첫 경련으로 발현된 지속성 열성 경련의 임상적 특성

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Clinical Characteristics of Status Epilepticus as the First Presentation of Fever Related Seizure in Children

Purpose: Status epilepticus (SE) is a neurological emergency disease because it can cause severe neurological complications. In order to avoid these complications, early diagnosis and appropriate treatment is required in SE. Febrile SE is the most common form of SE in children. We investigated the clinical characteristics and prognosis of patients with febrile SE is the first seizure of life.

Methods: We retrospectively reviewed the medical records of patients with SE as the first presentation of fever related seizures who visited our hospital from July 1996 to January 2013. Clinicodemographic characteristics, brain magnetic resonance imaging (MRI) and electro-encephalogram (EEG) findings, and anti-epileptic treatment were compared between two groups divided according to prognosis; fair vs. poor prognosis.

Results: Seventy-eight children were included in this study. The median age of the subjects was 20.0 months (interquartile range [IQR] 12.0–42.8). Fifty-one subjects had a fair prognosis, while twenty-seven subjects had a poor prognosis. Statistically significant differences was observed in the duration of seizure ($P=0.043$), the number of antiepileptic drugs ($P<0.001$) and the presence of abnormal EEG findings ($P<0.001$).

Conclusion: Children with febrile SE as the first seizure of life are likely to reveal a poor prognosis in those whose seizure last longer or are controlled only through high step anti-epileptic drugs. Thus, in order to ensuring a better prognosis for such patients, appropriate treatment is needed to stop the seizure.

Key Words: Status epilepticus, Fever, Epidemiologic study characteristics as topic

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Introduction

Status epilepticus (SE) is a neurological emergency condition capable of causing severe neurological complications. It has generally been accepted that SE is the situation in which a seizure or series of seizures persist for more than 30 minutes without recovery of consciousness between seizures¹⁾. Neurological sequelae have sometimes been reported as a complication of seizures lasting at least 20 minutes^{1,2)}. Some suggest that SE should be defined as a seizure lasting 5 minutes or more, because most clinical and electrographic seizures that last longer than 5 minutes often last longer than 30 minutes³⁾. SE can be classified according to semiology, duration, and underlying etiology. Of these, the classification according to duration, a higher mortality is observed in refractory SE (RSE) or more

prolonged SE lasting more than 12 hours⁴⁾. RSE, patients who do not respond to standard treatment regimens for status epilepticus, is the most severe form of SE and results in higher mortality and morbidity. Epilepsy is the most common sequela of SE, and permanent neurological sequelae have been reported in 3–16% of SE patients⁵⁾.

Many seizures, including SE, often occur with fever. Febrile seizure (FS) is defined as an epileptic seizure occurring in childhood after 1 month of birth, associated with a febrile illness that is not caused by an infection of the central nervous system (CNS), and without a previous history of any seizure⁶⁾. FS is the first leading cause of epileptic seizures in infancy and early childhood⁷⁾. Additionally, febrile illnesses are the most common cause of SE, accounting for 32–42% of all SE cases^{5,8,9)}. Prolonged FS, a new category of complex FS, is defined as a seizure lasting beyond 15 minutes and is associated with an increased risk of epilepsy, recurrent FS, or febrile SE¹⁰⁾.

The risk for developing an afebrile seizure is higher in a complex FS compared to a simple FS, particularly in seizures with a longer duration⁷⁾. Further in complex FS, including SE, brain damage can be induced by the long duration of seizure and the hyperthermia itself⁷⁾. Numerous studies have identified the risk factors of developing epilepsy or neurological complications after FS. However, to our knowledge, no study has examined the risk of developing neurological complications or poor prognosis in patients with febrile SE is the first seizure of life. Therefore, we aimed to investigate the different characteristics between groups with a fair prognosis and a poor prognosis, among patients with febrile SE is the first seizure of life.

