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Yamaguchi, Hiroshi ; Nishiyama, Masahiro ; Tokumoto, Shoichi ; Ishida, Yusuke ; Tomioka, Kazumi ; Aoki, Kazunori ; Seino, Yusuke ; Toyoshima,…

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Clinical Research Paper

Detailed Characteristics of Acute Encephalopathy with Biphasic Seizures and Late Reduced Diffusion: 18-year Data of a Single-center Consecutive Cohort

Hiroshi Yamaguchi, M.D., D.V.M.[a,b*]; Masahiro Nishiyama, M.D., PhD.[a]; Shoichi Tokumoto, M.D.[a,b]; Yusuke Ishida, M.D.[a,b]; Kazumi Tomioka, M.D, PhD.[a]; Kazunori Aoki, M.D.[c]; Yusuke Seino, M.D.[c]; Daisaku Toyoshima, M.D., PhD.[b]; Hiroki Takeda, M.D., PhD.[a]; Hiroshi Kurosawa, M.D.[c]; Kandai Nozu, M.D., PhD.[a]; Azusa Maruyama, M.D.[b]; Ryojiro Tanaka, M.D., PhD.[d]; Kazumoto Iijima, M.D., PhD.[a]; Hiroaki Nagase, M.D., PhD.[a]

[a] Department of Pediatrics, Kobe University Graduate School of Medicine, Hyogo, Japan
[b] Department of Neurology, Hyogo Prefectural Kobe Children's Hospital, Hyogo, Japan
[c] Department of Pediatric Critical Care Medicine, Hyogo Prefectural Kobe Children's Hospital, Hyogo, Japan
[d] Department of Emergency and General Pediatrics, Hyogo Prefectural Kobe Children's Hospital, Hyogo, Japan

*Corresponding author:
Hiroshi Yamaguchi, M.D., D.V.M.
Department of Pediatrics, Kobe University Graduate School of Medicine, Hyogo, Japan
7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan
Tel: +81-78-382-5111, Fax: +81-78-382-5050
E-mail: hiyamagu@med.kobe-u.ac.jp

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Key words: acute encephalopathy; children; epilepsy; electroencephalogram; emergency department; intensive care unit; pediatrics; seizure; status epilepticus

Abstract

Objective: Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a syndrome characterized by biphasic seizures with impaired consciousness. AESD is rare outside Asia, and consecutive cohort studies are therefore scarce. Herein, we aimed to describe the detailed characteristics of AESD, including clinical course, electroencephalogram data, laboratory data, imaging findings, treatment, and outcomes. *Methods:* We reviewed the clinical database and medical charts of 43 consecutive pediatric patients (<18 years old) who developed AESD between October 1, 2002, and September 30, 2019. *Results:* We found that AESD occurred even though patients did not develop prolonged seizures. A comparison between the two groups (first seizure duration <30 min and first seizure duration ≥30 min) revealed three main findings: first, patients with AESD who had shorter seizures had better prognosis than those with prolonged seizures; second, patients with AESD who had shorter seizures tended to have earlier occurrence of a second seizure; and third, high signal intensity on diffusion-weighted magnetic resonance imaging was observed mainly in frontal areas, not diffusely, in patients with shorter seizures, and in a broader area in patients with prolonged seizures. *Conclusions:* Our description of the detailed clinical picture of AESD may add new insight into its pathophysiology.

1. Introduction

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a syndrome characterized by biphasic seizures with impaired consciousness [1]. After several days (typically 3–9 days) from the first seizure, secondary seizures may occur. In addition, reduced diffusion in the cortical and subcortical white matter is seen on magnetic resonance imaging (MRI)—a finding known as "bright tree appearance (BTA)" [1-3]. Although viral infection represents the primary etiology of AESD [1], we have previously reported cases of trauma or bacterial infection accompanied by AESD-like pathology [4-6]. AESD is the most commonly reported encephalopathy syndrome, affecting 100–200 patients annually in Japan [7]. Its incidence is higher in Asian countries, especially Japan, and the genetic background may be a possible reason for the reported high incidence rate. The outcome of patients with AESD varies from normal to severe mental retardation, paralysis, and epilepsy. However, the mortality rate is relatively low (<5%) [2].

The initial symptom of AESD is generally a prolonged febrile seizure, and the pathogenic mechanism of AESD has been hypothesized as an excitotoxic injury with delayed neuronal death [8]. However, a mild form of AESD, with a brief seizure as the initial symptom, has been reported [1]. The pathophysiological differences between AESD with a first brief and prolonged febrile seizure are unknown.

Because AESD is rare outside Asia, consecutive cohort studies are scarce. Therefore, in this 18-year single-center, retrospective, consecutive cohort study, we aimed to describe the detailed characteristics of AESD. The detailed characteristics include the clinical symptoms, duration of seizures, reduced-lead electroencephalogram (EEG) data, laboratory data, MRI findings, treatment, and outcomes. Furthermore, for exploratory assessment, we compared the characteristics of patients with AESD who had a short first seizure (<30 min) with those who had a prolonged first seizure (≥30 min).

