syndrome had acute encephalopathy. Although this result can be largely overestimated, the incidence of acute encephalopathy among children with Dravet syndrome will be more frequent than that among general children. It is estimated that acute encephalopathy develops in 500–1,000 among 17 million children every year in Japan. These facts indicate that children with Dravet syndrome will be at an increased risk for acute encephalopathy.

It is remarkable that the seizure frequency before the onset of acute encephalopathy was relatively low in a majority of our patients. Three children had no seizures and seven had monthly seizures during the 3 months before the onset of encephalopathy. Given the refractory nature of Dravet syndrome, antiepileptic drug treatment was appropriate in our patients because of lower seizure frequency. We must be aware that acute encephalopathy can develop in children with Dravet syndrome unexpectedly, even if the seizures are well controlled by AEDs.

The neuroimaging findings and the severity of the sequelae in our children may be related to the type of *SCN1A* mutation, although statistical analyses could not be performed because of the small sample size. Children with truncation *SCN1A* mutations tended to have cerebral cortex–dominant lesions and a poor outcome. Those with no mutation or a missense mutation tended to have subcortical-dominant lesions with a relatively favorable outcome. This suggests that children with a truncation *SCN1A* mutation may develop more severe acute encephalopathy. There is an ongoing controversy on the genotype–phenotype correlation of *SCN1A* mutations. Further studies with more patients are necessary to clarify the relationship between the type of *SCN1A* mutation and the severity of acute encephalopathy.

Recent genetic studies have revealed that the mutation in the *PCDH19* gene encoding protocadherin 19 is present in some female patients with Dravet syndrome (Depienne et al., 2009; Marini et al., 2010). The patients with Dravet syndrome with *PCDH19* mutations share most of the hallmark features of Dravet syndrome with *SCN1A* mutation including early onset, seizures provoked by fever, frequent SE, and stagnation of development (De Jonghe, 2011). The relation between acute encephalopathy and *PCDH19* mutation will be a subject of future studies.

Fever-induced refractory epileptic encephalopathy in school-aged children (FIRES) is a recently proposed clinical entity (Nabbout et al., 2011). Acute phase of FIRES is characterized by seizures rapidly aggravating into SE a few days to 1 week after febrile illness. Severe seizures and poor outcome are similar between FIRES and acute encephalopathy in children with Dravet syndrome. However, there are some differences between these two conditions. Onset in most children with FIRES is after fever had disappeared, whereas onset of encephalopathy is usually associated with fever in children with Dravet syndrome. Although repeated seizures up to 100 per day are common in children with FIRES, a long seizure refractory against AEDs is characteristic in acute encephalopathy in children with Dravet syndrome. FIRES usually occurs in previously healthy children, but a delay in psychomotor development is not uncommon prior to acute encephalopathy in children with Dravet syndrome. Therefore, these two clinical entities will be distinguishable.

In conclusion, we reviewed the clinical and neuroimaging features of acute encephalopathy in 15 children with Dravet syndrome. The acute encephalopathy was characterized by fulminant manifestations with SE and subsequent deep coma. Diffusion-weighted images revealed two different patterns of brain lesions: cerebral cortical–dominant lesions and subcortical-dominant lesions. The outcome was mostly poor, with death or severe neurologic sequelae.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Original article

Prognostic factors in acute encephalopathy with reduced subcortical diffusion

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Abstract

Objectives: Acute encephalopathy with reduced subcortical diffusion (AED) covers a spectrum including not only typical acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) but also atypical AESD with monophasic clinical course, or more severe subtypes. Aim of this study is to analyze prognostic factors of AED. *Materials & methods:* We recruited 33 children with AED, that is, widespread diffusion restriction in cortical and subcortical structures. Their clinical courses, laboratory data, MRI, and the efficacy of treatment were analyzed retrospectively. *Results:* Of the 33 children, 20 were males and the mean age at diagnosis was 22 months. Eighteen children had good outcome and 15 had poor outcome. Univariate analysis showed loss of consciousness 24 h after the onset, prolonged seizure at the onset, and mechanical ventilation to be weak predictors of poor outcome. Maximal aspartate aminotransferase, alanine aminotransferase, and creatinine kinase levels were significantly higher in the poor outcome group. Multivariate analysis showed loss of consciousness 24 h after the onset and prolonged seizure at the onset to be poor predictors of AED. Treatment with steroids and/or immunoglobulins did not result in better outcome. *Conclusion:* Prolonged seizure at the onset and loss of consciousness 24 h after the onset were seen at early stages of severe AED. Using these features, a prospective study of early intervention in AED should be conducted to further analyze the efficacy of its treatment.

Keywords: Encephalopathy; Reduced subcortical diffusion; Predictors; Seizure; Treatment

1. Introduction

Acute encephalopathy is a generic term for acute brain dysfunction caused by various agents such as infection, metabolic disease, and systemic disorders. Magnetic resonance imaging (MRI), especially diffusion-weighted images, is useful for detecting brain lesions in children with acute encephalopathy. Recently, several subtypes of acute encephalopathies have been established on the basis of MRI findings and clinical manifestations. Acute necrotizing encephalopathy shows multiple focal lesions of edematous necrosis which are symmetrically distributed in the bilateral thalami and other brain regions [1].

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Hemorrhagic shock and encephalopathy syndrome (HSES) have been defined mainly by clinical symptoms including fever, shock, disseminated intravascular coagulation [2]. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion is characterized by reversible reduced diffusion in the corpus callosum at least involving the splenium [3].

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is also a recently established subtype of acute encephalopathies. The features of AESD are seizure onset with no MRI abnormality, recovery of consciousness during the acute period, followed by late clustering seizures with worsening of consciousness and reduced subcortical diffusion [3,4]. Several acute encephalopathy syndromes proposed recently have similar features to AESD. Acute infantile encephalopathy predominantly affecting the frontal lobes shows biphasic clinical course and late reduced diffusion in the subcortical white matter [5]. Biphasic seizures were observed in almost all patients with human herpes virus-6 encephalopathy with cluster of convulsions during eruptive stage [6]. Therefore, AESD can be used as an umbrella clinical entity including these subtypes of acute encephalopathies.

Among the features of AESD, reduced subcortical diffusion is an outstanding neuroradiological hallmark, and reduced subcortical diffusion is important for the diagnosis. However, recent reports showed that reduced subcortical diffusion may present with patients who are not totally compatible with the features of AESD [7–11]. Our previous study showed that bilateral reduced subcortical diffusion can be seen in patients with a monophasic clinical course or reduced diffusion on the first or second day of illness [7]. Toyoshima et al. reported a child with HSES who presented bilateral reduced subcortical diffusion [12]. Moreover, Komatsu et al. revealed clusters of subclinical seizures in AESD in association with worsening of consciousness, using amplitude-integrated EEG [13]. This suggests that late seizures can be missed without EEG monitoring. These facts indicate that acute encephalopathy with reduced subcortical diffusion (AED) covers a spectrum including not only typical AESD but also atypical AESD with monophasic clinical course, or more severe subtypes such as HSES [7–12].

As we previously reported, AED with central-sparing lesions were relatively mild compared with those with diffuse lesions. Additionally, coma observed within 24 h after onset, lack of a biphasic clinical course, and higher maximal aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine kinase (CK) levels were significantly correlated with patients with diffuse lesions versus those with central-sparing lesions [7]. However, little has been reported on prognostic factors or treatment efficacy in AED. The purpose of this study was to analyze prognostic factors and the efficacy of treatment in children with AED.

2. Materials and methods

We identified 196 children with acute encephalopathy with disease onset between January 1998 and May 2009 from the database of the Tokai Pediatric Neurology Society, consisting of pediatric neurologists from Nagoya University, Juntendo University, Nagoya City University, and the hospitals affiliated with these universities. Acute encephalopathy was defined as a condition characterized by decreased consciousness with or without other neurologic symptoms, lasting >24 h in children with infectious symptoms, such as fever, cough, and diarrhea. Bacterial meningitis or metabolic errors were excluded from the study. The patients with pleocytosis were included, when there was no evidence of direct invasion of pathogens to the central nervous system.