Materials and methods

This study was a retrospective study performed at the Department of Pediatrics of Inha University Hospital from July 1996 to January 2013. Subjects included in this study were children who were admitted with febrile SE as the first seizure of life. Only subjects with seizure duration over 30 minutes were included. Children who had suffered a previous febrile or non-febrile seizure were excluded. Patients with a history other than seizures, such as central nervous diseases or mental retardation, were all included. Medical records were reviewed and characteristics including sex, age, etiology of fever, type and duration of seizure, brain magnetic resonance imaging (MRI) findings, electroencephalogram (EEG) findings, anti-epileptic treatment, and prognosis were recorded.

The etiology of fever was classified as CNS versus non-CNS.

Etiologies of fever were categorized based on clinical symptoms and signs and on laboratory findings. Patients with pleocytosis in their cerebrospinal fluid (CSF) specimens were identified to have a CNS infection. CSF pleocytosis, defined as >10 cells/mm³¹¹⁾. Fever was defined as a body temperature of $\geq 38^{\circ}\text{C}$ ⁷⁾.

The duration of the seizure included both the time before entering the hospital and the time required in the hospital to stop all clinical signs of the first seizure activity or the time required to fully recovered patient's consciousness. When the seizure presented twice or more, the duration of the seizure was defined as the time until the all clinical signs of the last seizure activity, including fully sedation state by using anti-epileptic drugs (AEDs). The type of seizures was classified as per the categorization of the International League Against Epilepsy (ILAE): (1) Generalized seizures including tonic-clonic, absence, myoclonic, clonic, tonic, and atonic seizures and (2) focal seizures¹²⁾.

EEG and MRI were performed only on patients who needed second- or third-step AEDs, those with severe neurological complications, or those with focal seizures. EEG was performed during the period of fever

Any one of the following drugs was administered as the first-step AED for SE: diazepam (bolus of 0.15 mg/kg), midazolam (bolus of 0.2 mg/kg), or lorazepam (bolus of 0.1 mg/kg). The second-step AED included phenytoin and/or phenobarbital, 20 mg/kg given over 30 minutes as an infusion, which were administered to those in whom the initial therapy had failed. When seizure activity persisted after the initial and second-step AEDs, the patient was considered to have RSE, and the third-step AED, that is, continuous midazolam infusion immediately starting at 1 $\mu\text{g/kg/minute}$ up to 20 $\mu\text{g/kg/minute}$. Other therapies added to this latter step were excluded from the analysis.

Children who did not suffer from any type of convulsions include simple FS and did not show signs or symptoms of neurological deficits in the three months after their discharge were regarded as having a "fair prognosis". Children who had any seizures, epilepsy, neurologic deficits or death in the hospital or within three months after discharge were regarded as having a "poor prognosis". Clinicodemographic characteristics, brain MRI and EEG findings, and AED use were compared between the two groups, and were divided as per the prognosis: the "fair prognosis" group versus the "poor prognosis" group.

Statistical analysis was performed on the data using PASW (version 18.0.0). Significant differences between the fair prognosis group and the poor prognosis group were sought. Mann-Whitney U test was used for the comparison of continuous variables between the groups, and a Chi-square test or Fisher's exact test was used for the comparison of categorical variables between groups.

A *P* value of less than 0.05 was considered as significant.

This study was approved by the Ethics Committee of the Institutional Review Board of the INHA Hospital (IRB File Number 2017-03-029).

Results

Seventy-eight children were included in this study. Thirty-three patients (42.3%) were male, and the median age was 20.0 months (interquartile range [IQR] 12.0–42.8). Clinicodemographic characteristics of the subjects are presented in Table 1. Nine patients who were diagnosed with CNS infections had undergone culture and antigen tests for *Haemophilus influenzae*, *Pneumococcus*, *Meningococcus* and *Group B Streptococcus* (GBS) with CSF specimens. Two of the patients were positive for GBS and one was positive for *H. influenzae*.

Seizure activities in all the subjects stopped after receiving first to third step AEDs (Table 2).