2. Materials and Methods

2.1. Study design and patients

This retrospective, clinical observational study was conducted under the approval of the Ethics Committee of Kobe University and Hyogo Prefectural Kobe Children's Hospital, with a waiver of informed consent owing to the retrospective nature of the study. Hyogo Prefectural Kobe Children's Hospital is a multidisciplinary tertiary care center that has handled more than 1,200 cases of seizures at the emergency department (ED) over the past 18 years. In this study, we reviewed the clinical database and medical charts of Hyogo Prefectural Kobe Children's Hospital and collected data on demographics, clinical presentation, treatments, imaging findings, and laboratory tests from consecutive patients (aged <18 years old) who developed AESD between October 1, 2002, and September 30, 2019. If patients were transferred from another hospital, all data from the hospital at

presentation were included. Patients with apparent central nervous system infection (n = 6) (cerebrospinal fluid cells >8 cells/μL), apparent bacterial infection (n = 3), or a history of trauma (n = 2) were excluded from this study. Two cases of AESD-like pathology by bacterial infections and two cases by trauma were previously reported [4-6]. As a result, 43 patients with AESD were finally analyzed. Thirty-two patients (74.4%) were transferred from the previous hospital to our hospital (Table S1).

2.2. Definitions

Patients were diagnosed with AESD based on the clinical consensus and guidelines for acute encephalopathy in children [9]: 1) the disease develops during the fever stage of the infection, and other trigger-related conditions such as head trauma, other encephalopathy syndromes, and encephalitis are excluded; 2) convulsion develops on the same day or the day after fever onset; 3) convulsions recur, or consciousness deteriorates, 3–7 days after the onset of disease; 4) high signal intensity in the subcortical white matter or cortex is seen on diffusion-weighted imaging (DWI) 3–14 days after the onset of disease; and 5) residual lesions or atrophy are confirmed by computed tomography (CT), MRI, or decreased blood flow on single-photon emission CT (SPECT) on the frontal region or frontal and parietal regions 2 weeks after the onset of disease. AESD was diagnosed if criteria 3) and/or 4) and/or 5) were met in addition to 1) and 2). The diagnostic criteria in this guideline were modified by those published by Hoshino et al.[7]. In our hospital, AEDs for febrile status epilepticus were administered on an individual basis according to our hospital protocols [12]. Targeted temperature management (TTM) was induced based on the following criteria: 1) refractory status epilepticus; 2) elevated aspartate transaminase (AST) levels within 6 h of disease onset; and 3) impaired consciousness lasting longer than 6 h [10,11]. Central sparing was defined as restricted DWI that spared the perirolandic region on MRI. A short febrile seizure was defined as a seizure lasting <30 min and a prolonged febrile seizure was defined as a seizure lasting for ≥30 min or a recurrent seizure lasting ≥30 min without full recovery of consciousness. “Febrile” was defined as a temperature of more than 38 °C, within 24 h before or after convulsion [12]. Seizure onset was defined as the beginning of any neurological symptoms, such as convulsion or eye deviation [13]. Seizure duration was defined as from seizure onset according to information from caregivers to cease of seizure as confirmed by emergency department physicians. The definition of “non-convulsive seizure (NCS)” was in accordance with that reported by Claassen et al [19]. Regarding the counting of days, the day at which the event occurred was day 1. Neurological performance at baseline was assessed by the Pediatric Cerebral Performance Category (PCPC) scale, with a score of 1 representing normal performance; 2, mild disability; 3, moderate disability; 4, severe disability; 5, persistent vegetative state; and 6, death [14]. “Prognosis” was evaluated by PCPC.

2.3. Reduced-lead EEG application and interpretation

The application of a reduced-lead EEG system has been described previously [13]. Briefly, a portable digital EEG system was used (EEG-9100; Nihon Kohden Co., Ltd.), and digital recordings were made using four channels across the bilateral frontal and occipital regions, according to the International 10–20 system. EEGs were ordered when subclinical seizure activity was suspected by ED physicians after an initial clinical assessment. Therefore, the application of EEG and administration of AEDs were left to the discretion of the attending physicians [13].

2.4. Laboratory data and patient follow-up

All laboratory data were obtained after the first febrile seizure. If the patient was referred from another hospital, data from the previous hospital were used. Blood testing was not performed in some patients; the number of patients who underwent each test is described in Tables 1–3.

In our hospital, patients with AESD are followed at 1 month, 6 months, 1 year, and 2 years after the first febrile seizure. Some patients dropped out during the follow-up period or did not complete the follow-up period; details are also described in Tables 1–3. Etiology was confirmed by a rapid diagnosis kit for antibodies or by polymerase chain reaction (PCR) for DNA in blood or cerebrospinal fluid, as appropriate. However, not all patients were examined for the etiology of the disease.

2.5. Statistics

Results are expressed as number (%) or median [interquartile range (IQR) (1st quartile, 3rd quartile)]. The Mann–Whitney U test or Fisher's exact test was used when appropriate for statistical analysis of the results. The correlations were analyzed by Pearson's correlation coefficient. A p-value <0.05 was considered statistically significant. Analyses were performed using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Patient demographics

Patient demographics are shown in Table 1. We enrolled 43 patients with AESD (17 male and 26 female) with a median age of 19.3 months (IQR; 13.9, 27.9). Among the 43 patients, 30.2% and 4.7% had a past medical history of febrile seizure and epilepsy, respectively. Generalized convulsion was the most common type of first seizure (90.7%), and cluster convulsion was the most common type of second seizure (46.5%). The median duration of the first seizure was 53 min (IQR; 49.5, 56.5). The median number of days from the first to the second seizure was 5.0 (IQR; 4.0, 6.0). TTM and intubation were performed in 44.2% and 60.5% patients, respectively. Midazolam was the most commonly used AEDs for both first

and second seizures. During the study period, we encountered two cases of trauma and three cases of bacterial infection (two by *Streptococcus pneumonia* and one by *Enterococcus faecalis*) accompanied by AESD [4-6]. The detailed characteristics of each patient are shown in Supplementary Table S1. Example images of MRI in the short and prolonged seizure groups are shown in Fig. 1.