In this study, AED was defined as acute encephalopathy presenting with (1) seizure onset, and (2) widespread reduced diffusion in the cortex and/or subcortical white matter involving unilateral or bilateral hemispheres (Fig. 1). Children fulfilling both criteria were diagnosed as AED, with or without biphasic clinical course, although biphasic clinical course is typical in children with AESD. We also included patients with a typical biphasic clinical course and atrophic changes that later presented in the cortex and/or subcortical white matter on conventional MRI, in whom diffusion-weighted images had not been performed. Children with neurological problems prior to the onset of acute encephalopathy were excluded.

Finally, 33 children from 13 hospitals met the criteria above and were enrolled in the study. We assessed their demographics and a detailed history using a structured report form. Their clinical course, laboratory data, MRI report, treatment, and their neurodevelopmental outcome were evaluated retrospectively.

In this study, the following data were investigated: age at diagnosis, gender, past history, developmental problems, and previous or family history of epilepsy or febrile seizures. The following values of the clinical course were also investigated: use of antipyretics before the onset, prodromal illness, level of consciousness for the first 10 days after the onset, presence or absence of prolonged seizures and delirious behavior, maximum body temperature, use of antiepileptic drugs, and the presence or absence of shock. A prolonged seizure was defined as a seizure lasting for 30 min or longer. A biphasic clinical course was defined as recovery of consciousness within 48 h after the initial seizure, to the level where the patient is alert without stimuli with or without loss of orientation, followed by re-emergence of seizures and further deterioration of consciousness. All patients were hospitalized from the onset and consciousness level was closely inspected by attending pediatricians and nursing staffs. We collected the following laboratory data on the day

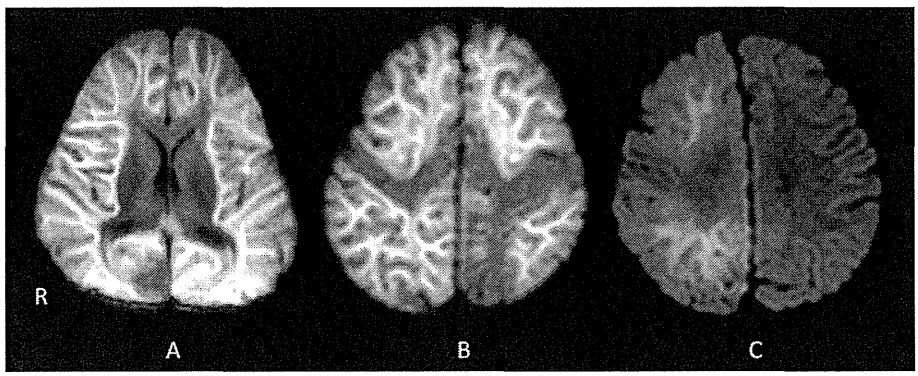

Fig. 1. Sample diffusion-weighted images of acute encephalopathy with reduced subcortical diffusion. (A) Diffuse reduced subcortical diffusion. Abnormal high intensities were observed in the whole subcortical white matter. (B) Bilateral reduced subcortical diffusion with central sparing. Abnormal high intensities were not observed in the bilateral central areas. (C) Unilateral reduced subcortical diffusion. Abnormal high intensities were not observed in the left hemisphere.

of admission and the worst values within 10 days after onset: platelet counts, AST, lactate dehydrogenase (LDH), CK, and cell counts and protein levels in the cerebrospinal fluid. The distribution of the brain lesion (unilateral or bilateral) was also obtained. Pleocytosis was defined as a leukocyte count of 8/mm^3 or more in cerebrospinal fluid. We examined whether or not there were any significances in patients characteristics, clinical symptoms, laboratory data, and treatment, before analyses. As a result, pleocytosis at the onset or within 10 days after onset did not have significant relationship with any factors studied in this study (data not shown).

Regarding treatment, we focused on the use of steroids and immunoglobulins. Early intervention was defined as steroid and/or immunoglobulin use within 48 h after the onset of AED. In our cohort, steroid treatment was administered in two regimens: steroid pulse therapy or intravenous dexamethasone. In cases with steroid pulse therapy, 30 mg/kg of methylprednisolone was administered for 3 days. Regarding intravenous dexamethasone, the dosage was 0.6 mg/kg/day for 2–5 days. Immunoglobulin was administered once at a dose of 1–2 g/kg to 11 patients, and five days at a dose of 400 mg/kg/day to one patient. None of our cohort went through high-dose barbiturate therapy, plasma exchange, or therapeutic hypothermia.

We divided the neurodevelopmental outcome of the patients into two groups: good and poor outcome. Trained pediatric neurologists judged the neurodevelopmental outcome as good when the patient had non-existent or mild cognitive and/or mild motor impairment, and patients were judged as poor when they had more severe neurologic impairment. The severity of cognitive impairment was classified according to the intelligence or development quotient as following: mild, 51–70; moderate, 30–50; and severe, <30. In the majority of patients, IQ or DQ were clinically estimated by the attending pediatric neurologists, although Wechsler Intelligent Scales for Children or Bayley Scales for Infant Development were performed in some patients. The severity of motor impairment was classified into three groups: mild if a patient could walk without support, moderate if a patient could sit without support but could not walk without support, and severe if a patient could not sit without support. The neurodevelopmental outcome was assessed beyond 6 month after the onset; if the patient was younger than 12 month of age at the onset, they were assessed beyond 18 month of age or at the point when walking was marked.

Statistical analyses were conducted using the Mann–Whitney *U*-test for numerical variables and the Fisher's exact probability test for categorical variables. Logistic-regression models were then used to further assess the association between variables and the neurodevelopmental outcome. Covariate factors for the logistic-regression model were selected from univariate analyses with p value < 0.2 or other factors that may relate to the outcome. Statistical analyses were performed with the SPSS software ver. 16.0 for Windows (SPSS Inc., Chicago, IL). A p value < 0.05 was deemed to indicate statistical significance. This study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

3. Results

3.1. Patient characteristics

Of the 33 children, 20 (61%) were males and the median age at diagnosis was 17 months (range, 4–92 months of age). One child had congenital adrenal hyperplasia with a daily oral steroid, and none had a history of epilepsy or developmental delay.

A pathogen in the prodromal illness was proven in 14 (42%) children: human herpesvirus (HHV)-6 in eight (24%), HHV-7 in 1 (3%), Coxsackie A virus in 2 (6%), influenza A in 1 (3%), mumps in 1 (3%), enteropatho-

genic *Escherichia coli* in 1 (3%). Additionally, three children (9%) were diagnosed with exanthema subitum from their clinical symptoms.

3.2. Patient characteristics, clinical courses, laboratory data, MRI, treatment, and the outcome

The neurodevelopmental outcomes were as follows: 18 children (55%) were judged to be good and 15 children (46%) were judged to be poor. Mild to severe cognitive impairment was present in 20 children (61%) and mild to severe motor impairment was present in 14 (42%). The patient with congenital adrenal hyperplasia had a good neurodevelopmental outcome. Among the 15 children with poor outcomes, nine had moderate or severe cognitive impairment and no or mild motor impairment, one had no cognitive impairment and moderate motor impairment, and five had both motor and cognitive impairment, ranging from moderate to severe.

Age of diagnosis, gender, past history or family history of febrile seizure, use of antipyretics before the onset, and interval between the prodromal illness and the AED onset were not related to outcome (Table 1). HHV 6 or 7 infection was more common in the children judged to have good outcomes ($p = 0.027$).

Four children (12%) were intubated during the acute stage; two at the onset, and the other two on days four and five. These four children had poor outcomes (Table 1). Moreover, 23 children (70%) with a decrease of consciousness 24 h after onset had a significantly higher rate of poor outcomes. Among them, all six children with coma 24 h after onset had poor outcomes. Twenty-five children (76%) were treated with antiepileptic drugs such as diazepam, phenobarbital, midazolam, or phenytoin within 48 h after the onset. Antiepileptic drugs within 48 h after the onset was not related to the outcome ($p = 0.604$) or to decreased consciousness 24 h after onset ($p = 0.170$). Biphasic course, a prolonged seizure at onset or any time during the acute stage, abnormal behavior, and maximal body temperature were unrelated to outcome. Two patients had shock at the onset, but both had good outcomes.