Brain MRI was performed in forty-five subjects, of whom twenty-nine (64.4%) had normal results and sixteen (35.6%) showed abnormal results. In subjects with an abnormal MRI result, leptomeningeal enhancement was the most common finding (n=5), followed by hypoxic brain damage (n=2), periventricular leukomalacia (n=2), and small arachnoid cyst (n=2). High signals in the left frontal and temporal lobe were observed in two patients, of whom one patient had a unilateral temporal lobe seizure, and the other had a normal EEG result. One patient revealed left

hippocampal sclerosis, with an ipsilateral site where epileptic discharge was observed in EEG. Severe hypoxic changes were also observed in one patient.

An EEG was performed in fifty-nine subjects. Ictal EEGs were conducted in four patients, and post-ictal EEGs were conducted in fifty-five patients. Thirty-nine patients had normal results, and twenty showed abnormal results. Of the subjects with an abnormal EEG result, eight showed abnormal background activities, nine had focal epileptic discharges, and three showed a mixed form of abnormal background activity and focal epileptic discharges. Two of the patients with focal epileptic discharge had partial seizures clinically. All the four patients who had undergone ictal EEGs revealed abnormal EEG results.

Fifty-one patients were discharged without any neurological sequelae, and never had a recurrence of seizures after being discharged. Twenty-seven patients had a poor prognosis, of whom twenty-two had a recurrence of seizures without fever, three had cerebral palsy, and two died during admission.

Comparison of clinicodemographic characteristics between the

Table 1. Clinical Characteristics of Study Populations

	Number (n=78)
Sex	
Male	33 (42.3%)
Female	45 (57.7%)
Age (months, median)	20.0 (12.0–42.8)
Duration of seizure (minute)	
30–60	28 (35.9%)
60–120	17 (21.8%)
>120	33 (42.3%)
Type of seizure	
Generalized tonic-clonic seizure	52 (66.7%)
Generalized tonic seizure	18 (23.1%)
Focal seizure	8 (10.3%)
Response to anticonvulsants	
1 st	25 (32.1%)
2 nd	36 (46.2%)
3 rd	17 (21.8%)
Etiology of fever	
Non-central nervous system	69 (88.5%)
Central nervous system	9 (11.5%)

Table 2. Anti-Epileptic Drugs for Control the Status Epilepticus

Steps of anti-epileptic drug	Number of cases
1 st	
Midazolam	71 (91.0%)
Diazepam	3 (3.8%)
Lorazepam	4 (5.1%)
2 nd	
Phenobarbital	18 (34.0%)
Phenytoin	13 (24.5%)
Phenobarbital+Phenytoin	22 (41.5%)
3 rd	
Continuous infusion of midazolam	17 (100.0%)

Table 3. Fever Related Status Epilepticus, Normal or Abnormal Prognosis

	Prognosis		<i>P</i> -value
	Fair (n=51)	Poor (n=27)	
Age (months)	27.6±19.9	26.6±25.5	0.081
Type of seizure			0.570
Generalized seizure	46	24	
Focal seizure	5	3	
Response to anticonvulsants			0.000
1 st	20	5	
2 nd	28	8	
3 rd	3	14	
Duration of seizure (minute)			0.043
30–60	23	5	
60–120	6	11	
>120	16	17	
Etiology of fever			0.623
CNS infection	6	3	
Non-CNS infection	45	24	

CNS, central nervous system.

fair prognosis group and the poor prognosis group revealed significant differences in the duration of seizures ($P=0.043$) and the number of antiepileptic drugs ($P<0.001$, Table 3). In the “fair prognosis” group, seizures were stopped by a first step AED in twenty patients, a second step AED in twenty-eight patients, and a third step AED in three patients. In the “poor prognosis” group, seizures were stopped by a first step AED in five patients, a second step AED in eight patients, and a third step AED in fourteen patients. The proportion of RSE subjects, who required a third step AED for seizure control, was significantly higher in the “poor prognosis” group compared to the “fair prognosis” group (3.8% vs. 61.5%, $P<0.001$).

We compared clinical characteristics of SE patients with fever and SE patients without fever (Table 4). The mean age of SE without fever group was older than that of children of SE with fever group. The generalized seizure was more common type of seizure in both SE groups. Results of EEG were only compared in patients of both SE groups who had performed EEG. However, no statistically significant differences were found in all part of clinical characteristics between the SE group with fever and the SE group without fever.