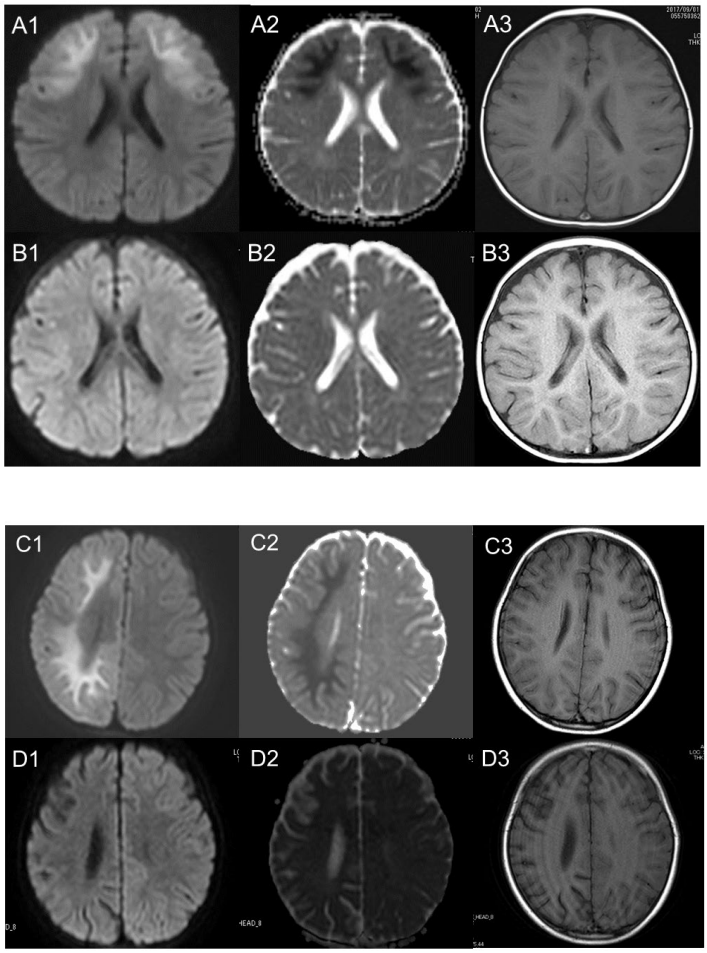

Figure 1. Example of sequential axial magnetic resonance imaging in the short and prolonged seizure groups.

Patient 3 in the short seizure group exhibited a high-intensity lesion in the bilateral frontal subcortical white matter as observed by diffusion weighted imaging (DWI) on day 3 after the onset (A1). Hyperintensity in DWI associated with hypointensity of apparent diffusion coefficient (ADC) (A2) indicated cytotoxic edema. T1 weighted imaging (T1WI) (A3) demonstrated no abnormalities on the same day. The hyperintensity area of DWI and hypointensity of ADC disappeared after 1 month from the onset (B1, B2) and T1WI showed no abnormalities (B3). Patient 24 in the prolonged seizure group showed a hyperintensity lesion in the right hemisphere by DWI (C1) with a hypointensity of ADC (C2) on day 8 after the onset (C3). T1WI (D1) demonstrated no abnormality on the same day. The hyperintensity area of DWI and hypointensity ADC disappeared after 1 month from the onset (D1, D2). T1WI showed right hemisphere atrophy (D3). Patient 8 in the prolonged seizure group showed a hyperintensity lesion in the anterior and parietal lesion by DWI (E1) with hypointensity of ADC (E2) on day 7 after the onset. T1WI (E3) demonstrated no abnormality on the same day. The hyperintensity area of DWI and hypointensity of ADC disappeared 15 months after the onset (F1, F2). T1WI showed that hemisphere atrophy occurred significantly on the right side compared to the left and an enlargement of the lateral ventricle was observed (F3).

3.2. Reduced-lead EEG monitoring, MRI, etiology, laboratory data, and patient prognosis

The results of reduced-lead EEG monitoring, MRI, etiology, laboratory data, and patient prognosis are shown in Table 2. EEG monitoring was performed in 32.6% (14/43) of patients during or after the first seizure and in 81.4% (35/43) of patients during or after the second seizure. Among the patients undergoing EEG monitoring, NCS was detected in 21.4% (3/14) and 31.4% (11/35) during or after the first and second seizure, respectively. They accounted for 7.0% and 25.6% of all patients (n=43) in first and second seizure, respectively. All patients performed MRI; the median number of days that MRI was performed was 6 (IQR; 5.0, 8.5). In patients who showed high signal intensity on DWI, the anterior area was the most affected (96.6%); 27.6% (8/29) of patients had diffuse hemisphere affected. The most common etiological factors were human herpes virus (HHV)-6 and influenza A virus; echovirus was found in three patients. Five patients were clinically diagnosed with exanthema subitum, and one patient was clinically diagnosed with hand-foot-and-mouth disease. The most notable laboratory finding was severe acidosis. The median PCPC was 1.0 upon the initial assessment and 2.0 at 1 month, 6 months, 1 year, and 2 years after the disease onset (IQR; 1.0, 1.5 (initial assessment); 1.0, 3.0 (6 months, 1 year, and 2 years)).

3.3. Association between the first seizure duration and the time between the first and second seizures

The duration of the first seizure was significantly associated with the time between the first and second seizures (R^2 = 0.179, p = 0.0113; Fig. 2). However, no relationship was found between age at initial assessment and the time between the first and second seizure (R^2 = 0.0371, p = 0.2574).

