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Early non-convulsive seizures are associated with the development of acute encephalopathy with biphasic seizures and late reduced diffusion

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Abstract

Introduction: Children with either febrile seizure or acute encephalopathy exhibit seizures and/or impaired consciousness accompanied by fever of unknown etiology (SICF). Among children with SICF, we previously reported those who have refractory status epilepticus or prolonged neurological abnormalities with normal AST levels are at a high risk for the development of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), considered to be caused by excitotoxicity. Non-convulsive seizures (NCS) are common in critically ill children and cause excitotoxic neuronal injury. The aim of this study was to elucidate the prevalence of NCS in the acute phase of children at a high risk for developing AESD and the relationship between NCS in the acute phase and neurological outcomes.

Methods: We studied 137 children with SICF at a high risk for developing AESD and who underwent continuous electroencephalogram monitoring (cEEG) upon admission to a tertiary pediatric care center at Hyogo Prefectural Kobe Children's Hospital between October 2007 and August 2018. Patient

characteristics and outcomes were compared between patients with NCS and without NCS.

Results: Of the 137 children, NCS occurred in 30 children; the first NCS were detected in cEEG at the beginning in 63.3 %, during the first hour in 90%, and within 12 hours in 96.7 %. Neurological sequelae were more common in NCS patients (20.0%) than in non-NCS patients (1.9 %; p=0.001). Five in 30 NCS patients (16.7 %) and 3 in 107 non-NCS patients（2.8 %） developed AESD (p=0.013).

Conclusion: The occurrence of NCS is associated with subsequent neurological sequelae, especially the development of AESD.

Keywords: acute encephalopathy with biphasic seizures and late reduced diffusion; children; epilepsy; electroencephalogram; non-convulsive seizure; non-convulsive status epilepticus

Introduction

Children with febrile seizure (FS) and acute encephalopathy (AE) exhibit seizures and/or impaired consciousness accompanied by fever of unknown etiology (SICF)[1]. FS is a transient condition in which children do not experience sequelae, and usually do not require intensive care. AE is defined as impaired consciousness lasting longer than 24 hours and is often associated with neurological sequelae and thus requires intensive care[2]. Because FS and AE are indistinguishable at the onset of SICF, we developed and validated a clinical prediction rule for neurological sequelae due to AE, which consists of the following 3 variables as predictive of poor outcomes: 1) refractory convulsive status epilepticus (RSE); 2) prolonged neurological abnormalities at 6 hours from onset, and 3) aspartate aminotransferase (AST) >90 IU/L within 6 hours of onset[3, 4]. Furthermore, we also found that children with SICF who have RSE or prolonged neurological abnormalities with normal AST levels (1) and/or 2) without 3)) are at a high risk for developing acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [3, 4]. While AESD is usually preceded by febrile status epilepticus (early seizure), followed by clustered

seizures (late seizure) at day 4 to 6 and thought to be caused by excitotoxicity, some patients (~20%) do not have prolonged early seizure[5]. Excitotoxicity is caused by prolonged seizures, regardless of whether these are convulsive or non-convulsive seizures (NCS)[6]. Recent studies have reported that NCS were found in 7%-46% of critically ill children in the intensive care unit (ICU)[7, 8] and 16.9% of children with altered mental status in the emergency room[9]. We hypothesized that neurological sequelae and development of AESD are associated with NCS around the early seizure. In this study, we aimed to retrospectively investigate the prevalence of NCS among children at a high risk for developing AESD and the association between NCS in the acute phase and neurological sequelae.