Laboratory data and outcomes are also shown in Table 1. None of the patients presented renal failure: urinary output was maintained and blood creatinine level was below 0.5 mg/dL. No laboratory data on admission was related to the outcome. Maximum AST, LDH, and CK values were higher in those with poor outcomes ($p = 0.005$, 0.034, and 0.025, respectively). The distribution of the lesion was not significantly related to outcome. Pleocytosis at the onset was present in eight children and was not correlated with outcome.

Steroids were administered in 24 children (73%) and, among them, 11 had steroid pulse therapy (Table 2). Steroids were used within 48 h after onset in eight children (24%), and two of them underwent steroid pulse therapy. Steroid use or steroid pulse therapy was not related to a good outcome. Immunoglobulin was administered to 12 children (36%) and three of them had immunoglobulin within 48 h of AED onset. Immunoglobulin was more commonly used in children with poor outcomes than those with good outcome. Treatment with steroid and/or immunoglobulin was unrelated to good outcome.

3.3. Multivariate analysis

Covariate factors for the logistic-regression models included family history of febrile seizure, prolonged seizure at the onset, biphasic clinical course, decrease of consciousness 24 h after the onset, age older than 2, HHV 6 or 7 related infection, and antiepileptic drug use within 48 h after the onset. Multivariate analysis showed that family history of febrile seizure ($p = 0.014$) and HHV 6 or 7 related infection ($p = 0.032$) was related to good outcome, while prolonged seizure at the onset ($p = 0.039$) and decrease of consciousness at 24 h after AED onset (0.022) were related to poor outcome (Table 3).

4. Discussion

This is the first reported study to overview the characteristics of AED as a broad spectrum covering AESD. We analyzed the characteristics and prognostic factors for AED including the efficacy of the treatment. In this study, we showed that prolonged seizure at onset, decreased consciousness 24 h after onset, mechanical ventilation, and higher maximum AST, LDH, and CK values were related to poor outcomes.

We recruited the subjects of this study with the emphasis on characteristic diffusion abnormalities, reduced subcortical diffusion. Thus, we used the term AED rather than AESD, considering that reduced subcortical diffusion can be observed in acute encephalopathies other than AESD. Some patients with reduced subcortical diffusion had a brief seizure only or even no seizure at onset [3]. Diffuse reduced subcortical diffusion was seen in patients with acute encephalopathy with monophasic and more severe clinical course [7]. At present, clear differentiation of AESD from its marginal subtypes is not easy. For this reason, we adopted simple and less robust inclusion criteria.

The pathogenesis of AESD is still unclear, but recent studies have suggested a relationship with excitotoxicity [4,14–17]. Studies using MR spectroscopy demonstrated that the amount of the glutamine/glutamate complex was elevated in patients with AESD, whereas the amount of these complexes in prolonged febrile seizures was normal [4,14]. A prolonged seizure may induce excitotoxicity, resulting in prolonged impairment of consciousness lasting over 24 h, leading to poor outcomes. Another possible explanation for the relationship between poor

Table 1
Patient characteristics, clinical course, laboratory data, MRI and outcome.

	Good outcome ($n = 18$)		Poor outcome ($n = 15$)		p value
Patient characteristics					
Age (months)	15	(4–40)	25	(8–92)	0.20
Male:female	10:8		10:5		0.55
Past history of febrile seizure	2	(11%)	3	(20%)	0.41
Family history of febrile seizure	8	(44%)	2	(13%)	0.058
Antipyretics before the onset	6	(38%)[*1]	3	(25%)[*2]	0.43
HHV 6 or 7 related infection	10	(56%)	2	(15%)	0.012
Interval from the prodromal illness to the onset of AED (days)	1	(0–5)	1	(0–6)	0.75
Clinical factors					
Mechanical ventilation	0		4	(27%)	0.033
Prolonged seizure at the onset	6	(33%)	11	(73%)	0.052
Prolonged seizure throughout	9	(50%)	12	(80%)	0.074
Biphasic clinical course	15	(83%)	9	(60%)	0.14
Unclear consciousness 24 h after onset	9	(50%)	14	(93%)	0.0094
Abnormal behavior	2	(11%)	4	(27%)	0.24
Maximum body temperature (°C)	40.0	(36.6–40.9)	39.7	(38.3–41.3)	0.55
Laboratory data					
PLT on admission ($\times 10^4$/mL)	23.1	(12.5–58.3)	32.9	(9.9–49.2)	0.10
AST on admission (IU/L)	44	(28–5685)	38	(28–235)	0.44
LDH on admission (IU/L)	336	(249–699)	387	(264–752)	0.49
CK on admission (IU/L)	112	(46–786)[*3]	137	(71–7395)	0.35
Sodium on admission (mmol/L)	134	(126–142)	135	(129–139)	0.65
Blood glucose on admission (mmol/L)	9.6	(2.3–19.8)	9.2	(2.8–24.4)	0.81
CSF cell count on admission (/mL)	3	(0–28)[*3]	3	(0–40)[*3]	0.51
Pleocytosis on admission	4	(31%)[*2]	4	(33%)[*3]	0.61
CSF protein on admission (mg/dL)	17	(6–24)[*3]	17	(8–117)[*3]	0.71
Minimal PLT ($\times 10^4$/mL)	14.5	(11.3–44.5)	18.0	(3.2–41.5)	0.20
Maximal AST (IU/L)	79	(35–239)	129	(88–4225)	0.005
Maximal LDH (IU/L)	538	(316–1381)	815	(264–5560)	0.034
Maximal CK (IU/L)	211	(52–6500)	749	(71–7395)	0.025
Minimal Sodium (mmol/L)	132	(126–141)	134	(126–139)	0.27
Maximal blood glucose (mmol/L)	8.7	(4.4–19.8)	10.3	(6.3–24.4)	0.20
Minimal blood glucose (mmol/L)	4.5	(2.3–6.3)	4.6	(3.2–5.1)	0.98
Maximal CSF cell count (/mL)	4	(0–233)[*4]	4	(2–3424)[*5]	0.32
Maximal CSF protein (mg/dL)	18	(10–31)[*4]	19	(8–117)[*5]	0.52
Pleocytosis within 10 days after onset	6	(38%)[*4]	5	(36%)[*5]	0.61
MRI					
Bilateral lesions	13	(72%)	12	(80%)	0.46

Data shown as median (range) or n (%).
The serum reference levels are as follows: PLT, 13.0–37.0 ($\times 10^4$/mL); AST, 10–40 (IU/L); LDH, 115–245 (IU/L); CK 57–434 (IU/L).
HHV 6 or 7, human herpes virus 6 or 7; AED, acute encephalopathy with reduced subcortical diffusion; PLT, platelet counts; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatinine kinase; CSF, cerebrospinal fluid.
[*1] $n = 17$.
[*2] $n = 13$.
[*3] $n = 12$.
[*4] $n = 16$.
[*5] $n = 14$.

outcome and prolonged seizure and/or reduced consciousness may be that severe brain damage was expressed as severe neurologic symptoms, such as severe seizures and impairment of brain function. It is important that a prolonged seizure at AED onset and decreased consciousness 24 h after onset, which are recognizable as an early stage of AED, did correlate with poor outcome.

In contrast, none of the laboratory data on admission predicted the outcome of AED. Thus, clinical symptoms, rather than laboratory data, are important to suspect more severe AED. However, the diagnosis or early intervention of AED is quite difficult when MRI abnormalities lack within the first few days after onset. It is difficult to distinguish whether a patient had AED or a

Table 2
Treatment efficacy in acute encephalopathy with reduced subcortical diffusion.