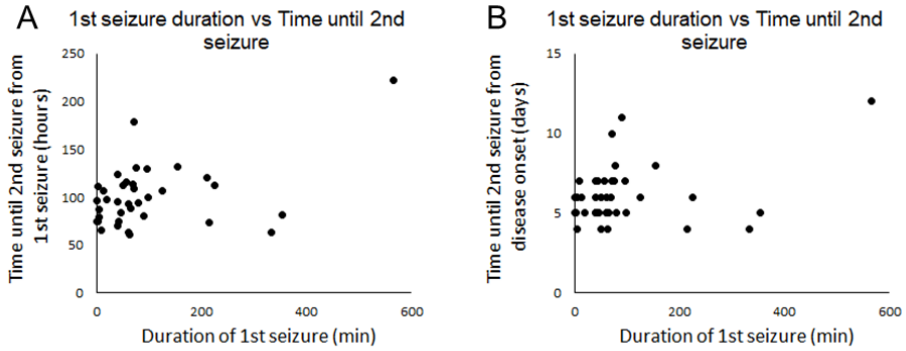

Figure 2. Association between the first seizure duration and the time between the first and second seizures in patients with AESD.

3.4. Distribution of first seizure duration

The distribution of the first seizure duration in patients with AESD are shown in Fig. 3. The distribution were as follows: >0 to <10 min (n=7, 16.3%), ≥10 to <20 min (n=1, 2.3%), ≥20 to <30 min (n=1, 2.3%), ≥30 to <40 min (n=0, 0%), ≥40 to <50 min (n=7, 16.3%), ≥50 to <60 min (n=3, 7.0%) and ≥60 min (n=24) (55.8%). The proportion of short seizure group and prolonged seizure group were 20.9% and 79.1%, respectively.

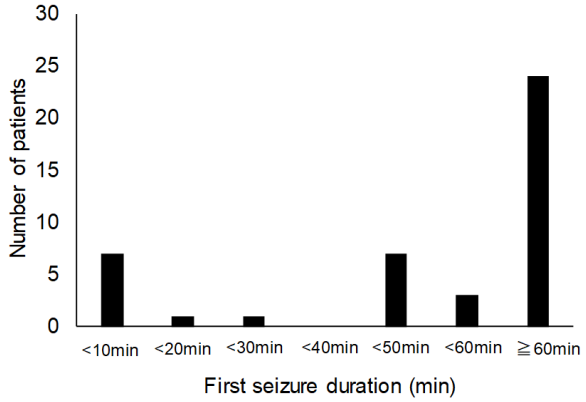

Figure 3. First seizure duration in patients with AESD.

3.5. Comparison of demographics, AED administration, and outcomes between patients with AESD with first seizure duration <30 min versus ≥30 min

Following the findings of first seizure distribution (Fig. 3), we compared the two groups (short seizure group [<30 min] and prolonged [≥30 min]) in terms of clinical symptoms, seizure duration, EEG data, laboratory data, the extent of brain lesions on the MRI scan, treatment, and outcomes. Despite the absence of a statistically significant difference, patients who had shorter seizures (<30 min) were younger than those with prolonged seizures (≥30 min). There were no differences in sex or past medical history of febrile seizures or epilepsy. The time between the first and second seizures tended to be shorter in the short seizure group, yet not significantly so. High signal intensity on DWI was observed mainly in the frontal area in the short seizure group and in a broader area in the prolonged seizure group (parietal area: 25.0% vs. 66.7%, posterior area: 12.5% vs. 52.4%, temporal area: 0% vs. 28.6%, thalamus: 0% vs. 14.3%, caudate nucleus: 0% vs. 4.8%, globus pallidus: 0% vs. 4.8%, hippocampus: 0% vs. 4.8% in the short vs. prolonged seizure group). When comparing the high-intensity DWI regions of MRI in the two groups in either the anterior only or in other regions, high-intensity regions in the short seizure group were more restricted to frontal areas than in the prolonged seizure group (62.5% vs. 14.3%, P=0.0118).

The proportion of patients who did not receive AEDs for the first seizure was higher in the short seizure group than in the prolonged seizure group (66.7% vs. 2.9%). However, no difference in the use of AEDs for the second seizure was noted between the two groups. No patients were assessed by reduced-lead EEG during or after the first seizure in the short seizure group, but 41.2% of patients in the prolonged seizure group were assessed, with 21.4% (3/14) showing NCS. Furthermore, while no patients showed NCS in the short seizure group during or after the second seizure, 35.5% (11/31) of patients in the prolonged seizure group showed NCS. Laboratory data revealed that white blood cells, creatinine, and glucose were significantly higher; creatinine kinase tended to be higher; and pH and base excess were significantly lower in the prolonged seizure group than in the short seizure group. PCPC was significantly worse in the prolonged seizure group at 1 month, 6 months, 1 year, and 2 years after disease onset.

4. Discussion

In this study, we described the detailed characteristics of patients with AESD. To our knowledge, this is the largest study of 18-year data of a single-center consecutive cohort on AESD thus far. We found that AESD occurred even though patients did not develop prolonged seizures. Then, we compared the characteristics of the short (<30 min) and prolonged (≥30 min) first seizure groups, and performed further comparisons based on these finding.

