Table 1
Etiology of status epilepticus and prognosis.

Etiology of status epilepticus	No. of patients (%)	No. of patients with poor outcome (in-hospital deaths)
Cryptogenic	23 (11.4%)	0
Febrile	93 (46.3%)	0
Acute symptomatic	33 (16.4%)	16 (2)
Acute encephalopathy with inflammation- mediated status epilepticus	21	13 (2)
Acute encephalopathy with biphasic seizures and late reduced diffusion	11	7
Hemorrhagic shock and encephalopathy syndrome	3	3(2)
Clinically mild encephalitis/encephalopathy with a reversible splenial lesion	3	0
Acute necrotizing encephalopathy	1	1
Unclassified	3	2
Bacterial meningitis	4	1
Viral encephalitis	3	0
Cerebrovascular accident	3	0
Septic encephalopathy	2	2
Progressive encephalopathy	1 (0.5%)	0
Remote symptomatic	32 (15.9%)	0
Febrile on remote symptomatic	19 (9.5%)	0

(IQ/DQ < 50; $n = 2$; motor palsy in 1), and mild mental retardation or developmental delay (IQ/DQ < 70; $n = 4$; motor palsy in 1). On the other hand, 3 patients were normalized at the follow-up examinations; DQs became normal in 2, and hemiparesis improved in 1. The duration from SE onset to normalization ranged from 6 to 12 months in the 3 patients. Further, 2 patients who had had cerebral palsy (DQs, 38 and 67) exhibited developmental deterioration at discharge. Their prognoses were profound developmental delay (DQ < 20) at the follow-up periods of 16 and 42 months, respectively. Thus, these 2 patients died in the hospital, and 14 patients with neurological sequelae at the last follow-up examination were classified as poor outcome (8.0%, 16/201).

Of the 182 patients who did not reveal any developmental deterioration or new-onset neurological deficit at discharge, 165 (90.7%) were followed-up for at least 0.5 months (median, 22 months; range 0.5–65 months). At the last clinical evaluation, they were all judged as having no developmental deterioration and no new-onset neurological deficits.

3.2. Etiology of status epilepticus

The SE etiologies are listed in Table 1. In every case with poor outcome at the time of the last follow-up examination, including 13 patients with AEIMSE, 2 with septic encephalopathy, and 1 with bacterial meningitis, the etiology was acute symptomatic. Overall, there were 21 patients with AEIMSE cases, and the 13 patients exhibiting poor outcomes included 2 fatalities due to HSES (Table 1). Furthermore, 11 of the 21 patients with AEIMSE were also diagnosed as having AESD, of which 7 exhibited poor outcomes.

In patients with febrile SE (93 patients), AEIMSE (21 patients), and febrile on remote symptomatic (19 patients), clinical diagnoses of acute infection were common cold in 74, influenza virus infections in 18, viral gastroenteritis in 12 (rotavirus infections in 5), exanthem subitum in 12, viral bronchitis in 8, mycoplasma bronchopneumonia in 2, pneumonia in 1, chickenpox in 1, hand-foot-and-mouth disease in 1, herpetic stomatitis in 1, streptococcal pharyngitis in 2, and unknown in 1.

3.3. Early predictors of poor outcomes

Possible predictors were first divided into 2 or more categories. If the factors were first divided into 3 or more categories (e.g., age, seizure duration, and laboratory date), they were rearranged into 2 categories before being used for statistical analyses (Table 2). Poor outcome was higher in frequency in the 1–12- and 13–24-month age groups than in the 25–48- and 49–188-month age groups. Therefore, age was categorized as ⩽24 and >24-months for statistical analysis. The rate of poor outcome was similar between the patients with past febrile seizures and those with afebrile seizures; therefore, past seizures were simply categorized as "none" and "present." With regard to seizure duration, poor outcome was higher in frequency in the 91–120-min and >120-min groups than in the <60-min and 60–90-min groups. Therefore, seizure duration was categorized as ⩽90 and >90 min for statistical analysis. With regard to serum sodium levels, the rate of poor outcome in the patients with 131–135 and <131 mmol/L was higher compared with that in the patients with >135 mmol/L. Therefore, serum sodium levels were categorized as >135 and ⩽135 mmol/L. The rate of poor outcome in

Table 2
Possible predictors that were first divided into 3 or more categories.

Possible predictor	Category	All patients	Good outcome	Poor outcome	Recategorization
		n = 201	n = 185 (%)	n = 16 (%)	
Age at onset of SE	1–12	29	24 (72.8)	5 (17.2)	≤24
(month)	13–24	48	38 (79.2)	10 (20.8)	
	25–48	63	63 (100)	0 (0)	>24
	49–188	61	60 (98.4)	1 (1.6)	
Past history of seizure	None	121	108 (89.3)	13 (10.7)	None
	Febrile seizure	45	43 (95.6)	2 (4.4)	Present
	Afebrile seizure	35	34 (97.1)	1 (2.9)	
Seizure duration	<60	147	138 (93.9)	9 (6.1)	≤90
(minutes)	60-90	17	16 (94.1)	1 (5.9)	
	91–120	28	25 (89.3)	3 (10.7)	>90
	>120	9	6 (66.7)	3 (33.3)	
Serum sodium levels	>135	116	109 (94.0)	7 (6.0)	>135
(mmol/L)	131–135	71	65 (91.5)	6 (8.5)	≤135
	<131	14	11 (78.6)	3 (21.4)	
Blood glucose levels	<61	3	1 (33.3)	2 (66.7)	<61/ >250
(mg/dL)	61-100	16	16 (100)	0 (0)	61-250
	101–250	163	154 (94.5)	9 (5.5)	
	>250	19	14 (73.7)	5 (26.3)	<61/ >250
Serum AST levels	<56	177	171 (96.6)	6 (3.4)	<56
(U/L)	56-100	18	12 (66.7)	6 (33.3)	≥56
	>100	6	2 (33.3)	4 (66.7)	
White blood cell count	<5,001	8	8 (100)	0 (0)	≤15500
(cells/mm^3)	5001–15500	138	127 (92.0)	11 (8.0)	
	15501–20000	18	15 (83.3)	3 (16.7)	>15500
	>20000	37	35 (94.6)	2 (5.4)	
Serum CRP levels	<0.19	67	65 (97.0)	2 (3.0)	≤2.00
(mg/dL)	0.19–2.00	89	82 (92.1)	7 (7.9)	
	2.01-4.00	20	16 (80)	4 (20)	>2.00
	>4.00	14	11 (78.6)	3 (21.4)	

SE, status epilepticus; AST, aspartate aminotransferase; CRP, C-reactive protein.

the patients with blood glucose levels of <61 or >250 mg/dL was higher compared with that in the patients with blood glucose levels of 61–100 or 101–250 mg/dL. Therefore, blood glucose levels were categorized as 61–250 and <61 or >250 mg/dL (<61/>250 mg/dL). With regard to serum aspartate aminotransferase

Table 3
Univariate analysis of early predictors for poor outcome.

