complicated by acute encephalopathy were presented in the mailing list of the Annual Zao Conference on Pediatric Neurology. These children invariably had fulminant clinical course and poor outcome. The need for research on this topic was advocated.

We recruited children with Dravet syndrome who had acute encephalopathy through the mailing list of the Annual Zao Conference on Pediatric Neurology, to clarify the features of acute encephalopathy in children with Dravet syndrome. We present the results of a retrospective review of 15 patients.

Methods

We collected patients who met the following criteria through the mailing list of the Annual Zao Conference on Pediatric Neurology: clinical diagnosis of Dravet syndrome, a history of acute encephalopathy, and no evidence of direct CNS infection, such as bacterial meningitis, severe metabolic derangement, or other systemic disorders that could cause a reduction in consciousness. The mailing list of the Annual Zao Conference includes >500 pediatric neurologists from all over Japan. In February 2010, the chief author (AO) announced the enrollment of the patients with Dravet syndrome who had acute encephalopathy within the last 5 years. The chief author provided a structured research form on the mailing list. The members of the mailing list were asked to fill out the research form and to send it by email to the chief author if they had potential subjects. We did not request the responses from the members who did not have any potential subjects or would have difficulty participating in this study for any reasons. The 16 potential subjects were reported to the chief author from 14 hospitals until June 2010. After careful inspection of the chief author, 15 subjects were confirmed to meet the inclusion criteria. These 15 patients were a subject of this study. The clinical course of patient 11 was presented elsewhere as a case report (Tsuji et al., 2011). The approximate number of the patients with Dravet syndrome who were regularly followed was available from 12 hospitals. According to these data, acute encephalopathy was observed in 13 of approximately 170 children with Dravet syndrome. The number of patients with Dravet syndrome in each hospital ranged from 2–56.

The clinical diagnosis of Dravet syndrome was made according to the International League Against Epilepsy (ILAE) classification (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). In this study, Dravet syndrome was diagnosed if all of the following characteristics were present: onset in the first year of life with hemiclonic or generalized seizures, frequent seizures provoked by fever, previously normal development, evolution of generalized spike-wave discharges, refractory to antiepileptic treatment, and subsequent delay in psychomotor development. Children without myoclonic seizures were included in the Dravet syndrome classification when they met all the characteristics described in the preceding. Acute encephalopathy was defined principally as a condition characterized by decreased consciousness with or without other neurologic findings, such as seizures, involuntary movement, and delirious behavior, lasting for >24 h in children with infectious symptoms including fever, cough, and diarrhea. However, barbiturate coma or continuous midazolam was administered in several patients. As to these patients, acute encephalopathy was diagnosed when prolonged coma was observed, even after the discontinuation of these drugs.

This study was approved by the institutional review board of Juntendo University Fac of Medicine. The patient's data were collected anonymously. Neuroimaging data were also collected after enrollment. We reviewed the clinical and neuroimaging features of the patients.

The outcomes of the patients were classified into the following four categories: mild sequelae (mild cognitive and/or motor impairment), moderate sequelae (moderate cognitive and/or motor impairment), severe sequelae (severe cognitive and/or motor impairment), and death. The severity of the cognitive impairment was classified according to the intelligence quotient or development quotient as follows: mild, 51–70; moderate, 30–50; and severe, <30. Intelligence quotient or developmental quotient was measured using Tsumori-Inage Developmental Assessment Test, Enjoji Analytical Development Test, KIDS Infant Development Scale, and Tanaka-Binet Intelligence Scales according to the age of the patient and the preference of each hospital. A formal assessment was not performed in some patients with apparently severe cognitive impairment. The severity of the motor impairment was classified into three groups: mild, if the patient could walk without support; moderate, if the patient could sit without support but could not walk without support; and severe, if the patient could not sit without support.