Hoshino et al. reported a nationwide questionnaire survey on the epidemiology of acute encephalopathy in Japan [7], showing that AESD was the most common syndrome in Japan (282 cases, 28.7%). The median age of those patients was 1.7 years, and there was female dominance (59.6%). The most common etiological factors were HHV-6 (38.2%), followed by influenza virus (9.5%). There were a low mortality rate and a high occurrence of neurologic sequelae. Full recovery occurred in 28.7% of patients, mild to moderate sequelae in 41.1%, severe sequelae in 25.1%, and death in 1.4%. In this study, the median patient age was 19.3 months, and there was also female dominance. AESD occurred mainly during infancy, probably due to brain immaturity. Although the reason for female dominance is unclear, genetic susceptibility may play a role. As for the etiological factors, HHV-6 and influenza virus were also the most common in our study. The reason as to why HHV-6 is so common is that it mainly affects children aged 1–2 years old. Contrary to Hoshino et al., who reported no cases of bacterial infection, we had three AESD similar cases of bacterial infection and two cases of trauma [4-6]. Half of our patients were followed up for 2 years. In the final follow-up visit, full recovery was observed in 19 patients (44.2%) (no change in PCPC between the first assessment and the final follow-up), mild to moderate sequelae occurred in 22 (51.2%) (an increase of 1 or 2 points in PCPC), severe sequelae occurred in 1 patient (2.3%) (an increase of >2 in PCPC), and death occurred in 0 patients (0%). The prognosis seemed to be better than that of the nationwide survey [7]. One of the reasons may be the treatment strategy for AESD in the present study.

The treatment strategy for AESD has not been established yet. Generally, according to the influenza encephalopathy guidelines, methylprednisolone pulse therapy, intravenous immunoglobulin, and other therapies that suppress inflammatory cytokines are used [2]. However, there is no evidence of efficacy for any of these therapies in patients with AESD. We have previously reported that TTM within 6 h after onset might prevent the occurrence of acute encephalopathy [15,16]. Early treatment, especially within 6 h, may be needed to improve the outcome of acute encephalopathy. In fact, most of our patients did not develop neurologic sequelae or mild neurologic sequelae, and no patient died. Some studies also reported that early introduction of TTM immediately after febrile status epilepticus (FSE) may reduce the occurrence of AESD [17,18]. However, the most important limitation of TTM therapy is that it is difficult to differentiate AESD from FSE at the early acute stage, and FSE may be treated unnecessarily with TTM. On the contrary, some patients were started TTM within 6 h and experienced a biphasic seizure. Therefore, further investigation to elucidate the efficacy of TTM and find biomarkers to differentiate AESD and FSE at the early onset is needed.

We found a significant association between first seizure duration and the time between the first and second seizures. Such associations have never been previously reported. In our study, one patient had a first seizure duration between 400 to 600 min; when the results from

this patient were excluded from our analysis, the aforementioned associations were no longer present. Therefore, we must be cautious when interpreting these results. The longer first seizure duration cases in our study were probably due to many cases of transfer from previous hospitals. Although the pathophysiology of the second seizure of AESD has been still unknown, delayed cell death due to excitotoxicity is hypothesized [3,8]. That is, many neurons may die at the early period of brain insult of seizure excitotoxicity and recover at least partially. Later, secondary deterioration with second seizure or cytotoxic edema follows, probably caused by extracellular accumulation of glutamine/glutamate complex (Glx), as described later. Therefore, one may think that the longer the seizure, the more severe the brain damage (more accumulation of Glx or cytotoxic edema) is and the earlier the second seizure occurs. We could not elucidate why there was a significant association between first seizure duration and time between the first and second seizures. Claassen et al. reported 570 consecutive patients who needed continuous EEG and comatose patients (severe patients) who required a longer duration to detect the first electrographic seizure [19]. We speculate that if the first seizure is longer and the damage is stronger, the brain may need a longer time to recover activity. More studies are needed to confirm our speculation.

One of the interesting results of this study was that 1 out of 5 AESD occurred even though patients did not develop prolonged seizures (≥30 min). Although a mild form of AESD has been reported in cases with a brief seizure as the initial symptom [1], there has been no report of a bimodal distribution of AESD. The most important concern is the accuracy of seizure duration. In this study, the onset of the seizure was set based on the caregiver's description, and seizure cessation was determined by the ED physicians. However, our study showed that markers of seizure severity [20, 21], such as white blood cells and glucose, were statistically higher; creatinine kinase tended to be higher; and pH and base excess were significantly lower in the prolonged seizure group than in the short seizure group. These laboratory data support the accuracy of seizure duration. Another interesting result of our study is that the functional outcomes as evaluated by the PCPC were significantly worse in the prolonged seizure group at 1 month, 6 months, 1 year, and 2 years after disease onset. This result was compatible with our results that prolonged seizure groups had broader abnormal hyperintensity of DWI by MRI.

In the present study, 20.9% of the patients with AESD had a short first febrile seizure (<30 min). The specific pathogenesis of AESD is still unknown. However, excitotoxic neuronal damage occurs as the result of an increase in the Glx during the acute phase of AESD, as demonstrated by proton MR spectroscopy [8]. Glx elevation occurs upon injury to astrocytes, which play an important role in the regulation of extracellular glutamate levels. This may cause necrotic neuronal cell death or apoptosis as well as glial swelling, ultimately resulting in brain edema [8]. Takanashi et al. showed Glx elevation during the subacute stage of AESD, which supported the idea that excitotoxic neuronal damage likely plays an

important role in the pathogenesis of AESD [8]. Interestingly, one of the patients with AESD who had a short febrile seizure also had increased Glx, suggesting that prolonged febrile seizure is not necessarily the cause of AESD. Recently, mitochondrial dysfunction has been proposed to be related to the pathophysiology of AESD with the thermolabile phenotype of carnitine palmitoyl transferase II variation [22]. This result is compatible because febrile seizures may consume an excess of energy in the brain, thus leading to secondary mitochondrial dysfunction. Therefore, such a genetic link was suspected. Unfortunately, we did not perform genetic testing. Vasospasm is another possible pathophysiological mechanism of AESD [23]. We have previously reported two cases of patients with head trauma who exhibited AESD-like biphasic seizure and BTA on MRI [4]. Head trauma increases the risk of vasospasm, and the central sparing of DWI on MRI indicates ischemic damage [23]. However, in this study, only approximately 3 of 4 cases showed central sparing. Therefore, the pathophysiology of AESD may involve a combination of astrocyte deficiency, vasospasm, and metabolic dysfunction.