Possible predictor	Variable	All patients $n = 201$ (%)	Good outcome $n = 185$ (%)	Poor outcome $n = 16$ (%)	Odds ratio	95% confidence interval	P value
Sex	Male	105 (52.2)	95 (90.5)	10 (9.5)	1.000		
	Female	96 (47.8)	90 (93.7)	6 (6.3)	0.633	0.221–1.841	0.395
Age at onset of SE (month)	>24	124 (61.7)	123 (99.2)	1 (0.8)	1.000		
	⩽24	77 (38.3)	62 (80.5)	15 (19.5)	29.758	3.842–230.495	0.001*
Motor or mental developmental delay		42 (20.9)	36 (85.7)	6 (14.3)	2.483	0.847–7.280	0.097
Past history of seizure		80 (39.8)	77 (96.2)	3 (3.8)	0.324	0.089–1.175	0.086
Pyrexia during SE (⩾38.0 °C)		134 (66.7)	120 (89.6)	14 (10.4)	3.792	0.836–17.199	0.084
Proconvulsant drug		15 (7.5)	12 (80)	3 (20)	3.327	0.833–13.291	0.089
Seizure duration (>90 min)		37 (18.4)	31 (83.8)	6 (16.2)	2.981	1.009–8.805	0.048*
Type of seizure	Generalized	131 (65.2)	120 (91.6)	11 (8.4)	1.000		
	Focal	70 (34.8)	65 (92.9)	5 (7.1)	0.839	0.280–2.519	0.755
Mode of seizure	Continuous	175 (87.1)	163 (93.1)	12 (6.9)	1.000		
	Intermittent	26 (12.9)	22 (84.6)	4 (15.4)	2.47	0.732–8.332	0.145
Intractability of seizure		36 (17.9)	29 (80.6)	7 (19.4)	4.184	1.443–12.128	0.008*
Biphasic seizure		13 (6.5)	8 (61.5)	5 (38.5)	10.057	2.817–35.903	0.000*
Serum sodium levels (mmol/L)	>135	116 (57.7)	109 (94.0)	7 (6.0)	1.000		
	⩽135	85 (42.3)	76 (89.4)	9 (10.6)	1.844	0.658–5.166	0.244
Blood glucose levels (mg/dL)	61–250	179 (89.1)	170 (95.0)	9 (5.0)	1.000		
	<61/>250	22 (10.9)	15 (68.2)	7 (31.8)	8.815	2.876–27.015	0.000*
Serum AST levels (U/L)	<56	177 (88.1)	171 (96.6)	6 (3.4)	1.000		
	⩾56	24 (11.9)	14 (58.3)	10 (41.7)	20.357	6.449–64.257	0.000*
White blood cell count (cells/mm^3)	⩽15,500	146 (72.6)	135 (92.5)	11 (7.5)	1.000		
	>15,500	55 (27.4)	50 (90.9)	5 (9.1)	1.227	0.406–3.708	0.717
Serum CRP levels (mg/dL)	⩽2.00	167 (83.1)	158 (94.6)	9 (5.4)	1.000		
	>2.00	34 (16.9)	27 (79.4)	7 (20.6)	4.551	1.563–13.252	0.005*

SE, status epilepticus; AST, aspartate aminotransferase; CRP, C-reactive protein.

Table 4
Multivariate logistic regression analysis of early predictors for poor outcome.

Possible predictor	Odds ratio	95% confidence interval	*P* value
Age at onset of SE ⩽24 month	17.714	1.808–173.558	0.014*
Seizure duration >90 min	4.412	0.826–23.567	0.083
Intractability of seizure	4.940	1.012–24.125	0.048*
Biphasic seizure	3.319	0.472–23.357	0.228
Blood glucose level <61/>250 mg/dL	7.101	1.114–45.266	0.038*
Serum AST levels ⩾56 U/L	9.905	2.055–47.729	0.004*
Serum CRP levels >2.00 mg/dL	7.261	1.315–39.583	0.023*

SE, status epilepticus; AST, aspartate aminotransferase; CRP, C-reactive protein.

(AST) levels, the rate of poor outcome in the patients with 56–100 and >100 U/L was higher compared with that in the patients with <56 U/L. Therefore, AST was categorized as <56 and ⩾56 U/L. With regard to white blood cell (WBC) count, the rate of poor outcome was variable in each group; therefore, WBC count was categorized as ⩽15,500 and >15,500 cells/mm^3. The rate of poor outcome in the patients with C-reactive protein (CRP) levels of <0.19 or 0.19–2.00 mg/dL was lower compared with that in the patients with CRP levels of 2.01–4.00 or >4.00 mg/dL. Therefore, CRP levels were categorized as ⩽2.00 and >2.00 mg/dL.

Serum AST, ALT, creatine kinase, and lactate dehydrogenase levels were positively associated with each other (e.g., the correlation coefficient between AST and ALT was 0.578, $P < 0.01$). Therefore, only AST levels were used as an independent factor for analysis.

Univariate analysis indicated that age ⩽24 months, seizure duration >90 min, intractability of seizure, biphasic seizures, blood glucose levels <61 or >250 mg/dL, AST levels ⩾56 U/L, and CRP levels >2.00 mg/dL were associated with poor outcome (Table 3). Multivariate analysis revealed that young age, seizure intractability, abnormal blood glucose levels, and elevated AST and CRP levels were statistically significant (Table 4).

4. Discussion

4.1. Predictors of poor outcome

In this prospective multicenter study of 201 children presenting with SE, 16 exhibited poor outcomes (14 neurological sequelae; 2 in-hospital deaths). Age ⩽24 months was an independent early predictor in this study. Old age is an established risk factor for SE-associated mortality and morbidity in adults [9,10], primarily owing to the age-dependence of the etiology, considering that most SE episodes in the elderly are due to acute CNS insults, which are generally associated with poor outcomes. In contrast, studies on pediatric SE have indicated that young age is a risk factor for SE-associated mortality and morbidity [6,11–14]. In fact, 15 of the 16 patients with poor outcomes in our study were ⩽24 months old, which was consistent with the finding of another study [12] in which infants and young children were reported as more susceptible to acute systemic or CNS insults, including bacterial meningitis, encephalitis, septic shock, and head trauma. One series reported that AEIMSE onset was most common in infancy and early childhood, with maximum incidence at the age of 1 year [7]. Therefore, it is possible that the poor outcomes observed in young children with SE might indicate increased susceptibility to a distinct set of etiologies associated with an inherently poor outcome.

Seizure intractability was another independent early predictor of poor outcome. It is not surprising that seizure intractability was related to SE-associated mortality and morbidity [10,14]. Lambrechtsen et al. [14] studied refractory SE in children, which was identical to seizure intractability (failure of the second anticonvulsive drug) in this study, and reported that in-hospital mortality and long-term morbidity were significantly higher in refractory SE than in aborted SE. They also found that predictors of poor outcome were young age (<5 years), long seizure duration, and acute symptomatic etiology [14]. On the other hand, long seizure duration (>90 min) was not significantly associated with poor outcome in this study. A positive association between longer seizure duration and higher mortality/morbidity has been reported as well [6,11,14–16], although not always confirmed [12]. It is still controversial whether long-lasting seizure activity directly contributes to brain injury because seizure duration is also related to etiology.

In laboratory data acquired at SE onset, abnormal blood glucose levels and elevated AST and CRP levels were early predictors of SE-associated mortality and morbidity in our multivariate analysis. High AST levels could indicate SE etiology because they are usually high in septic encephalopathy and some AEIMSE subtypes with poor outcomes such as HSES and ANE. Furthermore, in a study of influenza-associated encephalopathy, high AST levels were identified as one of the mortality predictors [17]. Serum CRP status is positive in bacterial infections, including bacterial meningitis and septic encephalopathy, which were the conditions associated with the most severe outcomes in this series. Several reports have examined the correlation between blood glucose levels and outcomes in SE [13,17–20]. In-hospi-

tal death and neurological sequelae were associated with hypoglycemia in the studies of pediatric SE [13,20]. In the present study, in 2 of 3 patients with hypoglycemia, 1 was in septic shock and another had bacterial meningitis, resulting in neurological sequelae in both. Therefore, hypoglycemia could also be related to the etiology. On the contrary, poor outcomes were reported to be associated with hyperglycemia in Japanese children with influenza-associated encephalopathy [17] and in an adult SE series [18]. Hyperglycemia is common in the early stage of SE and is caused by high catecholamine drive. Mild hyperglycemia (blood glucose level; 101–250 mg/dL) was not related to prognosis in the present study nor in the AESD study [19]. Hyperglycemia is known to be a risk factor for poor prognosis in the cerebrovascular disease. The results of the present study indicate that severe hyperglycemia (>250 mg/dL) is also a risk factor for poor outcome in pediatric SE.

4.2. Etiology of poor outcome

The most important finding of this study is that the etiology of SE-associated mortality and morbidity in Japanese children was different from that identified in other countries. AEIMSE was the major cause, whereas other common disorders such as bacterial meningitis infrequently induced SE-associated mortality and morbidity in Japanese children. AEIMSE accounted for 81.3% poor outcomes. The incidence of AEIMSE in Japan is 302 cases per year, with complete recovery in 56.2%, mild to moderate sequelae in 22.1%, severe sequelae in 13.5%, and death in 5.6% [7]. In other countries, SE-associated mortality and morbidity are usually caused by bacterial meningitis, viral encephalitis, progressive encephalopathy, cerebrovascular disorders, hypoxic–ischemic brain injury, or lung and cardiac complications [6,11,13–15,21].