Comparison of brain MRI and EEG findings between the “fair prognosis” group and the “poor prognosis” group revealed a significant difference in EEG findings between the two groups. The proportion of patients with abnormal EEG findings was significantly higher in the “poor prognosis” group compared to

the “fair prognosis” group (17.9% vs. 7.7%, $P<0.001$, Table 5).

Discussion

Seizures were classified as SE when they lasted longer than 30 minute, and the SE occurred in about 5% of the seizure population¹³. There have been several studies on the factors that aggravate the prognosis of SE. However, our study is the first to investigate patients with febrile SE is the first seizure of life; we also compare subjects to patients whose first seizure was SE, without febrile illnesses.

The duration of seizures affects the prognosis of SE; generally, longer durations of seizures are associated with a worse prognosis. Further, pediatric SE patients show a variety of signs and symptoms and have a worse prognosis compared to adult SE patients; such symptoms may be linked to neurological complications or even death¹⁴. In previous studies, neurological complications related to pediatric SE varied between 13% of severe complications and 20% of permanent sequelae^{15,16}. We also found that statistical association between seizure duration and prognosis in children with febrile SE. Ant, it seems that shorter seizure duration tends to show a relatively fair prognosis while the prognosis is worse with seizure lasting more than 2 hours. This is a similar result to the previous studies, but there is limit to making clear comparisons because the number of patient is not large enough.

The RSE patients who did not respond to suitable initial AED treatment, had a worse prognosis than SE patients¹⁷. In one meta-analysis, children accounted for 16% of mortality amongst those who were treated for RSE. Further, the mortality of RSE patients was affected more by symptomatic etiologies of seizures than that of idiopathic etiologies¹⁷. The duration of the seizure was not considered to be a criterion for classification of the RSE³. Additionally, we showed that patients who were diagnosed with RSE had a worse prognosis than patients with SE. All patients

Table 4. Clinical Characteristics of Status Epilepticus as the First Presentation of Seizure with Fever Versus Status Epilepticus without Fever

	SE with fever (n=78)	SE without fever (n=20)	P-value
Age (months, mean)	27.23±21.82	33.25±25.86	0.241
Sex			0.070
Male	33	13	
Female	45	7	
Type of seizure			0.135
Generalized seizure	70	20	
Focal seizure	8	0	
Response to anticonvulsants			0.718
1 st	25	8	
2 nd	36	9	
3 rd	17	3	
Duration of seizure (minute)			0.076
30-60	28	11	
60-120	17	6	
>120	33	3	
Prognosis			0.039
Fair	51	8	
Poor	27	12	
EEG			0.163
Normal	39	9	
Abnormal	20	9	

Table 5. Comparison of Brain Magnetic Resonance Imaging (MRI) and Electroencephalogram (EEG) Patterns between Normal or Abnormal Prognosis of Fever Related Seizure

	Prognosis		P-value
	Fair	Poor	
MRI (n=45)			0.237
Normal	21	9	
Abnormal	7	8	
EEG (n=59)			<0.001
Normal	32	7	
Abnormal	6	14	

with RSE were treated with continuous infusion of midazolam as a third-step AED, which had a better effect to stop seizures compared to other AEDs¹⁷⁾.

Generally, children who had suffered from SE at a younger age had a worse prognosis¹⁸⁾. However, in our study, there were no significant statistical differences in median age, between the fair and poor prognosis group at the first presented seizure of SE. Further, there were no differences in mean age between SE groups with and without fever.