Treatment	Good outcome ($n = 18$)	Poor outcome ($n = 15$)	p value
Within 48 h after onset			
Steroid use and/or IVIG	4 (22%)	5 (33%)	0.37
Steroid use*	2 (11%)	4 (27%)	0.24
Steroid pulse therapy	2 (11%)	0	0.29
IVIG	1 (6%)	2 (13%)	0.43
Throughout the clinical course			
Steroid use and/or IVIG	13 (59%)	13 (87%)	0.28
Steroid use*	8 (44%)	6 (40%)	0.80
Steroid pulse therapy	5 (23%)	6 (40%)	0.46
IVIG	3 (14%)	9 (60%)	0.010

Data shown as n (%).
IVIG, intravenous immunoglobulin.
* Steroid use excluding steroid pulse therapy.

Table 3
Multivariate analysis of factors related to acute encephalopathy with reduced subcortical diffusion.

Included factors	B (SE)	Odds ratio (95% confidence interval)	p value
Family history of febrile seizure	−4.2 (1.7)	0.015 (0.001–0.43)	0.014
HHV 6 or 7 related infection	−3.7 (1.6)	0.035 (0.002–0.75)	0.032
Prolonged seizure at the onset	3.0 (1.4)	19.8 (1.17–335.2)	0.039
Decrease of consciousness 24 h after the onset	4.0 (1.7)	51.9 (1.76–1535)	0.022

SE, standard error; HHV 6 or 7, human herpes virus 6 or 7.
Odds ratio <1 shows association with better outcome, and odds ratio >1 shows association with poorer outcome.

prolonged febrile seizure with post-ictal stupor. The factors we identified may be important for clinicians in starting early intervention.

Our analysis did not show significant efficacy of treatment with steroids and/or immunoglobulin. Early steroid pulse therapy has been reported to improve the prognosis in influenza encephalopathy and acute necrotizing encephalopathy [18–19]. Hypercytokinemia and hyperpermeability have been considered to be the main pathogenesis of these subtypes of acute encephalopathy. There have been several reports on cytokine levels in children with influenza-associated encephalopathy, including acute necrotizing encephalopathy and other subtypes of acute encephalopathy [20–22]. On the other hand, the cytokine levels of children with AESD were less elevated than those with other subtypes such as acute necrotizing encephalopathy [3,4,23]. The difference in the efficacy of steroids may be explained by differences in pathogenesis, according to the subtypes of acute encephalopathy. The timing of treatment is also important. Treatment for encephalopathy was started more than 48 h after the onset of the initial symptoms in a majority of our patients. A recent report stated that an axonal damage marker, tau protein, in cerebrospinal fluid in AESD was normal on day 1 and increased on day 3, between the initial and late seizures [17]. This suggests that treatment starting 3 days after onset may be too late to ameliorate brain damage. Although our study did not show the efficacy of steroids and/or immunoglobulin within 48 h, further prospective studies with a larger cohort are necessary to evaluate the early treatment of AED more precisely.

Multivariate analysis showed that family history of febrile seizures and HHV 6 or 7 infection may be related to favorable outcome. It is well-known that there is a genetic predisposition for febrile seizure. When a child has a first-degree relative with febrile seizures, the risk of febrile seizures is higher than that of general population [24,25]. We suggest that increased susceptibility to febrile seizures may also be related to increased susceptibility to acute encephalopathy and result in the excess of mild AESD among children with a family history of febrile seizures. Previous studies showed that HHV 6 infection is associated with the occurrence of febrile seizures [26]. HHV 6 or 7 infection may enhance the seizure susceptibility of each individual and increase the possibility of developing AESD in infected children. Further studies are required to clarify the relation between the outcome and the pathogen or susceptibility to febrile seizures.

There are several limitations to our study. We excluded children with more severe clinical course or with former neurological problems. This was done to

determine the efficacy of the treatment clearly, but may have resulted in a selection bias. Other limitations are related to the shortcomings of a retrospective study. For treatment, 26 children had steroid and/or immunoglobulin selected by the attending pediatricians, and seven children were not treated in the first 10 days after the onset, with no standard protocol. More intensive treatment was likely to be applied to more severely affected children. This bias will make it difficult to assess the efficacy of treatment. In order to clarify the efficacy of the treatment, prospective studies on early intervention with a standard protocol should be obtained. From this aspect, early diagnosis of AESD with objective findings is the most important problem to be solved. In our study, only 27% of patients had treatment within 48 h of the onset.

In conclusion, half of the children with AED had poor outcomes. Poor outcomes were related to prolonged seizure at the onset or mechanical ventilation support, decreased consciousness 24 h after onset, and higher maximum AST, LDH, and CK values. Treatment with steroids and/or immunoglobulins did not correlate with better outcome in our study. Prospective studies are necessary for further analysis of the efficacy of treatment.

Disclosure

We do not have any financial relationships with pharmaceutical companies, medical equipment manufacturers, biomedical device manufacturers, or any companies with significant involvement in the field of health care. This manuscript does not report results of clinical trial.

Conflict of interest statement

We have no conflict of interest in relation to this manuscript.

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Original article

Late-onset epilepsy in children with acute febrile encephalopathy with prolonged convulsions: A clinical and encephalographic study

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Abstract

The aim of this study is to analyze the characteristics of epilepsies as the sequelae of acute febrile encephalopathy with prolonged convulsions during childhood. Sixteen patients (M:F = 9:7) aged 2–13 years (mean 6.1 years) with history of febrile acute encephalopathy were retrospectively reviewed. These patients experienced febrile encephalopathy at the age of 11 months to 4 years, with 11 individuals presenting with findings of a biphasic clinical course ($n = 5$), frontal predominant ($n = 8$) lesions, and/or reduced diffusivity in the cerebral white matter on magnetic resonance imaging (MRI; $n = 3$). The remaining 5 patients had unilateral lesions that manifested the phenotype of hemiconvulsion–hemiplegia–epilepsy syndrome (HHES). Epilepsy emerged with a latent period of 2 months to 2 years after the acute phase of febrile encephalopathy. Head nodding or spasm with subsequent motion arrest and brief tonic seizures were the main seizure phenotypes. Ictal records of epileptic seizures were available in 9 patients. Epileptiform discharges with a focal or uneven distribution appeared at the seizure onset and lasted less than 1 s in all patients; these were followed by either generalized attenuation or fast activity in 8 patients with head nodding, spasm, or brief tonic seizures, and by localized fast activity in 1 patient with versive tonic seizures. Notably, the seizure onset area was often located outside the severe lesions on MRI, i.e., in the parietal areas in patients with frontal predominant lesions, and in the spared hemisphere of HHES. Although phenobarbital, zonisamide, carbamazepine, clobazam, clonazepam, and clorazepate were partially effective in some patients, daily seizures persisted in 11 patients. Callosotomy was performed in 2 patients, and beneficial effects were observed in both. These characteristics suggested a broad distribution of augmented excitability in these patients, resulting in the rapid propagation of epileptic activity in the initial phase of ictal phenomena. Thus, this study investigates the most severe subgroup of epilepsy following febrile acute encephalopathy and provides the basis for further exploration of the pathogenesis and treatment of characteristic seizures in this population.

Keywords: Acute encephalopathy; Acute infantile encephalopathy predominantly affecting the frontal lobes; Acute encephalopathy with biphasic seizures and late reduced diffusion; Head nodding

1. Introduction

Acute encephalopathy is a condition defined as rapid deterioration of brain function, and is caused by various etiologies. This condition is often provoked by febrile

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infections during infancy and early childhood, and several subtypes with distinct clinical features have been classically recognized: Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and acute necrotizing encephalopathy [1]. In addition, a category of acute encephalopathy that is characterized by the initial manifestation of prolonged febrile convulsions, biphasic clinical course, emergence of restricted diffusivity on magnetic resonance imaging (MRI) in the cerebral white matter at 3–8 days of illness ("bright tree appearance"), and a propensity for frontal lobe involvement has been recently proposed by Japanese child neurologists. This category has been termed acute encephalopathy of obscure origin with biphasic clinical course [2], acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF) [3], and acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [4]. Either of these terms may be applied to individual patients, depending on which of the aforementioned characteristics predominate or are lacking in their manifestations; however, these conditions are likely to represent the same entity. In addition, hemiconvulsion–hemiplegia–epilepsy syndrome (HHES) has as its onset prolonged febrile hemiconvulsion. Apart from patients with structural brain lesions due to vascular, infectious, and dysplastic etiologies [5], this clinical syndrome is characterized by residual epilepsy after a latent period, signal change on diffusion-weighted imaging, and genetic predisposition, which are similar to the characteristics of the aforementioned acute encephalopathy. Thus, many cases of HHES in Japan can be also regarded as hemispheric variants of this entity [6,7]. An inclusive concept of acute encephalopathy with febrile convulsive status epilepticus (AEFCSE) has also been proposed [1]. With hundreds of identified cases, this entity has been recognized as the most prevalent subgroup in acute febrile encephalopathy in Japan, and is becoming a social burden. The higher predominance of this condition in Japanese populations than in other countries, the family history of febrile convulsion in many cases, and the identification of *SCN1A* mutations in rare instances suggest a genetic predisposition for this type of acute encephalopathy [8,9], which may involve increased neuronal excitation and/or augmented inflammatory process in the central nervous system.