Materials and Methods

Patients

We retrospectively identified 562 children who underwent continuous electroencephalogram monitoring (cEEG) in a pediatric ICU (PICU) or emergency department because of seizures and/or impaired consciousness

accompanied by fever at Hyogo Prefectural Kobe Children's Hospital, a tertiary referral hospital, between October 2007 and August 2018. Among them, 290 children had: 1) refractory convulsive status epilepticus (RSE); and/or 2) prolonged neurological abnormalities at 6 hours from onset. Children with prior neurological abnormalities (cerebral palsy, epilepsy, known metabolic or genetic disorders) or factors affecting neurological outcomes, such as central nervous infections determined by pleocytosis or positive on polymerase chain reaction (PCR) or culture of cerebrospinal fluid (CSF), sepsis, or hyponatremia, were excluded. Because children with increased AST levels often develop fulminant encephalopathy caused by a cytokine storm or metabolic failure, such as Reye syndrome, hemorrhagic shock, and encephalopathy syndrome (HSES)[1, 3, 4], we excluded patients with marked elevation of AST level (>90 IU/L) within 24 hours of onset. Children with insufficient clinical record, and those who did not undergo a cEEG within 24 hours of onset were also excluded. A total of 137 children with SICF having RSE and/or prolonged neurological abnormalities with normal AST levels were considered to be at a high risk for developing AESD and studied (Figure 1). We registered the following patient

characteristics: sex, age, duration of hospitalization, length of total cEEG, latency to start cEEG recording from the onset, convulsive seizure before cEEG, duration of convulsive seizure. Outcomes included neurological outcomes evaluated 5-12 months from onset using the Pediatric Cerebral Performance Category Scale (PCPC) [10] and the development of AESD. Neurological sequelae were defined as PCPC score 2 or higher (2: mild sequelae 3: moderate sequelae 4: severe sequelae 5: vegetative state, 6: brain death). For children with NCS, EEG waveform morphology was described as below. Clinical profiles and outcomes were compared between patients with NCS in the acute phase (NCS patients) and those without NCS (non-NCS patients).

EEG recordings and interpretation

After admission to the PICU or after visiting the emergency department, a cEEG was carried out as soon as possible by the pediatrician. The cEEG method was described elsewhere [8, 9]. Briefly, cEEG was digitally performed using 4 channels (Fp1-A1, Fp2-A2, O1-A1, and O2-A2) according to the International 10-20 system. These electrodes are easy to use in a critical care setting, without needing a tape measure, by using only anatomic landmarks (pupils, ears, vertex,

and inion). A high-cut filter was used at 30 or 60 Hz and a time constant of 0.1 or 0.3 was used. EEG data were interpreted in real time by a pediatrician or pediatric neurologist. These data were reviewed again to determine the characteristics of the electrographic seizures by board-certified pediatric neurologists.

Electrographic seizures were defined and the EEG waveform morphology of the seizures were classified according to the following published criteria as any rhythmic electrographic pattern lasting >10 seconds with a clear onset and offset, and evolution in frequency, amplitude, or morphology[11, 12]. Seizures were characterized as NCS if there were no associated overt convulsive movements. Thus, seizures that showed only eye deviations or flaccid postures with impaired consciousness were included in the NCS.

Statistical analysis

Data were analyzed and compared between NCS patients and non-NCS patients with a chi-squared test and Mann-Whitney test. Statistical analyses were performed with STATA SE 10 for windows (STATA, College Station, TX, USA). p values <0.05 were considered significant.

Ethical approval

The present study was approved by the local ethical committee of Kobe University Graduate School of Medicine and Hyogo Prefectural Kobe Children's Hospital; the need for informed consent was waived given that this was a retrospective observational study.

Results

Identification and EEG characteristics of NCS

Among 137 children who were at a high risk for developing AESD, 30 (21.9 %) had NCS. The first NCS were detected within 12 hours in 29 (96.7 %) children (Figure 2). Of these patients, 63.3 % (19 of 30) had a seizure at the beginning of cEEG and 90.0 % (27 of 30) in the first hour of cEEG. Amongst EEG waveform morphologies, slow wave activity with rhythmical evolution was the most common (22 patients, 73.3 %) (Table 1). All but 1 (case 11) patient received anticonvulsant treatment.

Patient characteristics and neurological outcomes

As shown in Table 2, sex, age, duration of hospitalization, latency to start cEEG recording from the appearance of the first neurological symptoms, convulsive seizures before cEEG, duration of convulsive seizures, and the proportion of RSE were not significantly different between NCS patients and non-NCS patients. The length of total cEEG recordings were longer among NCS than among non-NCS patients. Six (20.0 %) in 30 NCS patients, as compared with 2 (1.9 %) in 107 non-NCS patients, had neurological sequelae (p =0.001). Five in 30 NCS patients (16.7 %) and 3 in 107 non-NCS patients (2.8%) developed AESD (p=0.013).