From another point of view, we speculate that nonconvulsive status epilepticus (NCSE) may be another cause of AESD in patients with short seizures. In this study, we showed that 9.3% of patients showed NCS in the second seizure (Table 1). In addition, patients with AESD monitored by reduced-lead EEG showed NCS during or after the first (21.4%) and second seizures (31.4%). EEG abnormalities or clustered subclinical seizures have been reported in patients with AESD, and some studies have demonstrated the advantages of EEG in diagnosing AESD [24]. Therefore, patients with short seizures may possibly have undetected subclinical seizures even though apparent convulsion stopped. In fact, only 3 of 9 patients who experienced short seizures received AED during the first episode of seizure. In addition, the mental status of only two patients showed immediate improvement after the first episode of seizure. Three patients showed somnolence; four patients showed motor dysfunction such as no ambulation, no sitting, or hemiparesis; and one patient had both somnolence and motor dysfunction. These neurological symptoms after the first seizure could have been caused by NCSE. Unfortunately, no patient with short first seizure underwent EEG in the ED during their first episode of seizure. Therefore, more studies are needed to confirm our speculation.

Although CT or MRI usually shows normal findings on day 1 or 2 in patients with AESD, BTA is typically shown between days 3 and 9. The affected lesions are usually in the frontal or frontoparietal cortex [1] and occasionally in the deep gray matter, including the basal ganglia and thalamus [25]. A previous study showed that brain lesions are more widespread in patients with severe AESD prognosis [25]. In the present study, all patients with short seizures showed bilateral frontal high intensity on DWI of MRI. However, patients with prolonged seizures showed more widespread lesions in the parietal, temporal, and occipital areas, thalamus, and caudate nucleus. In addition, the broad involvement of the

entire hemisphere was observed only in the prolonged seizure group. These results suggest that prolonged seizures may promote widespread brain damage and contribute to a worse prognosis.

The strengths of this study are the long-term data of consecutive patients with AESD and the detailed description of those patients. However, this study also has some limitations. First, although the number of patients included in our study was relatively large and the observation period was the longest compared to previous studies, our study was retrospective, and data were obtained from a single center. Second, as seizure duration was determined clinically, its accuracy may be questionable as the seizure information was obtained from the charts of emergency department physicians or databases. Therefore, we cannot describe more detailed neurological semiology. Third, comparing less severe patients and severe patients or elucidating factors related to neurologic sequelae was not studied because the prognosis of our study is quite better comparing to previous studies (the median PCPC was 2 even though our study included prolonged seizure patients). Finally, all our cases were evaluated using reduced-lead EEG. Due to the simplicity of the system, it is possible that EEG abnormalities were missed in the unmonitored areas of the brain. Nevertheless, despite these limitations, our study adds new insight into the pathophysiology of AESD.

In conclusion, we described the detailed clinical picture of AESD by retrospectively reviewing 18-year data of consecutive patients with AESD. Importantly, we found that 1 out of 5 AESD occurred even though patients did not develop prolonged seizures (≥30 min). A comparison between the two groups (first seizure duration <30 min and first seizure duration ≥30 min) revealed three main findings: first, patients with AESD who had shorter seizures had better prognosis than those with prolonged seizures; second, patients with AESD who had shorter seizures tended to have earlier occurrence of a second seizure; and third, high signal intensity on diffusion-weighted MRI was observed mainly in frontal areas, not diffusely in patients with shorter seizures, and in a broader area in patients with prolonged seizures. Future studies are needed to elucidate the pathophysiology of AESD.

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Conflicts of interest

The authors declare no conflicts of interest.

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Table 1. Demographics of the patients

Variables	Value
Age (months) (median (IQR))	19.3 (13.9, 27.9)
Sex (male), n (%)	17 (39.5)
PCPC upon initial assessment (median (IQR))	1.0 (1.0, 1.5)
PMH of febrile seizure, n (%)	13 (30.2)
PMH of epilepsy, n (%)	2 (4.7)
Clinical presentation	
Type of first seizure (n) (%)	
Generalized convulsion	39 (90.7)
Hemiconvulsion	4 (9.3)
First seizure duration (min), median (IQR)	53 (49.5, 56.5)
Biphasic clinical course, n (%)	40 (93.0)
Time of second seizure from initial seizure (days), median (IQR) (n=40)	5.0 (4.0, 6.0)
Time of second seizure from initial seizure (h), median (IQR) (n=36)	95.5 (78.3, 112.9)
Type of second seizure, n (%)	
Convulsion (cluster)	20 (46.5)
Convulsion (once, <30 min)	12 (27.9)
Convulsion (once, ≥30 min)	1 (2.3)
Ocular movement abnormalities only	3 (7.0)
NCS by EEG	4 (9.3)
None	3 (7.0)
TTM, n (%)	19 (44.2)
Steroid pulse, n (%)	7 (16.3)
Intubation, n (%)	26 (60.5)
AED	
First seizure	
DZPsp	10 (23.3)
DZPiv	20 (46.5)
MDLim	4 (9.4)
MDLin	2 (4.7)
MDLiv	21 (48.8)
MDLdiv	10 (23.3)
PBiv	6 (14.0)
f-PHTiv	18 (41.9)
Thiamylal or thiopental	14 (32.6)
LEV	1 (2.3)
None	7 (16.3)
Second seizure	
DZPsp	2 (4.7)
DZPiv	4 (9.3)
MDLiv	15 (34.9)
MDLdiv	8 (16.6)
PBiv	14 (32.6)
PBsp	2 (4.7)
f-PHTiv	10 (23.3)
Thiamylal	4 (9.3)
LEV	2 (4.7)
CBZpo	1 (2.3)
None	1 (2.3)

Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; div, drip infusion in vein; DZP, diazepam; EEG, electroencephalogram; f-PHT, fos-phenytoin; h, hour; im, intramuscular; in, intranasal; iv, intravenus; IQR, interquartile range; LEV, levetiracetam; MDL, midazolam; min, minute; NCS, non-convulsive seizure; PB, phenobarbital; PCPC, Pediatric Cerebral Performance Category; PMH, past medical history; po, per os; sp, suppository; TTM, targeted temperature management

Table 2. Results of patient EEG monitoring, MRI, etiology, laboratory data, and prognosis

Variables		Value
EEG monitoring, n (%)		
During or after the first seizure		14 (32.6)
During or after the second seizure		35 (81.4)
NCS detection, n (%)**		
During or after the first seizure		3 (21.4)
During or after the second seizure		11 (39.3)
MRI performed, n (%)		43 (100)
Days of performed MRI, median (IQR)		6 (5.0, 8.5)
MRI DWI abnormality, n (%)		29 (67.4)
Hemisphare affected		8 (27.6)
Area of high DWI in MRI***		
Anterior		28 (96.6)
Parietal		16 (55.2)
Posterior		12 (41.4)
Temporal		6 (20.7)
Basal ganglia		0 (0)
Thalamus		3 (10.3)
Cerebellum		0 (0)
Brainstem		0 (0)
Caudate nucleus		1 (3.4)
Globus pallidus		1 (3.4)
Hippocampus		1 (3.4)
Central sparing in MRI		
Yes		24 (82.8)
Etiology, n (%)		
HHV-6		4 (9.3)
Influenza A		4 (9.3)
Echovirus type3		2 (4.7)
Echovirus type9		1 (2.3)
RSV		1 (2.3)
Unknown		31 (72.1)*
Laboratory data (median (IQR))		
WBC	(n=40)	14,500 (9,058, 19,925)
Hb	(n=40)	11.9 (11.4, 12.5)
PLT	(n=40)	29.8 (20.3, 38.3)
AST	(n=40)	48 (35, 62)
ALT	(n=39)	20 (14, 28)
CK	(n=34)	131 (94, 190)
LDH	(n=37)	347 (300, 397)
CRE	(n=39)	0.32 (0.29, 0.40)
Na	(n=38)	136 (134, 138)
Ca	(n=33)	8.9 (8.7, 9.4)
GLU	(n=36)	186 (137, 257)
CRP	(n=38)	0.3 (0.2, 0.8)
pH	(n=31)	7.15 (6.95, 7.29)
BE	(n=29)	-9.4 (-13.3, -4.3)
Lac	(n=25)	3.3 (2.1, 4.8)
PCPC, median (IQR)		
Upon initial assessment	(n=43)	1.0 (1.0, 1.5)
Months after the event		
1	(n=42)	2.0 (1.0, 3.0)
6	(n=41)	2.0 (1.0, 3.0)
12	(n=36)	2.0 (1.0, 3.0)
24	(n=28)	2.0 (1.0, 3.0)

*Five patients were clinically diagnosed with exanthema subitum and one patient was clinically diagnosed with hand-foot-and-mouth disease.

**Calculation was conducted by number of patients detected/number of patients with the EEG monitoring.

***Calculation was conducted by number of patients detected/number of patients with MRI DWI abnormality.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, base excess; CK, creatine kinase; CRE, creatinine; CRP, C-reactive protein; DWI, diffusion-weighted image; EEG, electroencephalogram; GLU, glucose; Hb, hemoglobin; HHV, human herpes virus; IQR, interquartile range; Lac, lactate; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NCS, non-convulsive seizure; PCPC, Pediatric Cerebral Performance Category; PLT, platelet; RSV, respiratory syncytial virus; WBC, white blood cell count

Table 3. Demographics, AED administration, and outcomes between seizure duration <30 min (n = 9) and ≥30 min (n = 34) in patients with AESD