Despite the pertinent characterization of AEFCSE during the acute phase, the clinical features of this condition during the chronic phases have not been well delineated. Residual epilepsy as the sequela of AEFCSE is reported to complicate 65% of cases [10], but details are not available in terms of seizure phenotype, findings of electroencephalography (EEG), and response to antiepileptic treatment. We herein summarize the clinical and electrophysiological findings in post-AEFCSE epilepsy, which would provide a basis for the management of this patient population.

2. Subjects and methods

We identified 21 patients with a history of febrile acute encephalopathy who were admitted to our hospital between September 2007 and October 2011, mainly for evaluating residual epilepsy. All patients had disease onset with prolonged febrile seizures but no evidence of meningoencephalitis, including elevation of cerebrospinal fluid (CSF) cell counts and detection of pathogenic microorganisms in the CSF culture. Patients with Reye syndrome ($n = 1$), acute necrotizing encephalopathy ($n = 1$), severe anoxic episode during the course of encephalopathy ($n = 2$), and a preceding history of West syndrome/Lennox–Gastaut syndrome ($n = 1$) were excluded, and the clinical data of the remaining 16 patients were retrospectively reviewed through their medical charts (Table 1). These patients experienced encephalopathy with onset at the age of 11 months to 1 year and 10 months, and 11 individuals developed one or more of the findings of a biphasic clinical course ($n = 5$), frontal predominance ($n = 8$) and reduced diffusivity in the cerebral white matter on MRI ($n = 3$). The other 5 patients had unilateral lesions that manifested the phenotype of HHES. Thus, we could divide the patients into 2 groups: AEFCSE with bilateral hemisphere involvement ($n = 11$) and HHES ($n = 5$). None of these patients exhibited dysplastic lesions on MRI. The clinical findings of 1 HHES patient with an *SCN1A* mutation have been reported previously [11]. None of other patients had been examined by specific gene analysis.

To analyze epilepsy in these patients, data were collected with regard to the family history of convulsive disorders, past history of the patients, seizure phenotypes of residual chronic epilepsy, and developmental quotient assessed by either the Enjoji Developmental Assessment Scale or Kinder Infant Development Scale. We also reviewed the MRI findings on admission, ictal ($n = 12$) and interictal EEG, and magnetoencephalography (MEG; $n = 7$). Video EEG monitoring for ictal EEG recording was conducted using a standard 10–20 system. MEG was performed using a 204-channel MEG system (VectorView; Neuromag Co., Helsinki, Finland). Dipole sources with a goodness of fit greater than 80% were accepted and overlaid on the MRI results.

3. Results

3.1. Patient characteristics (Table 1)

The 16 patients (M:F = 9:7) were aged 2–13 years (mean 6.1 years) at the time of data collection. Two patients in the bilateral AEFCSE group had a history of febrile convulsions, and 1 patient in the HHES group had a history of epilepsy. All patients, including 2

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Table 1
Characteristics of patient.

Patient	Age	Sex	Past history	Family history	Onset of encephalopathy	Viral infection at the onset of encephalopathy	Frontal predominance	Biphasic course	Bright-tree appearance	Onset of epilepsy
Bilateral group (n = 11)										
1	10y	M			1y7m		+			1y9m
2	5y	M		FC	1y3m	Exanthema subitum	+			1y4m
3	13y	F	FC	FC	1y11m		+			4y8m
4	7y	M		FC	10m		+	+		1y6m
5	8y	F			1y3m		+		+	1y10m
6	7y	M		Epilepsy	1y3m			+		1y8m
7	9y	M			11m		+			1y2m
8	4y	F		FC	1y2m		+	+	+	3y6m
9	5y	M			1y10m		+		+	2y3m
10	3y	M	FC	FC	11m	HHV-6		+		1y10m
11	2y	F	FC		10m	HHV-6	+	+		1y4m
Unilateral group (HHES; n = 5)										
12	5y	F	Epilepsy	FC	1y4m	Rotavirus				7m
13	4y	F			1y1m	Exanthema subitum			+	1y3m
14	4y	M			1y8m					1y10m
15	4y	M	Birth asphyxia		1y4m	HHV-6				1y5m
16	8y	F	Neonatal hypoglycemia	FC	1y6m					2y

FC, febrile convulsion.

patients in the HHES group with a history of neonatal asphyxia or neonatal hypoglycemia, exhibited normal psychomotor development until the onset of encephalopathy. A family history of convulsive disorders was present in 6 patients (5 patients with febrile convulsion and 1 patient with epilepsy) in the bilateral group and 2 patients (2 patients with febrile convulsion) in the HHES group.

The patients experienced febrile encephalopathy at the ages of 11 months to 1 year and 10 months. HHV-6 and rotavirus were identified as causative pathogens for febrile illness in 3 and 1 patient, respectively, and an additional 2 patients presented with exanthema subitum at the onset of encephalopathy. Two patients had been administered theophylline for the treatment of asthmatic bronchitis. As previously mentioned, all of the patients manifested with prolonged febrile convulsion and subsequent impaired consciousness lasting longer than 48 h, and were diagnosed with acute encephalopathy. The duration of the initial seizure was longer than 30 min in 15 patients and 15 min in the remaining patient. The 5 patients with HHES presented with hemiconvulsions during this acute phase.

During the data collection period, the developmental quotient was below 20 in all 11 patients with bilateral AEFCSE, whereas it ranged 8–75 (mean 43) in the HHES patients. Four patients were ambulant, and an additional 4 individuals could maintain a sitting position or shuffle in the bilateral group; one individual was ambulant, and the other 3 could maintain a sitting position in the HHES group. The remaining patients were bedridden. One patient in the bilateral group was tube-fed; however, all of the other individuals could consume meals orally.

3.2. Seizure manifestations of late-onset epilepsy

In the bilateral AEFCSE group, epilepsy emerged at the ages of 1 year and 2 months to 4 years and 8 months, with an interval of 2 months to 3 years (7.8 months; mean) after resolution of the initial convulsions during the acute phase of illness. Multiple seizure types were observed in 4 patients. Seizure phenotypes in this group included head nodding with motion arrest ($n = 3$), spasm involving the trunk and extremities ($n = 2$), and versive ($n = 2$), brief tonic ($n = 5$, including 1 patient manifesting startle seizures provoked by auditory stimuli), myoclonic ($n = 1$), and complex partial ($n = 1$) seizures.

The onset of postencephalopathy epilepsy in the HHES group was between 1 year and 3 months and 2 years of age, with a latent period of 2–6 months after the acute phase, including 1 patient with a history of epilepsy with onset at the age of 6 months. Seizure manifestations in the 5 patients varied: hemitonic, head nodding with atonia/unilateral myoclonus, head nodding with fencing posture/brief tonic seizure provoked by startle, and generalized myoclonus/generalized tonic–clonic and complex partial seizures.

Overall, the duration of these seizures was less than 1 min. Seizures occurred daily, weekly, and monthly in 12, 1, and 1 patient, respectively, despite treatment with antiepileptics during the data collection period.