Discussion

In this study, we found NCS in 20 % of children who were at a high risk for developing AESD in the acute phase and children with NCS had neurological sequelae and developed AESD more frequently than children without NCS. To the best of our knowledge, this is the first study to reveal the association between NCS and subsequent neurological morbidity and development of AESD in children with seizures and fever without any other confounding factors.

Prevalence of NCS in children at a high risk for developing AESD, convulsive seizures prior to NCS, and detection of first NCS

NCS denote electrographic seizures without convulsive activity and often manifest as altered mental status or coma. We found NCS in 20 % of children at a high risk for developing AESD in the acute phase. The prevalence of NCS in these children is comparable to that among critically ill children or children with altered mental status in an ICU or emergency room setting, where it was reported to be 7% to 46%[7, 8]. Determining which children are at the highest risk for developing seizures may help optimize the use of limited cEEG resources. Several risk factors for electrographic seizures in children have been reported: younger age, preceding convulsive status epilepticus or clinically overt seizures, or presence of acute structural brain injury[7]. Unlike many other previous studies, in the present study, the prevalence of preceding convulsive seizures was not different between NCS and non-NCS patients and there was no significant difference in the median age between NCS and non-NCS patients. Although most past studies from ICU settings are etiologically heterogeneous, our study excludes patients with factors affecting neurological sequelae other

than seizures and fever. We suppose the difference in etiologies may have resulted in the differences in the outcome.

There is no consensus regarding the appropriate duration of cEEG to capture most of the NCS. In past observational studies of critically ill children, about half of the electrographic seizures were identified in the first hour and about 90%-100% were identified within the first 24-48 hours of monitoring[7]. The first NCS was detected in 90.0 % and 96.7 % of patients during the first hour and 12 hours of cEEG monitoring, respectively, which is earlier than in critically ill children. We consider that this may be because preceding convulsive seizures are more prevalent in children at a high risk for developing AESD than in critically ill children. Among the 19 (63.3 %) patients whose NCS was detected at the beginning of cEEG, some cases already had received treatment before arriving at our hospital. In these cases, cEEG revealed initial seizure activities continued without sufficient treatment. In the other 11 (36.7%) patients whose NCS were not detected at the beginning of cEEG, and in some patients whose NCS relapsed after initial NCS disappeared, cEEG might be a powerful tool to detect the continuous seizure activities or neuronal hyperexcitabilities.

Association between neurological outcome and NCS

The most powerful determinant for the outcome of non-convulsive status epilepticus (NCSE) is its etiology[13-15]. Although some studies demonstrated that the treatment delay or seizure burden of NCS/NCSE were also associated with the neurological sequelae[11, 16, 17], it is challenging to distinguish the effects of NCS/NCSE from those of an underlying disorder since most studies include SE of various etiologies. About 50% of SE cases in children are accompanied by fever[18]. Although febrile status epilepticus (FSE) is currently classified as an independent entity because of its favorable outcome[19], it is difficult to distinguish it from acute symptomatic SE such as acute encephalitis/acute encephalopathy without pleocytosis[20]. Therefore, FSE with neurological sequelae might be diagnosed as presumed encephalitis and classified as having acute symptomatic etiology. In this study, we attempted to clarify the effects of NCS on neurological sequelae. To this end, we studied children with seizures and fever, without any other factors affecting neurological injury, such as central nervous infection, or any prior neurological abnormalities. Furthermore, we excluded patients with high levels of AST, which is related to