Results

Demographic data

The demographic data of the patients before the onset of acute encephalopathy are shown in Table 1. There were seven boys and eight girls. The onset of Dravet syndrome ranged from 2–7 months of age. All but one child had a history of SE before the onset of acute encephalopathy. A mutation in the *SCN1A* gene was present in 9 of the 12 children in whom a *SCN1A* mutation was examined, including multiplex ligation-dependent probe amplification: It was a truncation mutation in six children and a missense mutation in three. Myoclonic seizures were recognized in 14 children. Cognitive impairment before the onset of acute encephalopathy was absent in three children, mild in three, moderate in seven, and severe in two. The frequency of seizures during the 3 months before the onset of acute encephalopathy was monthly in seven children and none in three. Five children had histories of one or more episode of SE and three had a

Table 1. Demographic features

Patient	Sex	Onset of DS (months)	*SCN1A* mutation	History of status epilepticus	Myoclonic Sz	CI before the onset of AE	Szs during 3 months before the onset of AE			AED at the onset of AE
							Frequency	Cluster	Status	
1	M	6	IVS 26-2 A>C	10	No	Moderate	None	0	0	VPA, CLB, KBr
2	F	3	L929del fsX934	Several	Yes	Moderate	Daily	0	0	VPA, CLB, CZP, KBr, ZNS, LTG
3	M	3	R568X	3	Yes	Moderate	Monthly	0	0	VPA, CZP, KBr
4	F	4	K1846fsX1856	15	Yes	Moderate	Weekly	0	1	VPA, ZNS, CLB
5	F	7	IVS4+1G>A	Several	Yes	None	Monthly	0	1	VPA, CZP
6	F	3	R701X	0	Yes	None	None	0	0	VPA, CZP, PB
7	M	2	A1339V	3	Yes	Mild	Monthly	1	0	VPA, ZNS, PB
8	F	4	Y145H	2	Yes	Moderate	Weekly	0	0	VPA, CZP
9	F	5	V1630L	1	Yes	Mild	None	0	0	VPA, CLB, KBr
10	F	6	None	4	Yes	Moderate	Weekly	1	0	VPA, CLB, PB, TPM
11	F	5	None	Frequent	Yes	Moderate	Monthly	0	4	VPA, CZP
12	M	4	None	3	Yes	None	Monthly	0	2	VPA
13	M	4	Not done	2	Yes	Severe	Weekly	1	0	VPA, CLB, PRM, SLT, AZA, ESM, CLZ
14	M	5	Not done	1	Yes	Severe	Monthly	0	0	VPA, ZNS, NZP
15	M	4	Not done	7	Yes	Mild	Monthly	0	4	VPA, CLB, ZNS

DS, Dravet syndrome; Sz, seizure; CI, cognitive impairment; AE, acute encephalopathy; SE, status epilepticus; VPA, valproate; CLB, clobazam; PB, phenobarbital; TPM, topiramate; PRM, primidone; SLT, sulthiame; AZA, acetazolamide; ESM, ethosuximide; CLZ, clorazepate; ZNS, zonisamide; NZP, nitrazepam; CZP, clonazepam; KBr, potassium bromide; LTG, lamotrigine.

Table 2. Acute encephalopathy and outcome

Patient	Onset of AE (months)	Prodromal illness	Pathogen	Duration of SE at the onset of AE	Treatment for the initial SE[a]	Maximum LOC	Outcome			
							Neurologic sequelae	Cognitive impairment	Motor impairment	Sz frequency after recovery
1	38	URI	ND	40 min	DZP	Coma	Severe	Severe	Severe	None
2	153	URI	ND	1 h	TP (2)	Coma	Severe	Severe	Severe	None
3	53	Flu	Flu A	4 h	DZP (2), PHT, TL, MDZ	Coma	Death			
4	45	URI	ND	50 min	DZP, MDZ	Coma	Severe	Severe	Severe	None
5	13	Subitum	HHV-6	1 h	MDZ	Coma	Severe	Severe	Severe	None
6	13	NSFI	ND	3 h	DZP, MDZ, PHT, PTB, TP	Coma	Death			
7	16	Subitum	ND	4 h	TL, MDZ (2), PB	Coma	Moderate	Mild	Moderate	Monthly
8	27	URI	ND	1.5 h	DZP, MDZ	Coma	Severe	Severe	Severe	None
9	45	URI	ND	50 min	DZP, MDZ	Coma	Moderate	Moderate	None	Monthly
10	61	URI	ND	2 h	MDZ (2), DZP (2)	Coma	Severe	Severe	Severe	None
11	15	URI	ND	2 h	DZP, MDZ, TL	Coma	Severe	Severe	Severe	None
12	8	URI	RSV	1 h	DZP (3), MDZ (3)	Coma	Severe	Severe	Severe	Monthly
13	92	URI	ND	1 h	DZP	Coma	Severe	Severe	Mild	Monthly
14	184	URI	ND	1 h	DZP (2), MDZ (4)	Coma	Death			
15	43	NSFI	ND	5 h	DZP, MDZ, PB, TP	Coma	Death			