AEIMSE was first described as acute encephalopathies of obscure origin in infants and children by Lyon et al. [22]. They reported 16 children, who after several days of infectious disease, exhibited acute-onset disturbance of consciousness, convulsions, and fever with no evidence of CNS inflammation. Since this first description, the following 4 specific syndromes (subtypes) of AEIMSE have been identified through clinical and pathological investigation: Reye's syndrome, HSES, ANE, and idiopathic hemiconvulsion–hemiplegia syndrome. With the development of advanced imaging techniques such as diffusion-weighted MRI, new clinical AEIMSE subtypes (AESD and MERS) have been recognized [3–5]. In this study, the most common AEIMSE subtype was AESD, which is characterized by convulsive SE at onset followed by secondary seizures (biphasic seizures) from days 3–7, resulted in mental deterioration in most patients.

AEIMSE can be distinguished from primary encephalitis on the basis of several characteristics. First, the symptoms, clinical course, and imaging findings of AEIMSE, particularly AESD, MERS, and ANE, are quite distinct from those of primary encephalitis irrespective of the pathogen [7]. Second, CSF results in patients with AEIMSE are usually unremarkable [1,23]. Third, viral and bacterial cultures are negative, and viral DNA can seldom be isolated from CSF and autopsied brain [1,23,24]. Fourth, inflammatory changes are usually not observed in the autopsied brain of patients with AEIMSE [1,23,24].

Reye's syndrome and HSES have been reported mainly from Europe and the United States of America, whereas their occurrence is rare in Japan. Idiopathic hemiconvulsion–hemiplegia syndrome is reported throughout the world. ANE is relatively common in East Asia, but it has also been reported from Europe and American countries. Although most studies on AESD have been reported from Japan, a few have been reported from outside Japan as well [25,26]. A recent report demonstrated that East Asians and Japanese might have a genetic susceptibility to AEIMSE [27,28]. We speculate, on the basis of the present study, that prolonged seizures during febrile infection and genetic susceptibility in young children greatly increase AEIMSE risk.

4.3. Limitations

First, the early predictors of SE-associated mortality and morbidity observed in this study may not be generalized because the underlying cause of SE in Japanese children was different compared with that in other countries. Second, this study was not population-based; therefore, milder SE cases might have been missed. Third, patients who did not show any developmental deterioration or new-onset neurological deficit at discharge were all judged as having no sequelae at follow-up clinical evaluation. Subnormal mentalities or minor developmental delays may have been missed.

5. Conclusion

Our results yielded 2 valuable clinical conclusions. First, younger pediatric patients presenting with seizure intractability should be examined systematically to identify the etiology because they are at high risk of poor outcomes. Second, pediatric patients with SE during febrile illnesses accompanied by abnormal glucose level, high serum AST, or CRP levels are at a higher risk of severe bacterial infection or AEIMSE.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.braindev.2014.08.004.

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Drugs indicated for mitochondrial dysfunction as treatments for acute encephalopathy with onset of febrile convulsive status epileptics

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ABSTRACT

We studied the efficacy of drugs indicated for mitochondrial dysfunction in the treatment of 21 patients with acute encephalopathy with onset of febrile convulsive status epilepticus at our hospital from January 2006 to December 2014. Among them, 11 patients had been treated with a mitochondrial drug cocktail consisting of vitamin B1, vitamin C, biotin, vitamin E, coenzyme Q10, and L-carnitine (prescription group) and 10 patients were not treated with the cocktail (non-prescription group). We retrospectively reviewed age, trigger, clinical form, treatment start time, and sequelae. Clinical form was classified into a biphasic group presenting acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) and a monophasic group. Sequelae were classified as (A) no sequelae group or (B) sequelae group, and differences in the interval between diagnosis and treatment were also evaluated. The sequelae were not different between the mitochondrial drug cocktail prescription and non-prescription groups, but significantly better in the group administered the mitochondrial drug cocktail within 24 h ($P = 0.035$). We expect that early treatment with a mitochondrial drug cocktail could prevent sequelae in acute encephalopathy with onset of febrile convulsive status epilepticus.

1. Introduction

Acute encephalopathy with onset of febrile convulsive status epilepticus has mainly been reported in East Asia and is classified into several subtypes according to the clinical course and neuroimaging findings. Acute encephalopathy with onset of febrile convulsive status epilepticus can be difficult to distinguish from febrile seizure status and often results in severe neurological dysfunction. In some patients with acute encephalopathy with onset of febrile convulsive status, the epilepticus shows a biphasic course, and such cases are designated as acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [19]. AESD is clinically characterized by prolonged (>30 min) febrile seizures as the initial neurological symptom on day 1, followed by secondary seizures (most often in a cluster of complex partial seizures) associated with deterioration of consciousness level at days 4 to 6. Between the biphasic seizures, most patients present continuous disturbance of consciousness level, but some patients have normal, clear consciousness with no neurological symptoms, which may lead to an initial misdiagnosis of febrile seizure status. MRI shows no acute abnormality during the first two days, but reduced diffusion appears in the subcortical white matter during days 3 to 9 [19,20,22].

One possible cause of acute encephalopathy is depletion of energy resulting from decreased mitochondrial function [11]. In mitochondrial diseases, various vitamins and coenzymes have been used clinically based on their effects on energy shortage and oxidative stress [13], and effectiveness has been reported at high doses [12]. Therefore, this study aimed to examine the efficacy of a combination of vitamin B1, vitamin C, biotin, vitamin E), coenzyme Q10, and L-carnitine as a mitochondrial drug cocktail in the treatment of acute encephalopathy.

2. Methods

We defined acute encephalopathy based on criteria that have been reported as follows: (a) acute onset of severe and sustained impairment of consciousness after a preceding infection and (b) exclusion of CNS inflammation [5,10,15], in addition to level of consciousness equal to or below 13 on the Glasgow Coma Scale and duration of impairment longer than 24 h, according to the diagnostic criteria of the Japanese research committee on influenza encephalopathy. Following a previous

Abbreviations: AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ANE, acute necrotizing encephalopathy; CPTII, Carnitine palmitoyl transferase II.

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Table 1
Summary of the 21 patients.

Patient	Gender	Age (months)	Triggers	Clinical form	Sequelae
1	M	62	Influenza A virus	Monophasic	A
2	F	13	HHV-6	Monophasic	A
3	M	13	HHV-6	AESD	A
4	F	7	HHV-6	AESD	A
5	M	171	Influenza A virus	Monophasic	A
6	F	63	Enterovirus	AESD	B
7	F	64	Unknown	Monophasic	B
8	F	36	Rotavirus	AESD	A
9	M	21	Unknown	AESD	B
10	F	28	Influenza A virus	AESD	A
11	F	11	Unknown	AESD	B
12	F	19	Influenza A virus	Monophasic	B
13	M	14	Unknown	Monophasic	A
14	M	9	HHV-6	AESD	A
15	F	76	Unknown	Monophasic	B
16	F	17	HHV-6	AESD	B
17	F	58	Unknown	Monophasic	B
18	M	72	Unknown	AESD	B
19	F	35	Unknown	Monophasic	A
20	F	47	Rota virus	Monophasic	A
21	F	54	HHV-6	AESD	B

Sequelae were classified as A; no, B; mild-moderate, or C; severe.
Patients administered the mitochondrial drug cocktail are colored gray (within 24 h are colored dark gray).

report [25], we defined febrile convulsive status epileptics as febrile seizures longer than 30 min. We retrospectively reviewed the medical records of the patients that the attending physician diagnosed with acute encephalopathy at our hospital from January 2006 to December 2014. Then, we selected patients that met the criteria described above. The cerebrospinal fluid was examined in all cases, and CNS inflammation was excluded.