fulminant systemic conditions caused by a “cytokine-storm”[3, 4]. In this study population, we revealed that NCS in the acute phase were associated with subsequent neurological sequelae and the development of AESD. AESD is a syndrome characterized by febrile seizures (usually >30 min) as the initial neurological symptom on day 1 (early seizure), followed by clustered seizures (late seizure) at day 4 to 6 with neurological sequelae. In patients with AESD, MRI shows no acute abnormality during the first 2 days and reduced diffusion appears in the subcortical white matter during days 3 to 9 and then disappears between days 9 and 25. Excitotoxic injury with delayed neuronal death is hypothesized to be a possible mechanism based on MR spectroscopic findings[21]. AESD is usually followed by febrile status epilepticus; however, radiological findings in AESD were not thought to be the result of prolonged seizures because studies on MRI imaging of status epilepticus did not report any abnormalities in subcortical white matter[22-24]. However, recent studies have reported that intensive treatment using EEG monitoring and targeted temperature management against childhood FSE could reduce neurological sequelae and the development of AESD[25-27]. In addition, NCSE was more

often found during the post-ictal coma of the first seizure in children with AESD with severe sequelae[5, 28]. In this study, we revealed a clear association between NCS in the acute phase and neurological sequelae and the development of AESD, adding further evidence to support the involvement of seizure burden in neurological injury and the development of AESD. Recently, a transient reduction in cerebral blood flow after febrile seizures was also reported to be a pathomechanism underlying AESD[29, 30]. Furthermore, recent studies have indicated that cerebral hypoperfusion is also observed in the post-ictal period of status epilepticus[31, 32]. Overall, we suppose that prolonged febrile seizures, including NCS and subsequent hypoperfusion in immature infant brains, could contribute to the development of neurological injury, and especially to clinical features of AESD in children with febrile status epilepticus. Although the identification and treatment of electrographic seizures by cEEG theoretically reduces seizure burden and ameliorates neurological sequelae, the clinical effectiveness for neuronal injury remains limited[33]. Our study highlights the need for clinical research to confirm the significance of early treatment for NCS in children at a high risk for developing AESD.

Study limitations

This study has several limitations. First, our sample size was relatively small, and the study design was that of a retrospective single-center study. Second, we measured outcomes using a simple outcome assessment tool (PCPC) for young infants, which may not reflect long-term outcomes, especially in terms of the cognitive function in school life. Third, we selected only 4 channels for cEEG monitoring. Although a previous study using 4 channels for EEG monitoring revealed a seizure detection accuracy characterized by 68% sensitivity and 98% specificity[34], it may be insufficient to detect all NCS. Fourth, the non-NCS group has a shorter cEEG implementation time than the NCS group, so there is a possibility that NCS is overlooked. Fifth, we did not study the treatment for seizures which may modify the outcomes. Finally, one may claim that AESD have more NCS than febrile status epilepticus because they are different pathological conditions by nature. Whether AESD develops as a result of NCS or whether a patient develops NCS due to AESD is a tautological issue and the present study cannot draw a conclusion. Further prospective studies are needed.

Conclusions

NCS was observed in 20 % of children at a high risk for developing AESD. Among children with NCS, 90% of the first NCS were detected in the first hour of cEEG. The occurrence of NCS is associated with subsequent neurological sequelae, especially the development of AESD.

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Conflicts of interest

The authors declare no conflicts of interest.

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Figure legends

Figure 1

Study enrollment procedure

AST: aspartate aminotransferase; cEEG: continuous electroencephalogram monitoring; AESD: acute encephalopathy with biphasic seizures and late reduced diffusion

Figure 2

Time elapsed between the start of continuous electroencephalogram monitoring (cEEG) and the detection of the first non-convulsive seizure (NCS) (n=30)

Table 1

Characteristics of electroencephalogram findings in patients with NCS (n=30)

1-a: Patients whose NCS were detected at the beginning of continuous EEG monitoring

Case #	Sex	Age (month)	Ictal finding of NCS	Treatment of NCS	PCPC	Duration of the convulsive seizure before cEEG monitoring (min)	Duration of NCS (min)	Total initial seizure duration (including convulsive and non-convulsive seizures) (min)	Neurological symptoms which might be NCS before cEEG monitoring