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3.3. Interictal and ictal EEG findings

At the onset of epilepsy, diffuse polyspike bursts with repetitive/periodic appearance characterized the interictal EEG of 5 patients in the bilateral AEFCSE group (Fig. 1A). Focal spikes were recorded in the other 11 patients, and the distribution was described as multifocal in 6 of them. The diffuse polyspikes were attenuated and evolved into rather localized epileptiform paroxysms during the follow-up period in all of the 5 patients (Fig. 1B). Among these patients, 3 patients showed the identical seizure manifestation of head nodding, spasm, or brief tonic seizures throughout the course despite the change in epileptiform activity. Myoclonus and complex

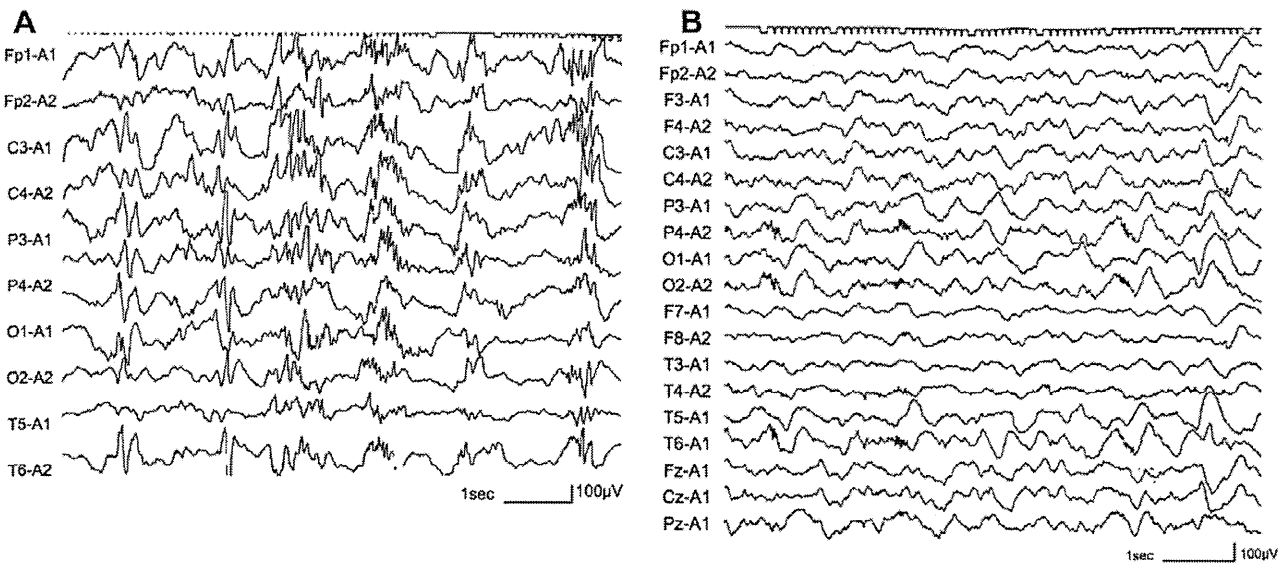

Fig. 1. Interictal electroencephalography (EEG) of a patient with bilateral acute encephalopathy with febrile convulsive status epilepticus (AEFCSE). The patient developed AEFCSE at the age of 1 year and 3 months and exhibited periodic bursts of diffuse polyspike activity at the onset of epilepsy (A). This pattern had disappeared at the age of 3 years and 4 months, and residual right posterior low-amplitude fast activity was observed (B).

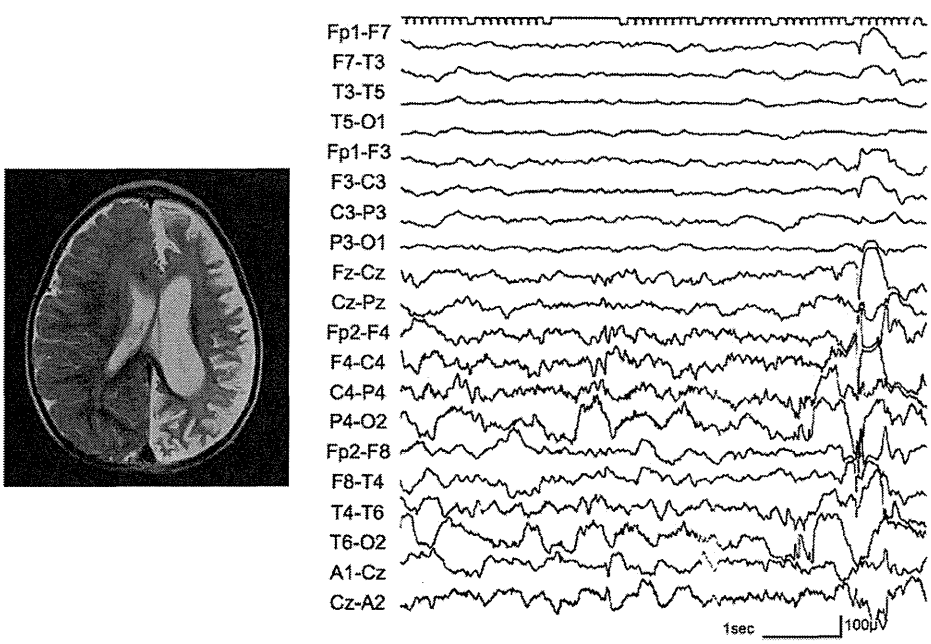

Fig. 2. T2-weighted magnetic resonance imaging (MRI) and interictal EEG of a patient with hemiconvulsion–hemiplegia epilepsy syndrome (HHES). The patient developed acute encephalopathy with hemiconvulsion–hemiplegia at the age of 1 year and 5 months. Atrophy of the left cerebral hemisphere, left-sided attenuated activity, and right-sided high-voltage slow waves with spike components were observed at the age of 2 years and 4 months.

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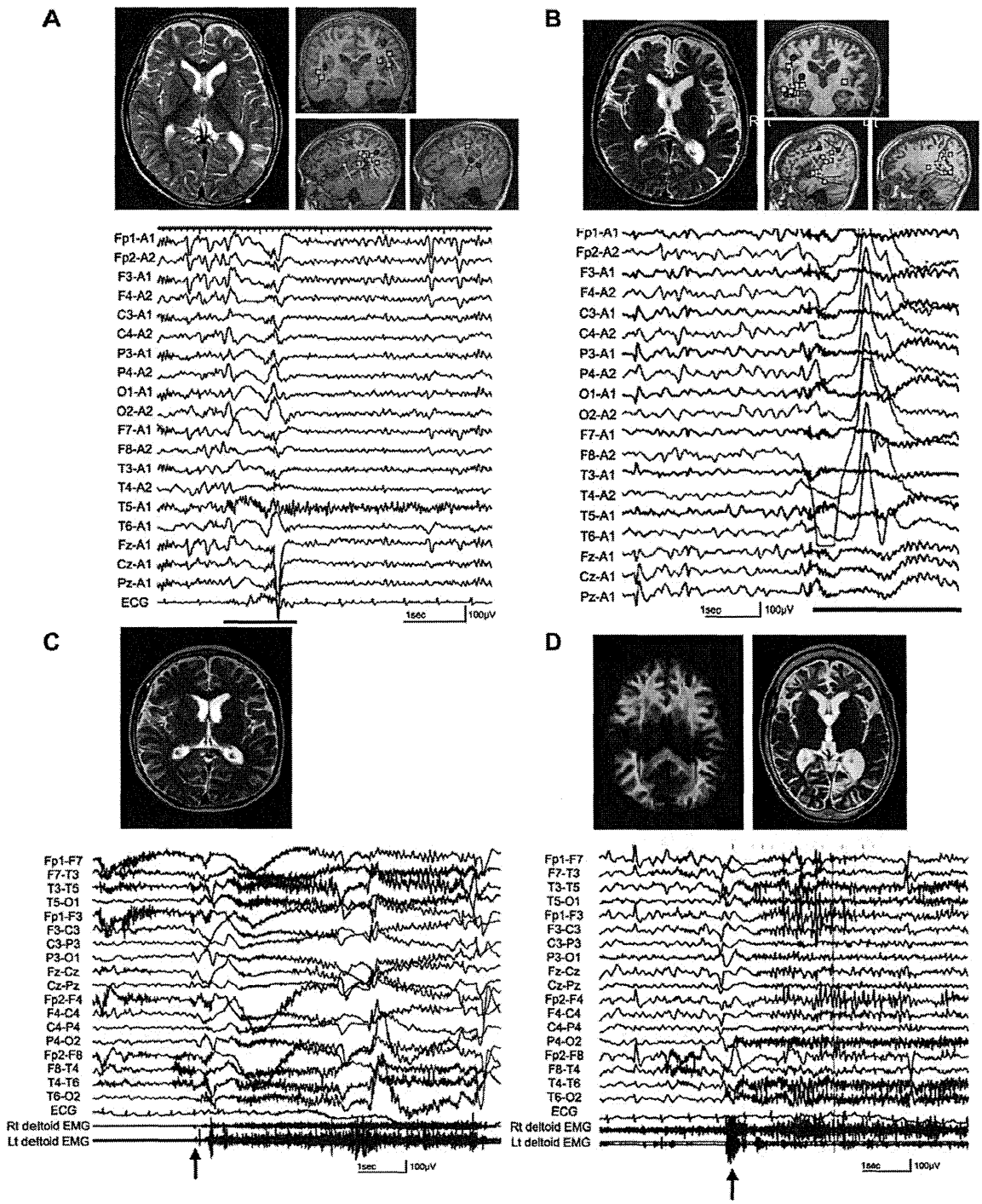