There were 23 patients with acute encephalopathy with febrile convulsive status epilepticus as an initial neurological symptom. Among them, 11 patients (Patients 1 to 11) had been treated with mitochondrial drug cocktails at our hospital since January 2009 (prescription group), after informed consent was obtained from the patient's family. For the mitochondrial drug cocktail, we used vitamin B1 (10 mg/kg), vitamin C (100 mg/kg), biotin (0.5 mg/kg), vitamin E (10 mg/kg), coenzyme Q10 (5 mg/kg), and L-carnitine (30 mg/kg). In all 10 patients, the 6 drugs were administered orally, except for 2 cases: patient 3 in which only vitamin C was administered via an intravenous drip, and patient 6 in which only vitamin B1 was administered through an intravenous drip. The cocktail administration period was defined as more than 5 days and until the medical condition was stable. As an additional treatment, steroid pulse therapy was started within 24 h of encephalopathy diagnosis in all 11 cases. A single course of steroid pulse therapy consisted of 30 mg/kg/day methylprednisolone for 3 days (cases 3 and 4 received 2 courses of steroid pulse therapy). Age, trigger, clinical form, time of initial treatment, and sequelae were retrospectively reviewed using medical records. For clinical form, AESD was diagnosed by the presence of both biphasic clinical course and MRI findings of late reduced diffusion.

There were 10 patients (all 6 patients with onset prior to January 2009, and 4 patients with the onset after January 2009, for whom we have not been involved in the initial treatments) with acute encephalopathy and onset of febrile convulsive status epilepticus at our hospital who were not treated with the mitochondrial drug cocktail (non-prescription group; patients 12 to 21). All of the non-prescription patients also received steroid pulse therapy that started within 24 h of diagnosis.

Two patients of the remaining 23 patients were excluded because only part of the six cocktail drugs was administered.

Sequelae were classified as (A) no sequelae group (having no obvious functional decline in motor or intelligence function) or (B) sequelae group (all others). The family and attending physician had determined the presence or absence of sequelae at the time of hospital discharge. The sequelae (A vs. B) of the mitochondrial drug cocktail prescription and non-prescription groups were compared. In addition, the sequelae of the total 21 patients (A vs. B) based on the treatment initiation time, i.e., within 24 h and others (over 24 h and non-prescription), were analyzed.

For statistical analysis, we employed the Fisher's exact test for comparison of case history between prescription group and non-prescription group, treatment initiation time within 24 h and others, and sequelae between the mitochondrial drug cocktail prescription and non-prescription groups. Student's *t*-test was applied to the average age values in the prescription and non-prescription groups and treatment initiation time within 24 h and others. In all patients, blood glucose, lactate, ammonia, pH, base deficit, and anion gap levels were examined, and normal values were confirmed during the course of the study. Additionally, in the past family history of the patients, there was nothing relevant to congenital metabolic disorders, and patients with suspected congenital metabolic abnormalities were not present. There were no patients who had been administered valproic acid or anesthetics. This study was approved by the local ethics committee of Chiba Children's Hospital.

3. Results

3.1. Case history

The 21 cases are summarized in Tables 1, 2. For the 11 patients in the prescription group, patient age ranged from 7 to 171 months (mean,

Table 2
Comparison of patients case history.

	Prescription and non-prescription n = 21			Treatment initiation time n = 21		
	Prescription n = 11	Non-prescription n = 10	P value	Within 24 h n = 5	Others n = 16	P value
Median age (months)	44.4	40.1	0.798	53.2	39.0	0.474
Gender (male)	4	3	1.000	3	4	0.182
Trigger						
HHV-6	3	3	1.000	3	3	0.115
Influenza A	3	1	0.587	2	2	0.228
Rota	1	1	1.000	0	2	1.000
Entero	1	0	1.000	0	1	1.000
Unknown	3	5	0.268	0	8	0.111
Clinical form (AESD)	7	4	0.395	2	9	0.635

Table 3
The effect of the mitochondrial drug cocktail (total 21 patients).

Group	A: None	B: Sequelae	Total	P value
Prescription	7 (33%)	4 (19%)	11 (48%)	0.395
Non-prescription	4 (19%)	6 (29%)	10 (48%)	
Total	11 (52%)	10 (52%)	21 (100%)	

44.4 months), and the trigger pathogens were identified as follows: human herpes virus 6 (HHV-6) (3 cases), influenza A virus (3 cases), rotavirus (1 case), enterovirus (1 case), and unknown (3 cases). The clinical form of acute encephalopathy was AESD in 7 patients and monophasic in 4 patients. For the 10 patients in the non-prescription group, patient age ranged from 9 to 76 months (mean, 40.1 months), and the trigger pathogens were as follows: HHV-6 (3 cases), influenza A virus (1 case), rotavirus (1 case), unknown (5 cases). The clinical form of acute encephalopathy was AESD in 4 patients and monophasic in 6 patients (Tables 1, 2). There was no significant difference in the case history both between prescription group and non-prescription group, and between treatment initiation time within 24 h and others (Table 2). In 10 cases (except for patient 8), the mitochondrial drug cocktail administration period was 5 to 23 days, with an average of 11.5 days. Patient 8 originally showed poor weight gain, and to consider the possibility of mitochondrial respiratory chain disorders, we continued the treatment for 10 months after encephalopathy until normal enzyme activity was confirmed by skin biopsy.

3.2. Sequelae

The distribution of the 21 patients was as follows: A, 11 cases; B, 10 cases. For the 11 patients in the prescription group, the distribution was as follows: A, 7 cases; B, 4 cases. The distribution for the 10 patients in the non-prescription group was as follows: A, 4 cases; B, 6 cases (Table 3). The patients were further divided into a biphasic group (AESD) and a monophasic group based on the clinical form of acute encephalopathy. For the 7 patients in the prescription group with AESD, the distribution was as follows: A, 4 cases; B, 3 cases. For the 4 patients in the non-prescription group with AEDS, the distribution was as follows: A, 1 case; B, 3 cases (Table 4). For the 3 patients in the prescription group with monophasic acute encephalopathy, the distribution was as follows: A, 2 cases; B, 1 case. For the 6 patients in the non-prescription group with monophasic acute encephalopathy, the distribution was as follows: A, 3 cases; B, 3 cases (Table 5).

There was no significant difference in the distribution of the severity of sequelae (A vs B) between the mitochondrial drug cocktail prescription and non-prescription groups in the total 21 patients and in both AESD and monophasic groups (Tables 3, 4, 5).

3.3. Importance of the time of treatment initiation

Finally, the total 21 patients' sequelae were compared based on the mitochondrial drug cocktail treatment initiation time: within 24 h and others (over 24 h or non-prescription). The sequelae of the 5 patients treated within 24 h of diagnosis were as follows: A, 5 cases; B, 0 cases. The sequelae of the 16 patients (treated over 24 h or non-prescription) were as follows: A, 10 cases; B, 11 cases. Sequelae were significantly better in the group administered the drug cocktail within 24 h ($P = 0.035$) (Table 6).

Table 4
Effect of the mitochondrial drug cocktail (11 AESD patients).

Group	A: None	B: Sequelae	Total	P value
Prescription	4 (36%)	3 (27%)	7 (64%)	0.303
Non-prescription	1 (9%)	3 (27%)	4 (36%)	
Total	5 (45%)	6 (55%)	11 (100%)	

Table 5
Effect of the mitochondrial drug cocktail (10 monophasic patients).

Group	A: None	B: Sequelae	Total	P value
Prescription	3 (30%)	1 (10%)	3 (30%)	0.571
Non-prescription	3 (30%)	3 (30%)	6 (60%)	
Total	6 (60%)	4 (40%)	10 (100%)	

4. Discussion

We studied the efficacy of a mitochondrial drug cocktail in the treatment of acute encephalopathy with onset of febrile convulsive status epilepticus. The most important finding in this study was that sequelae were significantly better in the group administered mitochondrial drug cocktail within 24 h.

The mechanism of acute encephalopathy with onset of febrile convulsive status epilepticus has not been sufficiently elucidated, and the condition is often classified into subtypes such as AESD, acute necrotizing encephalopathy (ANE), and other monophasic types in Japan [11, 24]. Excitotoxic injury with delayed neuronal death has been hypothesized as a possible mechanism of AESD, based on MR spectroscopic findings [11,20] and cytokine analysis of cerebrospinal fluid [7].