1	M	8.2	Right hemisphere 1.5 Hz spike & wave	DZP,MDL, Thi	3	212	31	243	right eye deviation
2	M	15.2	Right hemisphere 4-5 Hz rhythmic theta activity	MDL	1	135	24	159	
3	F	17.4	Bilateral occipital dominant 2-3Hz spike & wave	MDL	1	38	19	57	
4	F	18.5	Bilateral frontal dominant 1 Hz rhythmic delta activity	Thi	2	114	18	132	
5	M	22.8	Bilateral frontal dominant 2 Hz rhythmic delta activity	MDL,fPHT	1	68	7	75	
6	F	29.2	Bilateral occipital dominant 4 Hz spike & wave	MDL	1	70	15	85	cyanosis
7	F	29.9	Diffuse 3-4 Hz rhythmic theta activity	DZP	1	51	31	82	
8	F	38.3	Diffuse 3-4 Hz rhythmic theta activity	MDL	1	3	91	94	
9	F	41.5	Diffuse 4-5 Hz poly spike & wave	MDL	1	37	4	41	

10	M	43.8	Diffuse 1 Hz rhythmic delta activity	MDL	1	67	158	225	
11	M	48.6	Diffuse 1 Hz rhythmic delta activity	none	1	26	28	54	
12	F	48.8	Left hemisphere 2 Hz spike & wave	fPHT	1	257	22	279	tachycardia, cyanosis
13	F	54.6	Diffuse 3-4 Hz rhythmic theta activity	DZP	1	1	20	21	
14	M	58.8	Diffuse 1-2 Hz rhythmic delta activity	MDL,Thi,PB	1	24	193	217	
15	M	94.5	Diffuse 3-4 Hz rhythmic theta activity	MDL	1	no	4	N/A	
16	F	99.3	Occipital dominant 3 Hz spike & wave	MDL	1	60	25	85	
17	M	103.4	Bilateral frontal dominant 2Hz rhythmic delta activity	MDL,fPHT	1	45	12	57	

	F			MDL,Thi,P		295		331
18		107.4	Diffuse 3-4 Hz spike & wave	B	1		36	
19	F	119.7	Diffuse sharp waves	MDL	1	no	101	N/A

1-b: Patients whose NCS were not detected at the beginning of cEEG

Case #	Sex	Age (month)	Ictal finding of NCS	Treatment of NCS	PCPC	Neurological symptoms which might be NCS before cEEG monitoring

	M			MDL,Thi,P		
20		6.1	Right frontal dominant 3 Hz rhythmic delta activity	B	2	right eye deviation
21	F	8.1	Bilateral frontal dominant 1 Hz rhythmic delta activity	PB	3	
22	F	12.4	Diffuse 1 Hz rhythmic delta activity	MDL	1	left eye deviation
23	F	19.7	Diffuse 1-1.5 Hz rhythmic delta activity	MDL,Thi	3	
24	F	20.2	Right occipital dominant 1-2 Hz rhythmic delta activity	PB	2	
25	M	26.9	Diffuse 1-1.5 Hz rhythmic delta activity	MDL,Thi	1	
26	M	53.2	Diffuse 4-5 Hz rhythmic theta activity	MDL,PB	1	
27	F	54.3	Diffuse 5-6 Hz rhythmic theta activity	Thi	1	
28	M	82.5	Bilateral frontal dominant 3 Hz rhythmic delta activity	MDL,fPHT	1	

29	M	92.9	Diffuse 2-3 Hz rhythmic delta activity	DZP	1
30	M	138.6	Diffuse 2 Hz rhythmic delta activity	DZP	1

cEEG: continuous electroencephalogram, DZP: diazepam, fPHT: fosphenytoin, MDL: midazolam, N/A: not applicable, NCS: non-convulsive seizures, PB: phenobarbital, PCPC: pediatric cerebral performance scale, Thi: thiamylal

Table 2

Demographic characteristics and outcomes of patients with and without NCS (n=137)