AE, acute encephalopathy; LOC, loss of consciousness; Sz, seizure; Flu, influenza; URI, upper respiratory tract infection; Subitum, exanthema subitum; NSFI, nonspecific febrile illness; HHV-6, human herpesvirus 6; RSV, respiratory syncytial virus; DZP, diazepam; MDZ, midazolam; PB, phenobarbital; PHT, phenytoin; PTB, pentobarbital; TL, thiamylal; TP, thiopental.

[a]The AEDs until the cessation of SE are shown according to the order of administration. The numbers in the brackets indicate the number of the doses for each patient, when two or more doses were administered.

history of cluster seizures during the 3 months before the onset of acute encephalopathy. All children had been treated with antiepileptic drugs (AEDs), such as valproate, benzodiazepines, and bromide.

Acute encephalopathy

The clinical manifestations of the acute encephalopathy are shown in Table 2. The median age at the onset of acute encephalopathy was 44 months (range 8–184 months). Eleven children were younger than 5 years of age, whereas two were older than 10 years. All children had a febrile illness before the onset of acute encephalopathy. A pathogen was identified in three children: influenza A in one, human herpesvirus 6 in one, and respiratory syncytial virus in one. Rapid antigen test for influenza was negative in the other four children.

Neurologic findings of acute encephalopathy were characterized by a fulminant clinical course with SE and severe

loss of consciousness. All children had SE followed by deep coma as the initial manifestation of acute encephalopathy. The duration of SE ranged from 40 min to 5 h. Although AEDs were administrated without a delay in a manner similar to that with the previous events with SE in most patients, seizures were refractory and persisted for 1 h or longer in 12 patients. More than two doses of AEDs were necessary to control SE in 12. Deep coma was seen following SE in all patients, even when seizures were controlled with one dose of AEDs. The loss of consciousness persisted for 2 weeks or longer in 13 children. Seizures were observed in all children on the first day, in seven on the second day, and in four on the third day. Thereafter, seizures were observed in only two children during the course of the acute encephalopathy. Although SE was seen on the first day in all patients, it was subsequently seen in only two children during the course of the acute encephalopathy. Delirious behavior was not seen in any child. No child had a biphasic clinical course: that is, an onset with SE, transient recovery of consciousness, and late clustering seizures with a worsening of consciousness. Despite the severe neurologic symptoms, serious systemic circulatory failure was not seen during the first few days after onset in any but one patient (Patient 15), even in those who died later. Vital signs such as heart rate, oximetry, blood pressure, and urine output were continuously monitored in all patients. Mild and transient hypotension was observed in some patients and was treated appropriately with catecholamine and volume expander.

The laboratory examinations on admission revealed thrombocytopenia (platelet count $<10.0 \times 10^4/\mu l$) in five (33%). Elevated levels of aspartate transaminase (>100 IU/L), alanine transaminase (>80 IU/L), lactate dehydrogenase (>600 IU/L), and creatine kinase (>400 IU/L) were present in seven (47%), three (20%), seven (47%), and three (20%), respectively. Elevated blood urea nitrogen (>20 mg/dl) and creatinine (>1.0 mg/dl) were seen in three (20%) and three (20%), respectively. Hypoglycemia (blood glucose <40 mg/dl) was not observed in any child, but hyperglycemia (blood glucose >200 mg/dl) was seen in three (20%). An elevated serum ammonia level was not seen in any child, whereas metabolic acidosis was present in six children (40%).