Acute encephalopathy is more common in East Asia than in Europe or North America, indicating that genetic factors play an important role [2,11]. Carnitine palmitoyl transferase II (CPTII) polymorphisms [2,17], *SCN1A* mutations [14], and adenosine A2A receptor polymorphisms [16] have recently been reported as predisposing factors for the onset of acute encephalopathy. Among them, CPTII is the most likely etiological candidate for encephalopathy. A thermolabile CPTII phenotype and a CPTII polymorphism in Japanese patients with multiple types of acute encephalopathy have been reported [2,17]. Given that CPTII is an enzyme localized on the mitochondrial inner membrane that removes fatty acids from carnitine, CPTII deficiency leads to mitochondrial dysfunction and a lack of energy in the wake of severe infections [1,6,17,23]. Although further studies should target the relationship between CPTII polymorphism and treatment efficacy, the demonstrated involvement of mitochondrial dysfunction in acute encephalopathy suggests that mitochondrial drug cocktails should be explored for the treatment of acute encephalopathy [3].

There are no established treatments for mitochondrial dysfunction, but various vitamins and coenzymes have been clinically used based on their effects on energy shortage and oxidative stress [13], and effectiveness at high dose has already been reported [12]. Therefore, we employed vitamin B1 (10 mg/kg), vitamin C (100 mg/kg), biotin (0.5 mg/kg), vitamin E (10 mg/kg), coenzyme Q10 (5 mg/kg), and L-carnitine (30 mg/kg) as a mitochondrial drug cocktail based on previous reports [4,9,12,13,21]. We started prescribing mitochondrial drug cocktails to patients with acute encephalopathy approximately 6 years ago after obtaining informed consent. Although the dose of the mitochondrial drug cocktail was consistent and administration was subject to a unified protocol, the time from diagnosis to the start of prescription differed among the cases because their physicians determined their applications independently.

In this study design, there was no significant difference in the average age of the patients in the prescription and non-prescription groups. Although no significant relationship has been reported between the

Table 6
Effect of the mitochondrial drug cocktail (total 21 patients based on the treatment initiation time: within 24 h vs. others).

Treatment initiation time	A: None	B: Sequelae	Total	P value
Within 24 h	5 (24%)	0 (0%)	5 (24%)	0.035
Others (over 24 h or non-prescription)	6 (28%)	10 (48%)	16 (76%)	
Total	11 (52%)	10 (48%)	21 (100%)	

trigger pathogen and the type of encephalopathy [11,17], we found that HHV6 was the most common pathogen, followed by the influenza virus; this finding is in agreement with those of previous reports [8,18].

There was no significant difference in prognosis (A vs B) between the mitochondrial drug cocktail prescription and non-prescription groups among the 21 patients and in both AESD and monophasic groups, probably because of the small number of patients and the delay in starting the mitochondrial drug cocktail after the diagnosis of encephalopathy. However, no sequelae were observed in the 5 cases in which mitochondrial drug cocktail administration was initiated within 24 h of encephalopathy diagnosis. Given that the outcome was significantly better in the group administered the mitochondrial drug cocktails within 24 h, we consider that early administration within 24 h of diagnosis may provide a prophylactic effect.

Although there are reports of various vitamins and coenzymes as treatments for mitochondrial diseases [4,9,12,13,21] and a report of the combination of creatine monohydrate, coenzyme Q10, and alpha-lipoic acid as a "mitochondrial cocktail" for mitochondrial cytopathies [4], there are no reports in which a combination of various vitamins and coenzymes was administered for acute encephalopathy. Considering the mechanisms of these constituents, it is likely that the mitochondrial drug cocktail used in this study provides an effective treatment for acute encephalopathy. Moreover, there have been no obvious side effects in our patients, and administration of the drug cocktail was relatively easy.

The limitations of our study stem from retrospective analysis and the small number of patient, further prospective study in larger cohorts is necessary to conclude the observations; however, we consider that speedy administration of mitochondrial drug cocktails is worthwhile in cases of acute encephalopathy and in individuals with a high risk of encephalopathy (such as those with status epilepticus or spasm of the cluster associated with fever) because of the potential to prevent the development of sequelae or the onset of acute encephalopathy.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This study was approved by the local ethics committee of Chiba Children's Hospital.

Acknowledgement

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Original article

Efficacy and safety of fosphenytoin for acute encephalopathy in children

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Abstract

Purpose: To evaluate the efficacy and safety of fosphenytoin (fPHT) for the treatment of seizures in children with acute encephalopathy.

Methods: Using responses from physicians on the Annual Zao Conference on Pediatric Neurology mailing list we chose patients who met the following criteria: clinical diagnosis of acute encephalopathy and use of intravenous fPHT for the treatment of seizures. We divided the patients into two groups: acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) and other encephalopathies. The efficacy of fPHT was considered effective when a cessation of seizures was achieved.

Results: Data of 38 children were obtained (median age, 27 months). Eighteen children were categorized into the AESD group and 20 into the other encephalopathies group. fPHT was administered in 48 clinical events. The median loading dose of fPHT was 22.5 mg/kg and was effective in 34 of 48 (71%) events. The rate of events in which fPHT was effective did not differ according to the presence or absence of prior antiepileptic treatment, subtype of acute encephalopathy, or the type of seizures. One patient experienced apnea and oral dyskinesia as adverse effects of fPHT, whereas arrhythmia, hypotension, obvious reduction of consciousness, local irritation, phlebitis and purple grove syndrome were not observed in any patient.

Conclusion: fPHT is effective and well tolerated among children with acute encephalopathy.

Keywords: Fosphenytoin; Acute encephalopathy; Acute encephalopathy with biphasic seizures and late reduced diffusion; Efficacy; Safety

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1. Introduction

Seizures are one of the most common neurological symptoms among children with acute encephalopathy and evolve often into status epilepticus. The early cessation of seizures is generally accepted as desirable to improve the outcome in children with encephalopathy. However, seizures in children with acute encephalopathy are often refractory to antiepileptic drugs.

Recently in Japan, treatment for acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), a characteristic subtype of acute encephalopathy in children, has become an important issue. AESD is characterized by prolonged seizure onset or status epilepticus followed by secondary seizures (late seizures) associated with deterioration of consciousness and widespread reduced diffusion in the subcortical white matter on magnetic resonance imaging (MRI) [1]. Late seizures occur usually in clusters and are refractory to antiepileptic drugs. Seizure control is also important in children with other subtypes of acute encephalopathy, such as acute necrotizing encephalopathy (ANE) [2] and acute disseminated encephalomyelitis (ADEM).

Phenytoin (PHT) is a useful antiepileptic drug for the treatment of seizures in children with acute encephalopathy. PHT has a lesser effect on the level of consciousness [3] and we previously reported its efficacy for seizures in children with AESD [4]. However, PHT has been known to occasionally cause local irritation, phlebitis and intravenous fluid incompatibility. Purple glove syndrome is also known as a rare but serious side effect of PHT. Thus, pediatricians and pediatric neurologists in Japan tend to avoid administering PHT. Fosphenytoin (fPHT) is a water-soluble prodrug of PHT with a neutral pH value. The adverse effects of fPHT are less frequent than those of PHT. fPHT was marketed in Japan in 2011 and given to children with several subtypes of acute encephalopathy. At present, the efficacy and safety of fPHT for the treatment of acute encephalopathy in children have not been elucidated. We collected clinical data of children with acute encephalopathy treated with fPHT to determine its efficacy and safety. We also focused on the efficacy of fPHT in Japanese children with AESD, a common and problematic subtype of acute encephalopathy [5].

2. Methods

Using responses from physicians on the Annual Zao Conference on Pediatric Neurology mailing list we chose patients who met the following criteria: clinical diagnosis of acute encephalopathy and use of intravenous fPHT for the treatment of seizures. In this study, acute encephalopathy was defined as a condition characterized by decreased consciousness with or without other neurological findings, such as delirious behavior and seizures, lasting for 24 h or longer in children with infectious symptoms including fever, cough and diarrhea. The Annual Zao Conference mailing list includes more than 700 pediatric neurologists throughout Japan. From January 2012 to November 2013, we asked for enrollment of patients through the mailing list. A structured research form was given to the members of the mailing list to fill out if they had patients meeting the criteria. The completed research forms were returned to the first author by email. This study was approved by the Institutional Review Board of Juntendo University Faculty of Medicine. The patient data were collected anonymously.