Seizures with fever can occur in patients with CNS infections, however it usually appears with other signs or symptoms, such as neck stiffness or a bulging fontanel^{19,20)}. Children who had seizures with CNS infections needed more intensive care because they had a worse prognosis than children who had seizures without CNS infection etiologies^{9,21,22)}. In our study, nine patients showed pleocytosis, and three of them had been diagnosed as bacterial meningitis with documented pathogens. Those three patients who showed documented pathogens had RSE occurring by bacterial meningitis. One of three was dead during management, another had an afebrile seizure after being discharged, and the third one had a fair prognosis. In our study, there were no significant differences between fair and poor prognosis groups, in relation to the present or absence of CNS infection. However in some study, patient with SE by acute bacterial meningitis had the possibility of a worsening prognosis⁸⁾. This difference may be due to not considering antibiotic usage time or type, and it is one of limitation of this study. However, CNS infection is a common cause of acute symptomatic SE²³⁾. In addition, typical symptoms and signs of meningitis may not appear in convulsive SE, thus patients with SE were recommended lumbar puncture when there are no contraindications²⁴⁾. If an acute bacterial meningitis is suspected, the appropriate antibiotic must be used with the AED to improve prognosis.

However, in our study, there were no significant differences between fair and poor prognosis groups, in relation to the present or absence of CNS infection.

An EEG on FS patients showed abnormal results in patients who were older in age, had complex FS, or had a past history of neurological abnormalities²⁵⁾. Further, abnormal EEG results usually occurred in patients with seizure transitioning to epilepsy; however EEGs were not suitable to predict the evolving of FS to epilepsy²⁶⁾. Unlike in previous studies, the poor prognosis group had more abnormal EEG results, with statistical differences in patients who had SE as the first ever presentation of seizure-related fevers. Therefore, results of EEG deserve careful consideration, to predict the patients' prognosis in recurrent seizure attacks, progression of seizures to epilepsy, or occurrence of neurological

complications after treatment in SE patients with fever.

In a previous study, 33% of patients with prolonged FS showed abnormal MRI results, though the result had no statistical significance²⁷⁾. In our study, the 55% of patients who suffered from FIRES showed abnormal MRI results; however those results had no correlation with their prognosis²⁸⁾. Also in our study, there were more abnormal MRI results in the poor prognosis group than the fair prognosis group, even though there were no statistical differences between the two groups. A hippocampal volume reduction on the ipsilateral side of the seizure focus area, in the temporal lobe is often seen in patients with a history of FS²⁹⁾. Additionally, MRI results of patients with prolonged seizures include mainly signal hyper intensities in both temporal lobes²⁸⁾. Two patients showed hyper intensities in the temporal lobes on conducting an MRI, and one patient showed hippocampal volume reduction. Our results are consistent with those of other studies, in that some episodes of afebrile seizure occurred after hospital discharge in patients who had hippocampal volume reduction²⁹⁾.

The use of continuous infusion AEDs such as midazolam, propofol, and pentobarbital is successful in suppressing long-lasting seizures of over 30 minutes^{3,23)}. Midazolam is an effective and safe drug, with rapid clearance compared to other benzodiazepines. Complete control of seizures with midazolam, using continuous therapy was achieved in 96–97% of RSE patients. Further, midazolam continuous therapy has low toxicity and mortality rate in comparison to other drugs for RSE, such as pentobarbital and thiopental^{17,30,31)}. In our study, only one RSE patient who was treated with midazolam continuous therapy with or without other long-acting AEDs died. This result shows that a continuous therapy of midazolam is effective for children whose first SE is caused by a febrile illness.

Although there was no statistical difference in the clinical characteristics between SE patients with fever and those without fever, the seizures had a relatively longer duration in the former. This factor was in turn related to the prognosis of the SE patients. Our results could be supported by the finding that neuroinflammation could damage the brain, and enhance epileptogenesis. Recent reports propose that some inflammatory cytokines or molecule activation, cortical injury or other convulsant stimuli could occur due to FS and seizures with hyperthermia, especially in immature brains^{32,33)}. Further, recent reports suggest that a combination of anti-epileptic therapy and anti-inflammatory therapy targeted to block the activation of inflammatory signals could reduce neurological morbidity, and prevent intractable epilepsy^{32,34,35)}. These findings conclusively indicate that SE with febrile illness needs more active therapy.

This study has some limitations regarding follow-up interven-

tions. Patients who were analyzed in this study were followed for at least three months. Therefore, we cannot exclude the possibility of late-occurring complications or neurological sequelae in SE patients. Additionally, MRIs and EEGs were performed only in patients with seizures that had a severe or unusual clinical course. Also, for this reason, there was a limit to distinguishing nonconvulsive SE. Therefore, in further studies, the results of EEGs and MRIs in normal patients with seizures will be needed for better comparisons.