The neuroimaging findings are summarized in Table 3. Neuroimaging examinations were performed in 12 children during the first week. Three of them underwent computed tomography (CT) on the second day of illness, and marked brain edema was seen in all three. Magnetic resonance imaging (MRI) was performed in nine children and abnormal findings were seen in seven children. Two different distributions of brain lesions were observed on diffusion-weighted images: cerebral cortex-dominant lesions with or without deep gray matter involvement (Fig. 1A–D) and subcortical-dominant lesions (Fig. 1E,F). Five patients

Table 3. Neuroimaging findings

	Acute phase		Recovery phase	
Patient	Days after AE onset	Neuroimaging findings during the acute phase	Days after AE onset	Neuroimaging findings during the recovery phase
1	6	HIA in cerebral cortex, and caudate and lentiform nuclei on DWI	31	Diffuse atrophy on MRI
2	0	No abnormalities on MRI	10	HIA in cerebral cortex and corpus callosum on DWI
	4	HIA in cerebral cortex, caudate nuclei, thalami, and cerebellum on DWI		
3		Not done		Not done
4	0	HIA in cerebral cortex and subcortical WM on DWI	14	Diffuse atrophy on MRI
5	0	HIA in cerebral cortex, lentiform nuclei, and thalami on DWI	34	Diffuse atrophy on MRI
6	1	Marked brain edema on CT		Not done
7	0	No abnormalities on MRI	7	Mild atrophy on MRI
8	1	Marked brain edema on CT	68	Diffuse atrophy on MRI
9	0	HIA in subcortical WM on DWI	13	Mild atrophy on MRI
10		Not done	19	Mild atrophy, striatal necrosis on MRI
11		Not done	21	Diffuse atrophy on MRI
12	3	HIA in subcortical WM on DWI	21	Diffuse atrophy on MRI
13	1	No abnormalities on MRI	33	Diffuse atrophy on MRI
14	1	HIA in cerebral cortex, thalami, and cerebellum on DWI		Not done
15	1	Marked brain edema on CT		Not done

AE, acute encephalopathy; HIA, high intensity areas; WM, white matter; DWI, diffusion-weighted images; CT, computed tomography; MRI, magnetic resonance imaging.

