성 경련의 재발과 관련된 위험인자 및 예후에 대해 알아보고자 하였다.

방법: 2009년 1월부터 2015년 12월까지 열성경련을 주소로 고려대 학교 구로, 안암, 안산 병원 응급실에 내원한 6세 이상의 소아환자를 대상으로 하였으며, 정보수집은 차트리뷰 및 환자 보호자에게 병력청취를 하였다. 방문한 모든 환자 중 6세 이후에 첫 열성경련이 발생한 환자 79명을 대상으로 나이, 성별, 가족력 및 발달지연 여부, 경련의 양상 등을 분석하였으며, 추후의 비열성 경련의 위험인자를 확인하기 위해 Cox 회귀모형 및 Kaplan-Meier 생존분석을 사용하였다.

결과: 총 247명의 환자들이 6세 이후 열성경련을 경험하였으며, 이중 뇌전증의 과거력이 있거나 열성경련의 과거력이 있는 경우를 배제하였으며, 추적기간 6개월 미만인 경우도 대상에서 제외하였다. 총 79명의 환자들이 6세 이후 첫 열성경련이 발생하였으며, 평균 추적기간은 34.9 ± 25.7 (mean $\pm$ SD) 달이었고, 7명의 환자에서 최종적으로 비열성 경련이 추적기간 중에 발생하였다. 경련재발의 누적 발생률은 추적기간 기준으로 6개월에 4%, 1년에 6%, 2년에 9%였으며, 비열성 경

런 재발과 관련된 인자는 통계적으로 증명되지 않았다.

결론: 이 연구는 6세 이상의 열성 경련 환자들을 대상으로 예후에 대해 연구한 첫 다기관 연구로서, 추적기간 동안 비열성 경련의 발생은 첫 경련 이후 2년 내에 9%에서 나타났다. 보다 정확한 예후를 평가하기 위한 장기간의 전향적 연구들이 필요할 것으로 생각된다.

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