	First seizure duration: <30min	Number of patients assessed	First seizure duration: ≥30min	Number of patients assessed	p value
Age (months), median (IQR)	14.0 (13.7, 17.7)	n=9	19.8 (14.3, 32.3)	n=34	0.0782
Sex (male), n (%)	4 (44.4)	n=9	13 (38.2)	n=34	1.0000
PMH of febrile seizure, n (%)	1 (11.1)	n=9	12 (35.3)	n=34	0.2366
PMH of epilepsy, n (%)	0 (0.0)	n=9	2 (5.9)	n=34	1.0000
Duration of first seizure (min), median (IQR)	4.0 (2.0, 8.0)	n=9	72.0 (51.8, 118.5)	n=34	<0.0001*
Days from initial symptom until first seizure	2.0 (1.0, 2.0)	n=9	1.5 (1.0, 2.0)	n=34	0.8829
Days from fever until first seizure	1.0 (1.0, 2.0)	n=9	1.0 (1.0, 2.0)	n=34	0.9038
Time from first until second seizure (h)	87.0 (74.5, 97.8)	n=9	100.3 (81.1, 117.9)	n=27	0.1765
Days of performed MRI, median (IQR)	6.0 (5.0, 6.0)	n=9	7.0 (5.0, 9.0)	n=34	0.1995
High-density DWI detected in MRI, n (%)	8 (88.9)	n=9	21 (61.8)	n=34	0.2307
Hemisphare affected, n (%)	0 (0.0)		8 (38.1)		0.0662
Area of high DWI in MRI, n (%)**		n=9		n=21	
Anterior	8 (100)		20 (95.2)		1.000
Parietal	2 (25.0)		14 (66.7)		0.0923
Posterior	1 (12.5)		11 (52.4)		0.0926
Temporal	0 (0)		6 (28.6)		0.1477
Basal ganglia	0 (0)		0 (0)		-
Thalamus	0 (0)		3 (14.3)		0.5402
Cerebellum	0 (0)		0 (0)		-
Brainstem	0 (0)		0 (0)		-
Caudate nucleus	0 (0)		1 (4.8)		1.000
Globus pallidus	0 (0)		1 (4.8)		1.000
Hippocampus	0 (0)		1 (4.8)		1.000
Anterior only	5 (62.5)		2 (9.5)		0.0079**
Central sparing in MRI, n (%)	8 (100)		16 (76.2)		0.0433**
AED administration for the first seizure, n (%)		n=9		n=34	
None	6 (66.7)		1 (2.9)		<0.0001**
Pre-hospital	1 (11.1)		2 (5.9)		0.5151
First line	1 (11.1)		5 (14.7)		1.0000
Second line	1 (11.1)		13 (38.2)		0.2307
Third line	0 (0)		14 (41.2)		0.0204**
AED administration for the second seizure, n (%)		n=9		n=31****	
None	2 (22.2)		5 (16.1)		0.6446
Pre-hospital	0 (0)		0 (0)		-
First line	1 (11.1)		2 (6.5)		0.5450
Second line	5 (55.6)		22 (71.0)		0.4371
Third line	1 (11.1)		2 (6.5)		0.5450
EEG monitoring, n (%)					
During or after the first seizure	0 (0)		14 (41.2)		0.0204**
During or after the second seizure	4 (44.4)		31 (91.2)		0.0055**
NCS detection, n (%)		n=9		n=34	
During or after the first seizure	-		3 (21.4)***		-
During or after the second seizure	0 (0)		11 (35.5)***		0.0433**
Intubation, n (%)	1 (11.1)	n=9	25 (73.5)	n=34	0.0012**
Laboratory data, median (IQR)					
WBC	5,345 (4,825, 9,698)	n=6	16,100 (11,675, 20,638)	n=34	0.0112*
Hb	12.0 (11.1, 12.1)	n=6	11.9 (11.4, 12.6)	n=34	0.7329
PLT	25.6 (15.9, 37.7)	n=6	29.8 (22.9, 37.9)	n=34	0.6091
AST	47 (41, 52)	n=6	48 (34, 70)	n=34	0.7909
ALT	21 (16, 22)	n=6	18 (14, 29)	n=33	0.9533
CK	94 (90, 119)	n=6	139 (105, 200)	n=28	0.0946
LDH	308 (292, 376)	n=6	351 (300, 409)	n=31	0.4966
CRE	0.27 (0.24, 0.31)	n=6	0.33 (0.29, 0.40)	n=33	0.0428*
Na	136 (134, 139)	n=6	136 (134, 138)	n=32	0.8721
Ca	9.1 (8.6, 9.3)	n=6	8.9 (8.7, 9.5)	n=27	0.8154
GLU	112 (94, 134)	n=5	197 (174, 272)	n=31	0.0042*
pH	7.36 (7.29, 7.39)	n=4	7.07 (6.95, 7.28)	n=27	0.0315*
BE	-2.6 (-3.5, -1.8)	n=3	-10.4 (-13.8, -6.4)	n=26	0.0264*
PCPC, median (IQR)					
Initial assessment	1.0 (1.0, 1.0)	n=9	1.0 (1.0, 2.0)	n=34	0.2345
Months after the event					
1	1.0 (1.0, 2.0)	n=9	2.0 (2.0, 3.0)	n=33	0.0081*
6	1.0 (1.0, 1.0)	n=9	2.0 (1.0, 3.0)	n=32	0.0138*
12	1.0 (1.0, 1.3)	n=8	2.0 (2.0, 3.0)	n=28	0.0088*
24	1.0 (1.0, 1.3)	n=4	2.0 (2.0, 3.0)	n=24	0.0362*

*Mann-Whitney U test identified significant differences.

**Fisher's exact test identified significant differences.

***Calculation was conducted by number of patients detected/number of patients with the EEG monitoring.

****Three patients did not show second seizure. Therefore, 31 patients were analyzed.

*****Calculation was conducted by number of patients detected/number of patients with MRI DWI abnormality.

Abbreviations: AED, antiepileptic drug; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, base excess; CK, creatine kinase; CRE, creatinine; DWI, diffusion weighted image; EEG, electroencephalogram; GLU, glucose; h, hour; Hb, hemoglobin; IQR, interquartile range; Lac, lactate; LDH, lactate dehydrogenase; m, minute; MRI, magnetic resonance imaging; NCS, non-convulsive seizure; PCPC, Pediatric Cerebral Performance Category; PLT, platelet; PMH, past medical history; WBC, white blood cell count