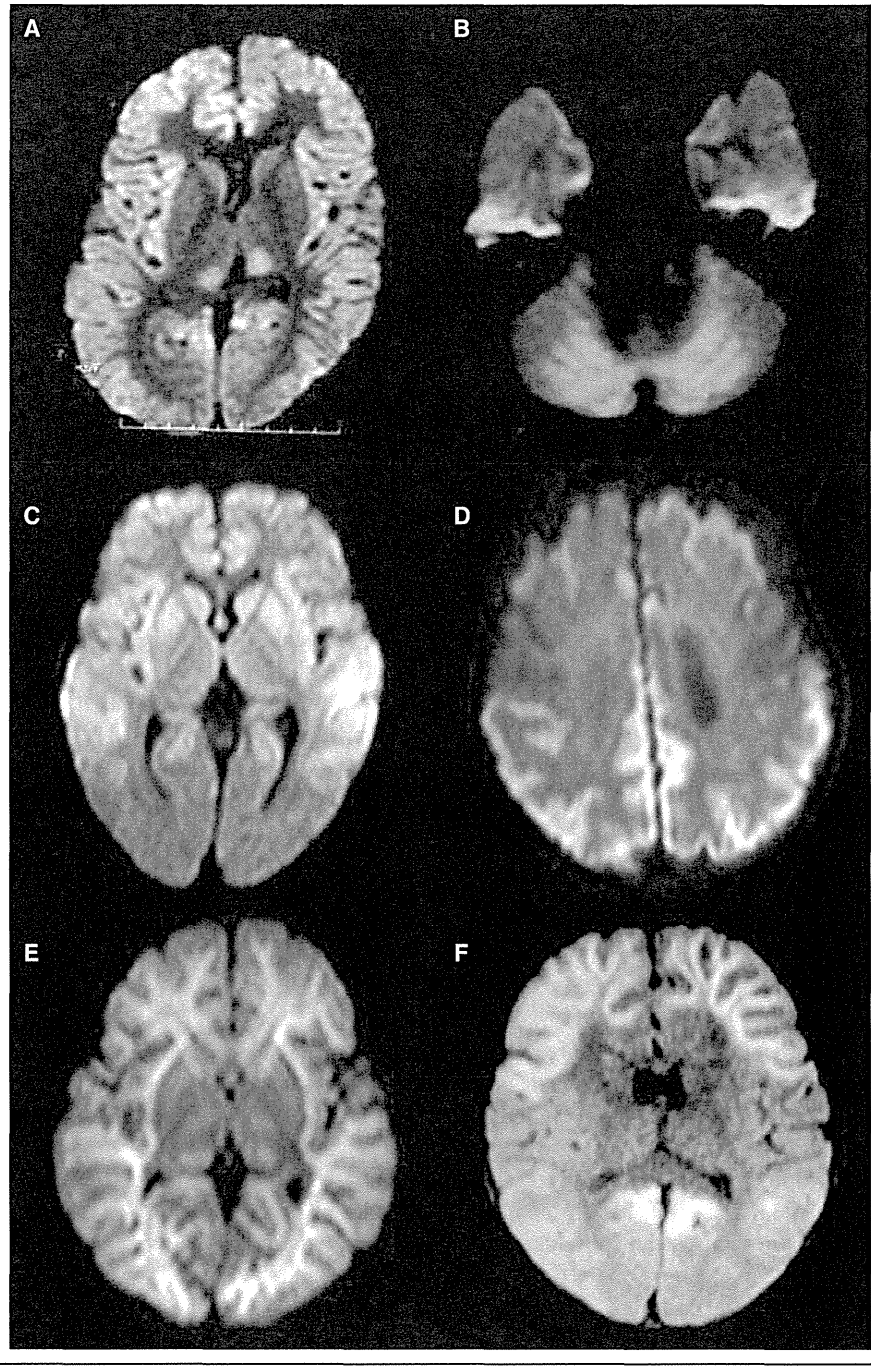

Figure 1.
Diffusion-weighted images. (**A**, **B**) Patient 15, 1 day after the onset of acute encephalopathy. Abnormal high intensities were observed in the cerebral cortex, thalami, and cerebellar hemispheres. (**C**) Patient 1, 6 days after the onset of acute encephalopathy. Abnormal high intensities were seen in the cortex in the frontotemporal region bilaterally and the caudate and lentiform nuclei bilaterally. (**D**) Patient 5, on the day of onset of acute encephalopathy. Abnormal high intensities were present in the cortex in the temporal-parietal-occipital region bilaterally. Slightly high intensities were also recognized in the cortex in the frontal region bilaterally. (**E**) Patient 12, 3 days after the onset of acute encephalopathy. Abnormal high intensities were seen in the entire subcortical white matter. (**F**) Patient 9, the day of the onset of acute encephalopathy. Abnormal high intensities were observed in the subcortical white matter in the frontal and mesial occipital regions bilaterally.

(Patients 1, 2, 4, 5, and 14) had cerebral cortex-dominant lesions. In addition to cortical lesions, caudate lesions were observed in two children, lentiform nuclei lesions in two, thalamic lesions in three, and cerebellar lesions in two. In three children, these lesions were present within the first 2 days after the onset. Two patients (Patients 9 and 12) had subcortical-dominant lesions: One patient had diffusion abnormalities in the entire subcortical white matter and the other had bilateral frontal lesions. No child with subcortical-dominant lesions had deep gray matter involvement. Among six children with cerebral cortex–dominant lesions, four had truncation mutations and one had no *SCN1A* mutation. *SCN1A* mutation was not assessed in the other two children. As to the two children with subcortical-dominant lesions, one had a missense mutation and the other had no *SCN1A* mutation. MRI after recovery from the acute encephalopathy was performed in 11 children. Marked, diffuse atrophy of the cerebral hemispheres was observed in seven children and mild atrophic changes in the other four.

Regarding treatment, barbiturate coma was administered in 7 children and continuous midazolam infusion in 12 during the clinical course. Phenobarbital and phenytoin were used in two and three children, respectively. Artificial ventilation was required in 12 children. Steroid pulse therapy was performed in eight, steroid other than pulse therapy in four, and intravenous immunoglobulin in five. Selective or systemic hypothermia was applied in four children.