Fig. 3. MRI, magnetoencephalography (MEG), and ictal EEG of patients with bilateral AEFCSE. Dipoles with a goodness of fit exceeding 90% are drawn in yellow, and those with a goodness of fit of 80–90% are drawn in green. (A) A 5-year-old boy with a history of AEFCSE at 1 year and 3 months of age. MRI revealed diffuse cerebral atrophy, and dipole sources were identified bilaterally in the parietotemporal areas. The bar under the EEG tracing indicates the period of head nodding and forward bending of the trunk on sitting; an irregular train of sharp waves of less than 1 s preceded this event, and the waves were followed by diffuse attenuation or slow waves and subsequently by widespread slow waves superimposed by fast activity. Subsequently, diffuse, low-amplitude 10-Hz activity lasted several seconds, during which the patient appeared vacant with motion arrest. (B) Another 5-year-old boy with a history of AEFCSE at 11 months of age. Frontal predominant brain atrophy and bilateral dipoles over parietotemporal areas were observed. Brief tonic seizure (bar) was initiated by a parietal-predominant spike, followed by fast activity with left-sided predominance. (C) A 3-year-old boy with AEFCSE at 11 months of age. MRI revealed diffuse and mild brain atrophy. A tonic seizure was provoked by a handclap (arrow); EEG revealed diffuse slow waves superimposed by right-sided fast activity in the initial startle phase, followed by diffuse attenuation/10-Hz activity during the tonic phase of the seizure. (D) A 5-year-old boy with AEFCSE at 1 year and 10 months of age. A seizure emerged as a spasm at the beginning that was preceded by a parietal sharp wave (arrow), followed by fast activity in the T6 area, and subsequently followed by sharp wave bursts with bifrontal predominance during the tonic phase, accompanied by versive movement to the right side. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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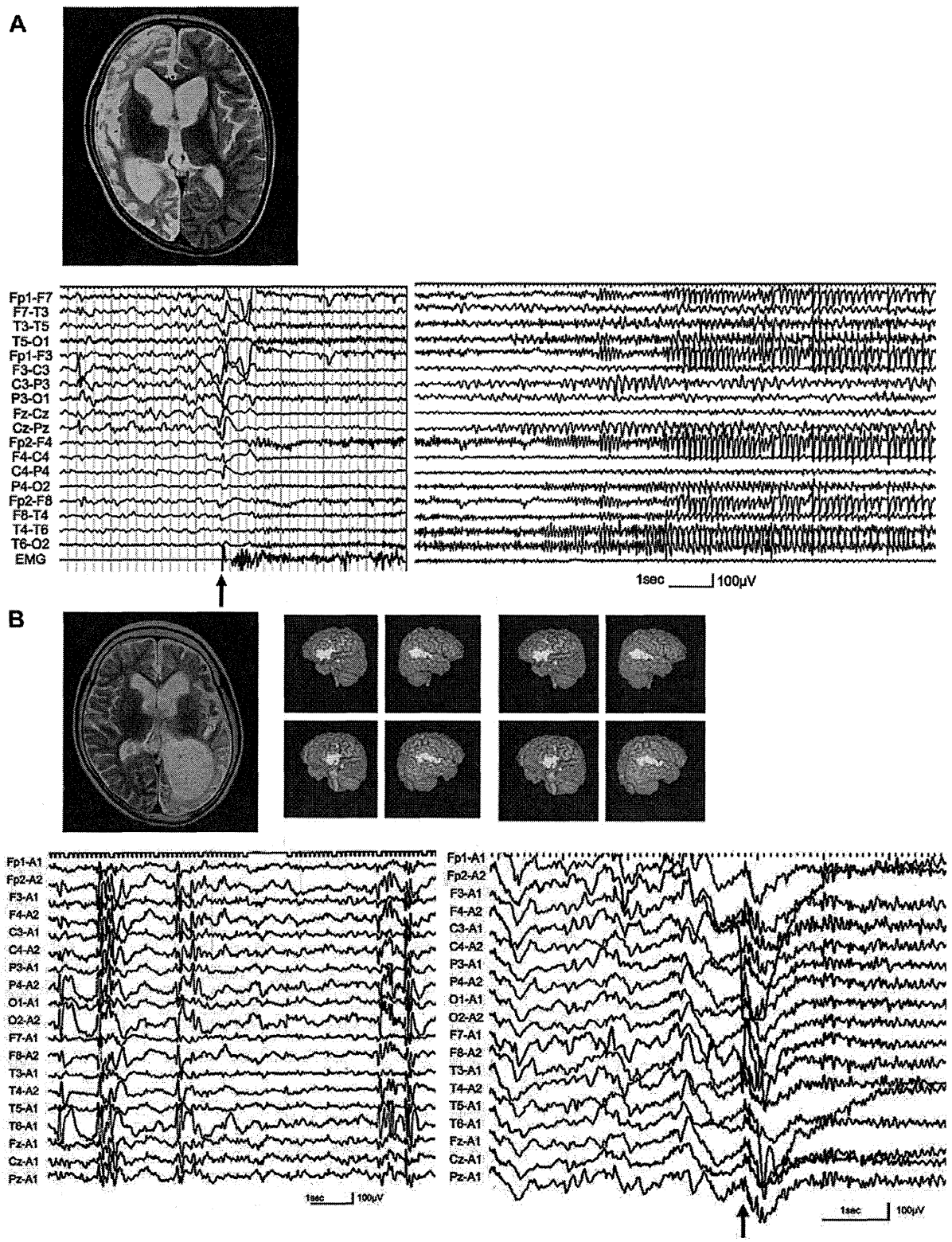

Fig. 4. MRI, MEG, and EEG of patients with HHES. (A) A 4-year-old boy with a history of HHES at the age of 1 year and 4 months. The right cerebral hemisphere was severely atrophic (top). On ictal EEG (bottom), an isolated spike in the C3/Cz areas (arrow) initiated a sudden tonic extension of the right extremities during sleep with bending of the head to the right. This was successively followed by diffuse attenuation, recruitment of 6–7-Hz activity with left centroparietal predominance, and then bursts of bifrontal spikes. (B) An 8-year-old girl with HHES at the age of 4 years. The left posterior hemisphere was severely atrophied. Dipole sources were clustered at the right supramarginal and superior temporal gyri and the left inferior frontal gyrus. On interictal EEG, epileptic discharges appeared with right-sided predominance (bottom left). Ictal EEG of head nodding with subsequent tonic extension of extremities revealed polyspikes with probable right frontal predominance (arrow) and subsequent generalized fast activity (bottom right).