The following items were included in the research form: age, gender, subtypes of acute encephalopathy, preexisting medical condition, prodromal illness and its pathogen, onset of acute encephalopathy, EEG monitoring, type of seizure (status epilepticus or clustering seizures), treatment for acute encephalopathy (steroids, intravenous gamma globulin, hypothermia), outcome, efficacy and adverse events of fPHT. We also asked the participants to describe the scheme of seizure time course and the use of antiepileptic drugs. In this study, AESD was defined as acute encephalopathy presenting with onset of prolonged seizures or status epilepticus, biphasic clinical course characterized by late worsening of consciousness along with clustering seizures or status epilepticus and widespread reduced diffusion in the cortex and/or subcortical white matter involving unilateral or bilateral hemispheres [1]. Any encephalopathy that did not meet the definition of AESD was classified into other encephalopathies. The efficacy of fPHT was categorized as follows based on clinical observation: effective; cessation of seizures, partially effective; 50% or more reduction in frequency and/or duration of seizures, ineffective; incompatible with the former two conditions.

Statistical analysis of the efficacy rate between the two groups was performed by Fisher's exact probability test for qualitative variables using the SPSS Statistics version 17.0 software (SPSS Inc., Tokyo, Japan). Statistical significance was accepted at a level of $p < 0.05$.

3. Results

The data of 38 children were obtained from 16 hospitals. fPHT was administered for 48 clinical events.

3.1. Demographic data

Demographic data are shown in Table 1. The age at onset of acute encephalopathy ranged from 16 days to 163 months (median, 27 months). There were 22 males (58%) and 16 females (42%). Eighteen children were categorized into the AESD group and 20 into the other encephalopathies group. Among subjects with other encephalopathies, two children were diagnosed as

Table 1
Demographic data of the patients.

	Total $n = 38$	AESD $n = 18$	Other encephalopathies $n = 20$
Age at onset (months)	27 (0.5–163)	22.5 (9–163)	23 (0.5–97)
Sex (M:F)	22: 16	13: 5	9: 11
Preexisting medical conditions			
None	37	17	20
Cerebral palsy	1	1	0
Prodromal illness			
Upper respiratory infection	16	8	8
Exanthema subitum	9	7	2
Gastroenteritis	5	0	5 (Rota in 4 and Noro in 1)
Influenza	3	1	2
Mycoplasma pneumonia	2	1	1
RSV bronchiolitis	1	0	1
Bacteremia	1	1 (*Moraxella catarrhalis*)	0
Herpes simplex encephalitis	1	0	1
EEG monitoring			
Intermittent EEG	16	10	6
Continuous EEG	5	2	3
Continuous aEEG	2	1	1
None	15	5	10
Treatment for acute encephalopathy			
Methylprednisolone pulse	31	16	15
Intravenous immunoglobulin	10	5	5
Hypothermia	4	1	3

The numerical variables were shown as median (range).
AESD: acute encephalopathy with biphasic seizures and late reduced diffusion, RSV: respiratory syncytial virus, aEEG: amplitude-integrated EEG.

having mild encephalopathy with reversible splenial lesion [6], one as ADEM, one as ANE and one as herpes simplex encephalitis. No specific diagnosis of acute encephalopathy was made in the other 15 children. The most common prodromal illness was non-specific upper respiratory infection, followed by exanthema subitum. EEG monitoring during the treatment with fPHT was performed in 23 children. However, continuous standard EEG or amplitude-integrated EEG (aEEG) was performed in only seven patients. Methylprednisolone pulse therapy was the most common treatment for the acute encephalopathy.

fPHT was used for 48 clinical events (Table 2) and was administered in two events during a single course of acute encephalopathy in eight children with AESD and two with other encephalopathies. Types of seizures were status epilepticus in 17 events and clustering seizures in 31. Before fPHT administration, no drugs were used in 18 events and one drug in 18. Two or more antiepileptic drugs were used in 12 events before fPHT administration and midazolam was the most frequently used, followed by diazepam.

Table 2
Background information at fPHT administration.

	Total $n = 48$	AESD $n = 26$	Other encephalopathies $n = 22$
Types of seizures			
Status epilepticus	17	9	8
Cluster	31	17	14
Number of AEDs before fPHT			
None	18	11	7
1	18	8	10
2	11	6	5
3	1	1	0
AEDs used before fPHT			
Midazoram	20	13	7
Diazepam	16	7	9
Thiopental	4	2	2
Phenobarbital	3	1	2

AED: antiepileptic drugs, fPHT: fosphenytoin.

3.2. Efficacy of fPHT

The median loading dose of fPHT was 22.5 mg/kg (range, 15–28 mg/kg). The median rate of injection was 2.8 mg/kg/min (range, 0.05–3.6 mg/kg/min). Serum PHT level was measured in 18 patients. The median serum PHT concentration was 10.55 μg/mL (range, 0.6–13.5 μg/mL) at 6–24 h after the initial administration.

Among a total of 48 clinical events, fPHT was effective in 34 (71%). Other antiepileptic drugs were used and failed to control seizures in 30 clinical events. Even

Table 3
Efficacy of fPHT.

	Total $n = 48$	AESD $n = 26$	Other encephalopathies $n = 22$
Status epilepticus			
Effective	11	6	5
Partially effective	2	0	2
Ineffective	4	3	1
Clustering seizures			
Effective	23	13	10
Partially effective	4	2	2
Ineffective	4	2	2

AESD: acute encephalopathy with biphasic seizures and late reduced diffusion.

in such situations, fPHT was effective in 21 events (70%). fPHT was effective in 19 of 26 (73%) clinical events in children with AESD and 15 of 22 (68%) events in children with other encephalopathies. The rate of events in which fPHT was effective did not differ between AESD and other encephalopathies. Regarding the type of seizures, fPHT was effective in 11 of 17 (65%) events with status epilepticus and 23 of 31 (74%) events with clustering seizures (Table 3). The rate of events in which fPHT was effective did not differ according to the type of seizure.

3.3. Adverse effects of fPHT

Arrhythmia, hypotension, obvious reduction of consciousness, local irritation, phlebitis and purple grove syndrome were not observed in any patient. One patient with apnea and oral dyskinesia had an unusually elevated serum PHT level (27.8 μg/mL) after a loading dose of 22.5 mg/kg followed by three maintenance doses of 7.5 mg/kg (84 h after the initial administration). fPHT was administered *via* peripheral venous line in 46 events and central venous line in 2. Extracellular fluid or maintenance solution was used and intravenous fluid incompatibility was not observed in any patient.

4. Discussion

In this study we showed that fPHT was effective and well tolerated when used for seizures in children with acute encephalopathy. fPHT efficacy did not differ according to subtype of acute encephalopathy or type of seizure. The rate of adverse effects was very low.

Complete cessation of seizures was achieved in 71% of children with acute encephalopathy. PHT efficacy was similar even after other antiepileptic drugs failed to control seizures. However, determining if fPHT is superior to other antiepileptic drugs is difficult. Presently, reports on the efficacy of other epileptic drugs for the treatment of seizures in children with acute encephalopathy are unavailable. The clinical effectiveness of fPHT in children with status epilepticus also remains unclear. Because fPHT is completely metabolized to PHT by phosphatases of the liver, red blood cells and many other tissues [7], its efficacy is comparable to that of PHT. Studies on the efficacy of PHT for the treatment of status epilepticus are limited [3]. In a randomized study of adults with status epilepticus, PHT was used as a first-line treatment in the early phase of status epilepticus with a success rate of 43.6%, which was inferior to treatment with lorazepam (64.9%) [8]. Agarwal et al. reported an 88% efficacy rate of PHT after diazepam failure in children and adults with status epilepticus, which was similar to intravenous valproate [9]. Comparative studies are necessary to determine the efficacy of individual antiepileptic drugs.

Complete cessation of seizures was obtained in approximately two-thirds of clinical events in children with AESD. Late seizures that appear along with deterioration of consciousness and MRI abnormalities are an outstanding feature of AESD and are often refractory to benzodiazepines. Excitotoxicity is considered to be closely related to the pathogenesis of AESD and seizure control is presumed important for avoidance of secondary brain damage [10,11]. In addition, AESD is a common subtype of acute encephalopathy in Japan and a majority of affected children have neurological sequelae, such as intellectual disability and attention deficit hyperactivity disorder [1]. While the superiority of fPHT to other antiepileptic drugs is presently uncertain, as mentioned above, we suggest that fPHT can be a drug of choice in cases of status epilepticus or clustering seizures in children with AESD, due to its high efficacy rate.