This study implies that the duration of seizures, and the number of AEDs used to stop seizures are related to the prognosis of patients with febrile SE is the first seizures of life. Therefore, it is important to take appropriate treatment to stop seizure, such as use appropriate AEDs as soon as possible after seizures occur. Ultimately, appropriate treatment in patient with first febrile illness-related seizures of life could be prevented from escalating to the SE or the RSE, thus ensuring a better prognosis for patients by decreasing mortality and modality.

요약

목적: 간질지속증은 소아에서 심각한 신경학적 후유증이 생길 수 있기 때문에 신속한 진단 및 치료가 필요한 신경학적 응급 질환이다. 간질지속증으로 인해 발생할 수 있는 합병증과 후유증을 피하기 위해서는 신속한 진단과 적절한 치료가 반드시 필요하다. 간질지속증의 원인으로서는 여러 가지가 있으나, 이러한 원인들 중에서도 열과 동반하여 나타나는 지속성 경련이 원인이 되는 경우가 가장 흔하다. 본 연구는 이와 같은 열과 동반하여 나타나는 지속성 경련이 생애 처음으로 발병하여 간질지속증으로 진행되는 환자들에 대해 여러 임상적 특성 및 예후를 알아보고자 하였다.

방법: 1996년 7월부터 2013년 1월까지 인하대병원에 내원한 1개월에서 6세까지의 소아 78명을 대상으로 진행하였다. 첫 경련이 열과 관련하여 발생 후 30분 이상 지속성 경련으로 나타났던 소아들을 대상으로, 성별, 연령 분포 및 원인 질환, 경련의 형태 및 지속 시간, 항경련제에 대한 반응, 뇌파 및 뇌 자기공명영상결과, 예후 등을 기록지를 통해 후향적으로 분석하였다.

결과: 환자들 나이의 중앙값은 20.0개월이었으며(interquartile range [IQR] 12.0-42.8), 처음 경련이 나타난 나이와 경련의 예후 사이의 통계적 관련성은 없었다. 경련의 형태는 전신근간대성경련이 52건(66.7%), 전신강직성경련이 18건(23.1%)으로 전신성 경련이 대부분을 차지하였다. 발열의 원인은 중추신경계 감염이 9건(11.5%), 비 중추신경계 감염인 경우가 69건(88.5%)였다. 경련의 양상, 감염의 종류는 지속성 경련의 예후와 특별한 상관관계를 보이지 않았다. 경련이 조절되기까지 사용한 총 항경련제의 단계 수는, 1단계 25건(32.1%), 2단계 36건(46.2%), 3단계 17건(21.8%) 이었고, 3단계 이상의 항경련제까지 사용해야 경련이 조절될 경우 예후가 더욱 나쁜 것으로 나타

났다($P<0.001$). 경련이 조절되지 않고 지속된 시간은 30분-1시간 28명 (35.9%), 1시간-2시간 17명(21.8%), 2시간 이상 지속된 경우가 33명(42.3%)이었으며, 지속시간과 예후 사이에는 통계적 관련성이 있는 것으로 나타났다($P=0.043$). 뇌파에서 이상을 보인 경우는 총 20명이었고, 뇌자기공명영상 촬영에서는 총 16명이 비정상적인 결과를 보였으며, 뇌파의 이상유무는 예후와 관련성을 보이는 것으로 나타났다($P<0.001$).

결론: 발열과 함께 생애 처음으로 나타난 경련이 열성 간질지속증으로 발현하는 경우 환자의 예후는, 경련이 조절될 때까지 사용한 항경련제의 수 및 경련의 지속 시간, 그리고 뇌파의 이상 유무와 관련성을 갖는다. 그러므로, 열과 관련한 생애 첫 경련이 지속되고 있는 상황에서 경련을 멈추기 위한 적절하고 적극적인 치료가 필요하다.

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