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partial seizures in the other two 2 patients were replaced by spasm and brief tonic seizures a few years after the onset of epilepsy. The patients with HHES commonly exhibited attenuated background activity over the affected hemisphere, and polymorphic epileptic activity with spikes, polyspikes, sharp waves, and high-voltage slow waves predominantly over the spared hemisphere (Fig. 2).

Ictal EEG of epileptic seizures was available for 6 bilateral AEFCSE and 3 HHES patients. Regardless of the seizure manifestations, the ictal EEG data in the bilateral AEFCSE group were characterized by the onset with brief discharges with focal or uneven distribution (Fig. 3). In 5 patients, head nodding and spasm appeared during or just after these initial discharges. This initial phase was also present in the seizures regarded as brief tonic (Fig. 3B–D), where short-lasting muscle contraction at their beginning was identified. Another phase of motion arrest (Fig. 3A) or tonic phase (Fig. 3B–D) ensued, during which generalized attenuation or fast activity persisted on EEG (Fig. 3A–D), accompanied by brief bursts of sharp waves with bifrontal predominance in 1 patient (Fig. 3D). In the remaining patient with brief tonic seizures and subsequent automatism, focal fast activity remained localized to the frontal areas at its onset. The initial discharges presented as irregular trains of sharp waves (Fig. 3A) or a complex of spikes, slow waves, and fast activity with an uneven distribution (Fig. 3B–D). Notably, the regional predominance of this initial activity migrated to other areas during its brief duration of less than 1 s in a few patients, e.g., frontal to right hemispheric predominance (Fig. 3A) or parietal to right temporal areas (Fig. 3D). We also noted similar brief initial discharges of spikes (Fig. 4A) and sharp waves (Fig. 4B) with uneven distributions and subsequent generalization in the HHES group. Hemispheric lateralization of these initial discharges appeared with predominance on either the affected side (not shown) or the less affected side (Fig. 4A and B).

3.4. Localization of dipole sources in the interictal MEG investigation

MEG was performed in 5 bilateral AEFCSE and 2 HHES patients. In the former group with either frontal predominance or diffuse involvement during the acute phase, the dipole sources tended to cluster in the frontoparietotemporal junction areas, including the supramarginal and angular gyri (Fig. 3A and B). In HHES, dipole sources were identified at the right parietotemporal junction and left inferior frontal gyrus in 1 patient with left hemispheric lesions (Fig. 4B) and at the left precentral gyrus in another patient with left-sided lesions. No relationship was noted between the seizure onset areas on the ictal EEG and the areas of dipole clustering.

3.5. Effect of antiepileptic treatment and surgical intervention on postencephalopathy epilepsy

The number of antiepileptics that had ever been administered for persistent epilepsy in each patient was 2–12 (mean 4.8). Two patients in the bilateral AEFCSE group were seizure-free under treatment with valproate sodium (VPA) and zonisamide (ZNS) or carbamazepine (CBZ) and ZNS. For the remaining patients, drugs that had beneficial effects in apparently reducing the frequency and intensity of seizures were clonazepam for 3 of 5 patients; clobazam for 2 of 8 patients; clorazepate dipotassium for 2 of 3 patients; ZNS for 4 of 8 patients; CBZ for 3 of 6 patients; phenobarbital for 2 of 7 patients; VPA for 1 of 8 patients; potassium bromide for 1 of 3 patients; and lamotrigine for 1 of 4 patients. Phenytoin ($n = 3$), gabapentin ($n = 3$), acetazolamide ($n = 2$), topiramate ($n = 4$) and levetiracetam ($n = 1$) did not confer any beneficial effects. Callosotomy was conducted in 2 patients; hundreds of daily head nodding seizures in 1 bilateral AEFCSE patient were completely controlled for longer than 1 year after total callosotomy, and brief tonic seizures with frequent falls in an HHES patient became limited to focal myoclonus after partial callosotomy.

4. Discussion

The outcome regarding the intellectual and motor disabilities in this series of AEFCSE patients was severer compared to the reported prognosis of AEFCSE. According to a report on 10 patients with AIEF, 9 recovered to be ambulant, and 3 regained the ability to speak in sentences [3]. In another series of AEFCSE patients at a rehabilitation center, motor and intellectual disabilities were reported to persist in less than 30% and 90% of the 68 patients, respectively [10]. As the patients in the present study were referred to our hospital for the evaluation of intractable epilepsy, they should be regarded as representing the severest subgroup of AEFCSE. This selection bias may also have relationship to the high proportion of family histories of convulsive disorders in this patient group. Thus the patients are not representative of the whole AEFCSE group; however, the data here provide considerable information for understanding and managing AEFCSE patients in the chronic phase.

The HHES group displayed a somewhat different seizure manifestation than the bilateral AEFCSE group. Although one case was accompanied by a "bright tree appearance," no patient exhibited frontal predominance or a biphasic clinical course in the present series. The diffuse polyspike activity during the chronic phase in the bilateral AEFCSE group was not observed in the HHES group. The involvement of bilateral hemispheres may be essential for these characteristics, although the

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differential pathomechanisms explaining why either of these conditions affects individual patients remain to be elucidated. It is also unclear whether the residual diffuse polyspike activity during the chronic phase itself might have a detrimental effect on the brain function of certain patients as a type of epileptic encephalopathy.

In both of these groups, the presence of a latent period before the emergence of residual epilepsy was common to those with epilepsy after viral encephalitis, and this period was reported to be 0.8 ± 1.9 years [12] or 3.82 ± 3.7 years [13]. The prevalence of residual epilepsy in patients with AEFCSE has been reported to be as high as 65% [10], whereas that in patients with viral encephalitis with early seizures was 22% [14]. The cause of this high risk of complications is unclear, but the genetic propensity of neuronal excitability leading to febrile encephalopathy might have a relationship with this late epileptogenicity in AEFCSE.

In the majority of patients with bilateral AEFCSE in this study, ictal EEG revealed that the seizures were triggered by epileptic activity with an uneven distribution that spread either rapidly or after a brief migrating period to result in diffuse desynchronization or fast activity. Short-lasting motor phenomena of head nodding and spasm accompanied the initial phase of triggering activity (Fig. 3A), lasting into the phase of desynchronization to manifest as brief tonic seizures (Figs.3B–D and 4B) in some cases. These EEG findings and the biphasic motor manifestation do not accompany tonic seizures in typical symptomatic localization-related epilepsies, but they are reminiscent of the findings in epileptic spasms [15] and some cases of startle epilepsy [16]. Presumably, these characteristics represent the wide epileptogenic zone with multiple foci of augmented excitability, located within and outside the severely affected cortical regions in each case of the present series. This assumption is also applicable to the results in the HHES group; multifocal independent foci on interictal EEG involving the both hemispheres, propagation of epileptic activity that is faster and more widespread than usual, and the onset of ictal discharge in the contralesional hemisphere have been recognized in this syndrome [5,17]. These findings may again support the idea that bilateral AEFCSE and HHES could be regarded as a spectrum of disorders with a common entity. On the other hand, the characteristics of epilepsies in these groups may represent those in children subjected to catastrophic brain insults during infancy or early childhood. In addition, it remains to be elucidated whether the genetic predisposition for these syndromes involving the less severely affected brain regions are responsible for the pathogenesis of intractable postencephalopathy epilepsy. Despite these limitations in interpretation of the findings in this series of patients, the seizure and EEG characteristics are distinct from the findings regarding medial temporal lobe epilepsy due to hippocampal sclerosis that evolves after prolonged febrile convulsion in infancy. This fact would merit worldwide recognition.

In summary, we delineated for the first time the characteristics and prognosis of late-onset epilepsy in children with acute encephalopathy with onset of febrile prolonged convulsion. These findings provide useful information for the management of this chronic illness is children as well as clues to investigate the background condition related to the propensity for febrile encephalopathy.

Disclosure

None of the authors have any conflict of interest to disclose. Dr. Saito Y was supported for conduction of this study by Grant-in-Aid for Research on Measures for Intractable Diseases, No. H23-Nanji-Ippan-78, from the Ministry of Health, Labour and Welfare, Japan.

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