An important advantage of fPHT is its lack of sedative effect [3]. During the management of acute encephalopathy, evaluation of consciousness is important, especially in children. Excessive sedation was not observed in any patient, whereas sedative effects were evident after intravenous administration of benzodiazepines and phenobarbital. For this reason, fPHT may be superior to these drugs in children with acute encephalopathy.

Adverse effects of fPHT were infrequent in our study. fPHT is easier to administer than PHT because of its water solubility and neutral pH value [12,13]. A neutral pH level results in less common occurrence of serious reactions at the injection site, such as purple glove syndrome and skin necrosis. In our study, none of the children experienced complications at the injection site. The water solubility of fPHT contributes to lessening of the occurrence of intravenous fluid incompatibilities; indeed, route obstruction was not reported in this study. One of our patients with apnea and oral dyskinesia had a higher serum PHT level than the other patients. Several studies have suggested that maintaining the serum PHT concentration may be difficult in children because of their rapid elimination and cytochrome P450 enzyme induction [14]. Therefore, the patient with apnea and

oral dyskinesia might have metabolized fPHT poorly. Therapeutic serum level monitoring is necessary to reduce adverse effects of fPHT. Additionally, cardiovascular adverse effects—such as hypotension and arrhythmia—are the most serious complications of fPHT. Cardiovascular adverse effects were not observed in our patients, probably because the rate of infusion was usually monitored by the attending physicians. Continuous monitoring of electrocardiogram and blood pressure should be performed and the injection should be performed slowly when administering fPHT.

This study had several limitations. First, the data on efficacy and adverse effects may be inaccurate due to the retrospective design of the study. Prospective studies are necessary to determine the efficacy and safety of fPHT. The efficacy and safety of fPHT and other antiepileptic drugs were not compared. Whether fPHT is appropriate for patients with acute encephalopathy remains uncertain due to the lack of previous data on PHT. The results of this study suggested that fPHT is useful for patients with acute encephalopathy. Comparisons between fPHT and other epileptic drugs should be performed to determine the appropriate agent for use in patients with acute encephalopathy. The paucity of continuous EEG/aEEG monitoring is also problematic. Recent studies using continuous EEG monitoring have indicated the presence of nonconvulsive seizures in critically ill children or those with altered mental states [15,16]. Nonconvulsive seizures are difficult to recognize without EEG monitoring; thus, the efficacy of antiepileptic drugs should be determined on the basis of continuous EEG monitoring. Although aEEG is less sensitive, it can be useful for surrogate monitoring. Presently, continuous EEG/aEEG monitoring is not available in a majority of tertiary emergency hospitals in Japan; this must be overcome in the near future.

In summary, we showed that fPHT is effective and well tolerated among children with both AESD and other acute encephalopathies. Its efficacy did not differ according to the type of seizure and the presence or absence of prior antiepileptic treatment. fPHT can be useful for the treatment of seizures in children with acute encephalopathy. Further prospective studies comparing fPHT and other antiepileptic drugs should be performed to determine the appropriate treatment for children with acute encephalopathy.

Disclosure

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

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Intrathecal overproduction of proinflammatory cytokines and chemokines in febrile infection-related refractory status epilepticus

INTRODUCTION

Status epilepticus is one of the most common neurological emergencies in children and adults. Febrile status epilepticus cases are often associated with inflammatory neurological diseases caused by specific pathogens or antineuronal autoimmunity. In addition, there is a subgroup of super-refractory status epilepticus triggered by fever and having no known cause.[1] This condition is designated as either acute encephalitis with refractory, repetitive partial seizures (AERRPS)[2] or febrile infection-related epilepsy syndrome (FIRES).[3] The pathogenesis of AERRPS/FIRES is currently unknown. A close relationship between febrile illness and status epilepticus suggests deleterious effects of inflammation and autoimmunity on the onset and progression of seizure. However, immune mechanisms in human status epilepticus associated with isolated fever have not been fully elucidated.

We report a comprehensive study of the inflammatory mediators in paediatric cases of AERRPS. We show a marked upregulation of proinflammatory cytokines and chemokines in the cerebrospinal fluid (CSF) of patients with this condition.

METHODS

We defined AERRPS using the criteria shown in online supplementary table S1. Between April 2010 and July 2013, 14 patients with AERRPS and 14 patients with other inflammatory neurological diseases (OIND) were enrolled in the study. Serum and CSF specimens from patients with AERRPS and OIND were collected between 0 and 39 days from the onset of neurological symptoms. Eighteen patients with non-inflammatory neurological diseases (NIND) served as a control group. Additionally, the Shizuoka Institute of Epilepsy and Neurological Disorders provided us with 13 conserved CSF specimens from patients with AERRPS who fulfilled the same criteria, which we also included in our analysis. There was no significant difference in age or gender among AERRPS, OIND and NIND groups (see online supplementary table S2). Serum and CSF levels of cytokines and chemokines were measured by Bio-Plex Suspension Array System (Bio-Rad, Hercules, California, USA) according to the manufacturer's protocols. Statistical significance among the three groups was analysed by non-parametric Kruskal-Wallis tests followed by post hoc Steel-Dwass non-parametric multiple comparison procedures. Relationships between two variables were determined by Spearman's partial rank correlation coefficient. Compensation for multiple comparisons was not performed. The results are shown as means±SD and $p<0.05$ was considered significant (see online supplementary methods for details).

RESULTS

Serum analysis showed significant differences in the concentrations of 16 analytes among the three groups: 6 analytes were upregulated and 10 were downregulated in the AERRPS group compared with either NIND and/or OIND groups (see online supplementary table S3). Analysis of CSF demonstrated significant differences in the concentrations of 22 analytes and all except CXCL12 and vascular endothelial growth factor were upregulated in the AERRPS group compared with either NIND and/or OIND groups (see online supplementary table S4). Among them, interleukin (IL)-6, IL-8 and CXCL10 were increased most strikingly (figure 1A). Although serum and CSF concentrations of IL-6 (figure 1B, E), IL-8 (figure 1C, F) and CXCL10 (figure 1D, G) in the AERRPS group were significantly higher than that of the NIND group, the changes were more drastic in CSF than in serum.

We estimated the correlation among the CSF concentrations of eight cytokines and chemokines with p values<0.001 in online supplementary table S4 (CXCL9, CXCL10, IL-6, IL-8, CXCL1, macrophage colony-stimulating factor, CCL13 and CCL26, online supplementary table S5). CXCL9 and CXCL10 ($R=0.905$, $p=9.09\times10^{-11}$, online supplementary figure A), and IL-8 and CXCL1 ($R=0.724$, $p=1.96\times10^{-5}$, online supplementary figure B) were correlated the strongest.

DISCUSSION

There is growing evidence to support the involvement of neuroinflammation in ictogenic and epileptogenic processes. Proinflammatory cytokines play a crucial role in this process. Studies using experimental animal models have demonstrated IL-1β expression in microglia and astrocytes after seizures and that IL-1β itself can enhance neuronal excitability.[4] Based on these findings, a hypothesis has been proposed that the vicious cycle consisting of seizure activity and inflammation contribute to the further progression of inflammation-mediated status epilepticus.[1] However, this paradigm has not been definitively demonstrated in human status epilepticus.

The pathogenesis of AERRPS/FIRES remains controversial. Based on occasional CSF pleocytosis, an immune-mediated pathogenesis has been implicated in FIRES and AERRPS.[2] The biphasic clinical course and the absence of infectious agents suggest a possible infection-triggered process rather than an infectious disease.[5] Central nervous system (CNS) pathology of FIRES is devoid of inflammatory infiltrations,[3] suggesting little contribution of systemic adaptive immunity to this condition.