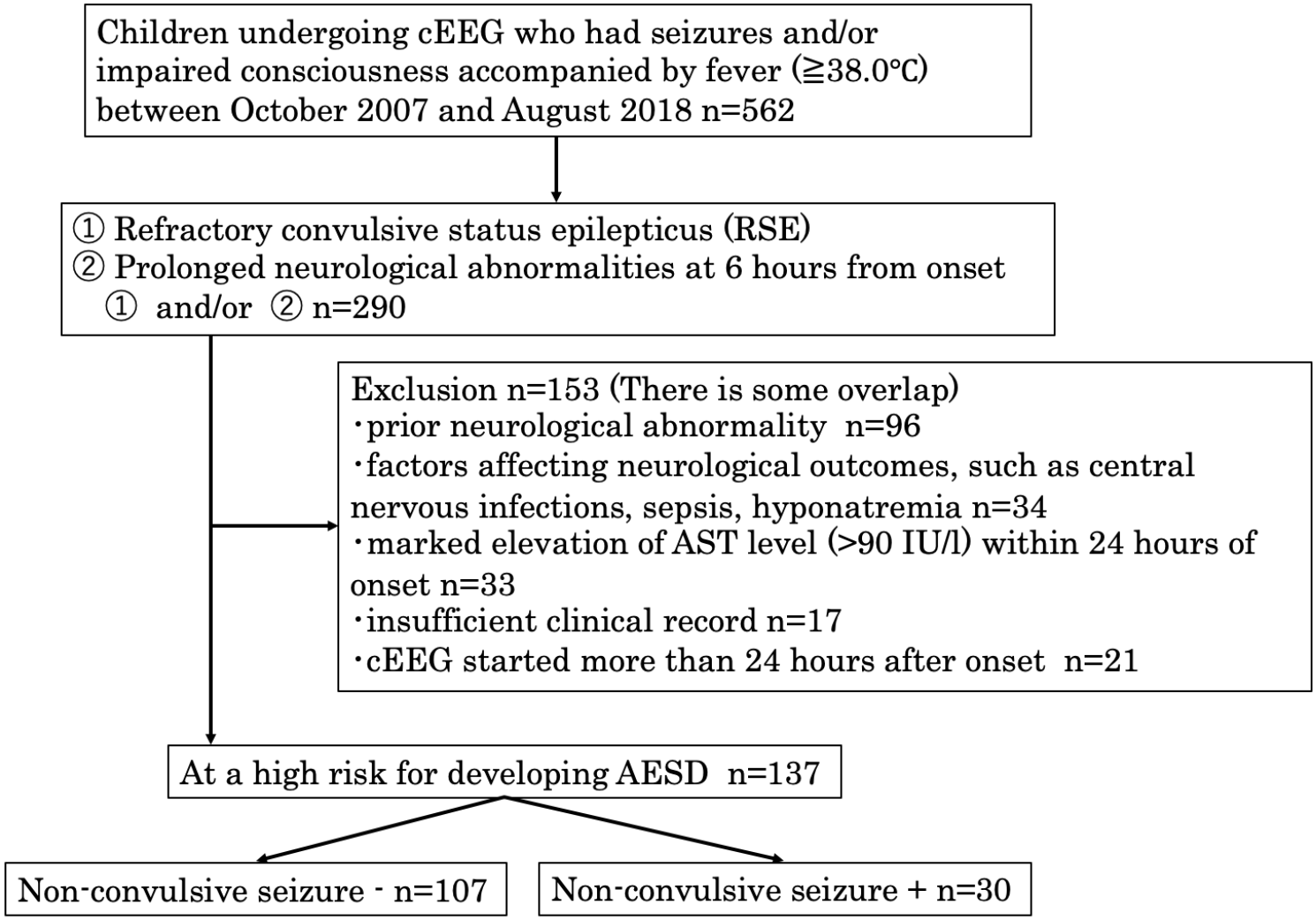
	NCS (+) n=30	NCS (-) n=107	*p* value
Patient characteristics			
Sex, male/female	14/16	51/56	0.923
Age, month after birth, month, median (IQR)	42.65 (19.7-82.5)	24.5 (16.2-61)	0.1802
Duration of hospitalization, days, median (IQR)	8.5 (6-15)	8 (5-12)	0.3175
Length of total cEEG, minutes, median (IQR)	3393 (299-6601)	584 (38-5400)	0.016
Latency to start cEEG recording from appearance of first neurological symptoms, minutes, median (IQR)	275 (87-410)	252 (130-469)	0.3638
Convulsive seizure before cEEG, no. / total (%)	25/30 (83.3)	95/107 (88.8)	0.53
Duration of convulsive seizures, minutes, median (IQR)	63 (24-114)	74 (34-145)	0.3524
Total initial seizure duration including NCS, minutes, median (IQR)†	85 (57-217)	N/A	
Refractory status epilepticus, no. / total (%)	11/30 (36.7)	56/107 (52.3)	0.129