This study demonstrates for the first time the upregulation of certain cytokines and chemokines in AERRPS. It is noteworthy that proinflammatory cytokines (IL-6, macrophage migration inhibitory factor (MIF) etc) and chemokines (CXCL10, IL-8, etc) were selectively upregulated. In sharp contrast, most T-cell-associated cytokines (IL-2, IL-17A, etc) and homoeostatic chemokines (CCL21, CXCL12, etc) remained unchanged or were downregulated. These findings provide strong evidence for the involvement of innate inflammation in the pathogenesis of AERRPS. Changes in cytokine and chemokine levels were more prominent in CSF than in serum, suggesting that inflammation primarily takes place in CNS. It is currently unknown whether intrathecal inflammation is a cause or effect, and it is possible that an exaggerated immune response is a secondary phenomenon due to refractory status epilepticus. It is difficult to use patients with non-inflammatory status epilepticus as a control group because patients with this condition are usually not recommended for CSF analysis.

In conclusion, the present study unveiled a previously unrecognised relationship between a group of proinflammatory cytokines/chemokines and refractory status

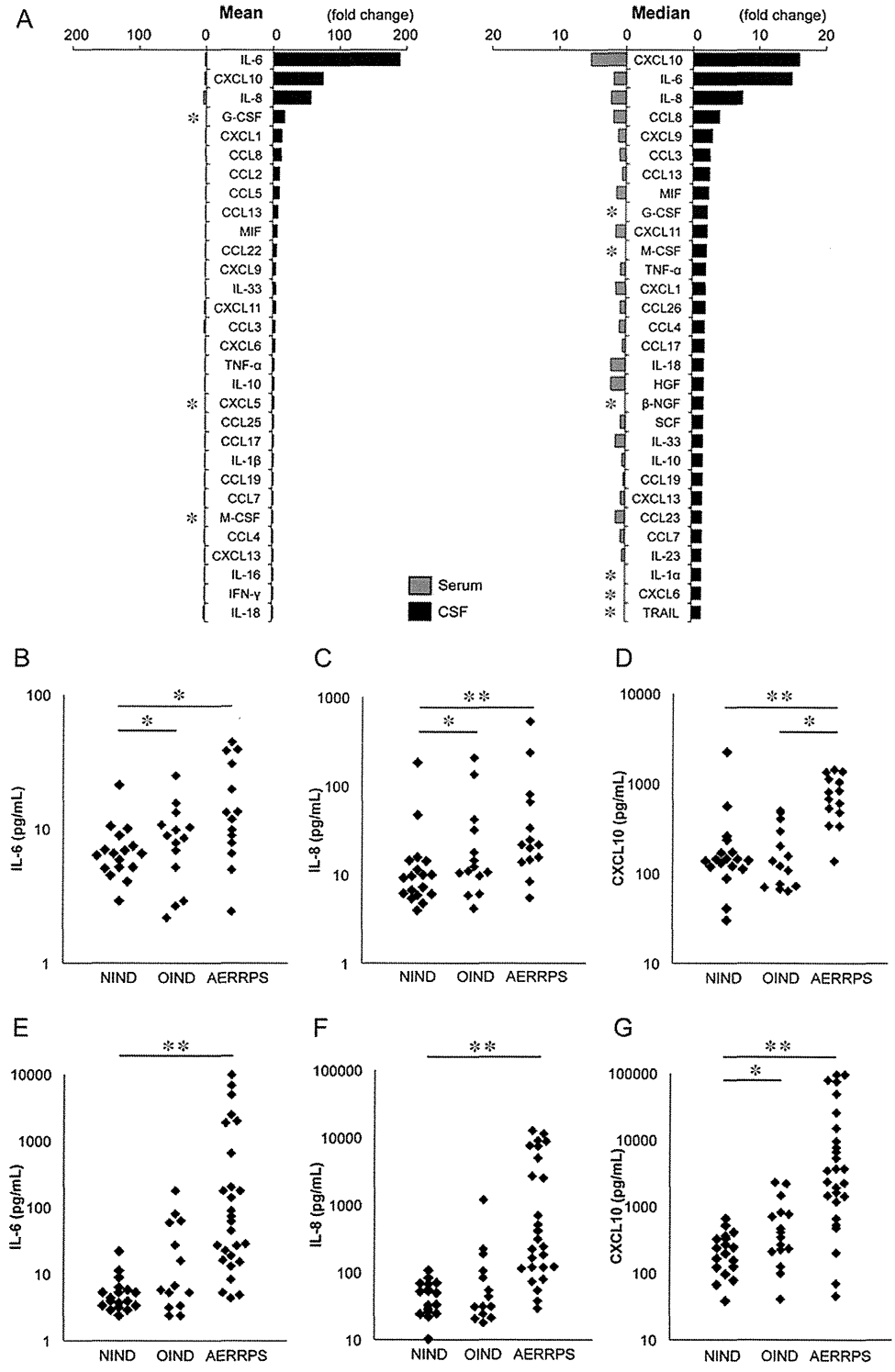

Figure 1 Serum and CSF concentrations of cytokines and chemokines. (A) The most highly upregulated cytokines and chemokines in the CSF of patients with acute encephalitis with refractory, repetitive partial seizures (AERRPS). The fold change was determined by comparing the mean (left) and median (right) concentrations of each cytokine/chemokine in the AERRPS and non-inflammatory neurological diseases (NIND) groups (calculated as AERRPS group per NIND group). The 20 most upregulated analytes in the CSF of the AERRPS group are listed. Asterisk indicates analytes that were immeasurable in more than one-half of the serum samples. (B–D) The serum levels of IL-6 (B) and IL-8 (C) in the AERRPS group were significantly higher than the levels in the NIND group, and CXCL10 (D) in the AERRPS group was significantly higher than the levels in NIND and other inflammatory neurological diseases (OIND) groups. (E–G) The CSF levels of IL-6 (E), IL-8 (F) and CXCL10 (D) in the AERRPS group were significantly higher than the levels in the NIND group. The y-axis is presented in log scale (B–G). *p<0.05 and **p<0.01, Steel-Dwass tests.

epilepticus in a human disease. These findings may provide important clues to understand the pathomechanism of and to develop effective treatment strategies for inflammation-related seizure disorders.

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Intrathecal overproduction of proinflammatory cytokines and chemokines in febrile infection-related refractory status epilepticus

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FULL-LENGTH ORIGINAL RESEARCH

Seizure characteristics of epilepsy in childhood after acute encephalopathy with biphasic seizures and late reduced diffusion

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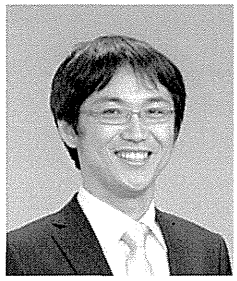

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Summary

Objective: The aim of this study was to clarify characteristics of post-encephalopathic epilepsy (PEE) in children after acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), paying particular attention to precise diagnosis of seizure types.

Methods: Among 262 children with acute encephalopathy/encephalitis registered in a database of the Tokai Pediatric Neurology Society between 2005 and 2012, 44 were diagnosed with AESD according to the clinical course and magnetic resonance imaging (MRI) findings and were included in this study. Medical records were reviewed to investigate clinical data, MRI findings, neurologic outcomes, and presence or absence of PEE. Seizure types of PEE were determined by both clinical observation by pediatric neurologists and ictal video–electroencephalography (EEG) recordings.

Results: Of the 44 patients after AESD, 10 (23%) had PEE. The period between the onset of encephalopathy and PEE ranged from 2 to 39 months (median 8.5 months). Cognitive impairment was more severe in patients with PEE than in those without. Biphasic seizures and status epilepticus during the acute phase of encephalopathy did not influence the risk of PEE. The most common seizure type of PEE on clinical observation was focal seizures (n = 5), followed by epileptic spasms (n = 4), myoclonic seizures (n = 3), and tonic seizures (n = 2). In six patients with PEE, seizures were induced by sudden unexpected sounds. Seizure types confirmed by ictal video-EEG recordings were epileptic spasms and focal seizures with frontal onset, and all focal seizures were startle seizures induced by sudden acoustic stimulation. Intractable daily seizures remain in six patients with PEE.

Significance: We demonstrate seizure characteristics of PEE in children after AESD. Epileptic spasms and startle focal seizures are common seizure types. The specific seizure types may be determined by the pattern of diffuse subcortical white matter injury in AESD and age-dependent reorganization of the brain network.

KEY WORDS: AESD, Bright tree appearance, Children, Epileptic spasm, Post-encephalopathic epilepsy, Startle seizure.

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