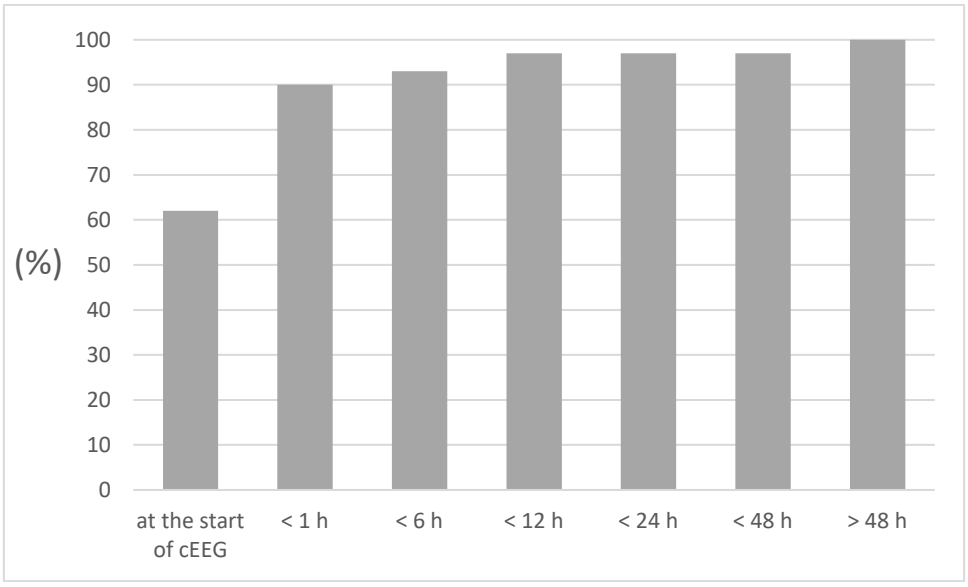
Prolonged neurological abnormalities at 6 hours from onset, no. / total (%)*	19/27 (70.4)	69/93 (74.2)	0.692
Outcomes			
Neurological sequelae, no. / total (%)	6/30 (20.0)	2/107 (1.9)	0.001
Development of AESD, no. / total (%)	5/30 (16.7)	3/107 (2.8)	0.013

AESD: acute encephalopathy with biphasic seizures and late reduced diffusion; cEEG: continuous electroencephalogram monitoring; IQR: interquartile range; N/A: not applicable; NCS: non-convulsive seizures

† : The data is derived from only the patients who had a convulsion prior to cEEG and NCS at the beginning of cEEG (n=17)

*: Patients who received continuous anti-epileptic drugs administration at 6 hours from onset


Children undergoing cEEG who had seizures and/or impaired consciousness accompanied by fever (≧38.0℃) between October 2007 and August 2018 n=562
① Refractory convulsive status epilepticus (RSE)
② Prolonged neurological abnormalities at 6 hours from onset ① and/or ② n=290
Exclusion n=153 (There is some overlap)
・prior neurological abnormality n=96
・factors affecting neurological outcomes, such as central nervous infections, sepsis, hyponatremia n=34
・marked elevation of AST level (>90 IU/l) within 24 hours of onset n=33
・insufficient clinical record n=17
・cEEG started more than 24 hours after onset n=21
At a high risk for developing AESD n=137
Non-convulsive seizure - n=107
Non-convulsive seizure + n=30


100
90
80
70
60
50
40
30
20
10
0
(%)
at the start of cEEG
< 1 h
< 6 h
< 12 h
< 24 h
< 48 h
> 48 h