The outcome in these children was invariably poor (Table 2). Four children died; nine survived with severe sequelae and two had moderate sequelae. All but one surviving child had moderate or severe cognitive impairment, and nine had moderate or severe motor impairment. In contrast, the seizure frequency after recovery was reduced, compared with that before the onset of acute encephalopathy in most surviving patients. Seven children had no seizures after recovery and four had monthly seizures. Although no statistical analysis was performed because of the small number of children, the outcome was relatively worse in children with a truncation mutation than in those with a missense mutation. Of six children with truncation mutations, two died and the other four survived with severe sequelae. Of three children with missense mutations, moderate sequelae were seen in two and severe sequelae in one. Three children without *SCN1A* mutations had severe sequelae.

Discussion

Our study revealed that acute encephalopathy can be an important complication of Dravet syndrome. A catastrophic clinical course is the outstanding feature of acute encephalopathy in children with Dravet syndrome. Some authors have recently reported children with Dravet syndrome accompanied by acute encephalopathy (Chipaux et al., 2010; Takayanagi et al., 2010; Tang et al., 2011). The clinical course of these patients is characterized by severe SE, followed by massive neurologic regression and marked brain atrophy. These features are similar to those in our patients. Sakauchi et al. (2011) conducted a questionnaire survey on the causes and prevalence of deaths related to Dravet syndrome. They reported that acute encephalopathy with SE was the cause of mortality in 21 (36%) of 59 patients who died. Berkovic et al. (2006) found de novo mutations of *SCN1A* in 11 of 14 children with alleged vaccine encephalopathy. These patients may have had acute encephalopathy, like our patients. Moreover, Kobayashi et al. (2010) performed a mutational analysis of *SCN1A* in 15 children with various types of acute encephalopathy. A missense *SCN1A* mutation was detected in a patient with a history of acute encephalitis with refractory, repetitive partial seizures. These facts suggest that Dravet syndrome or *SCN1A* mutation may be a genetic predisposition of acute encephalopathy induced by infection.

We considered the catastrophic neurologic conditions in our patients as acute encephalopathy rather than severe SE, although it is well known that pyrexia can cause SE leading to severe neurologic sequelae or even death in children with Dravet syndrome (Oguni et al., 2001; Dravet et al., 2005a). The SE triggered by fever in children with Dravet syndrome is not usually followed by severe neurologic deterioration (Oguni et al., 2001; Dravet et al., 2005a,b). Postictal motor deficit may be observed in some patients after SE, but motor function usually recovers within a few hours. In contrast, our patients were characterized by severe neurologic deterioration and marked brain lesions on MRI. These neuroimaging abnormalities are distinct from those reported in Dravet syndrome including temporal sclerosis, nonspecific atrophic changes, and increased intensities in the white matter (Oguni et al., 2001; Dravet et al., 2005b; Siegler et al., 2005; Striano et al., 2007). Hypoxic ischemic damage in association with systemic circulatory failure may explain the widespread brain lesions. However, serious hypoxia and/or systemic circulatory failure were not observed in any but one patient during the first few days. On the other hand, SE and prolonged impairment of consciousness are core neurologic symptoms of acute encephalopathy induced by infectious diseases (Togashi et al., 2004; Nagao et al., 2008; Wada et al., 2009). Diffusion abnormalities on MRI are often observed in children with acute encephalopathy, even without serious hypoxia or systemic circulatory failure (Takanashi et al., 2006; Okumura et al., 2009). On the basis of these observations, we considered that the SE in our patients will be derived from acute encephalopathy in itself from the start of seizures, not from epilepsy.

We found two different patterns of diffusion abnormalities on MRI in our cohort: reduced diffusion in the cortex and deep gray matter and that in the subcortical white matter. The distribution of the diffusion abnormalities was unique in patients with cortical and deep gray matter involvement. Thalamic involvement is a remarkable feature of acute necrotizing encephalopathy (Mizuguchi, 1997). However, diffusion abnormalities of the cortex have not been reported in children with acute necrotizing encephalopathy. Studies of *scn1a* mRNA expression in mice have shown that *scn1a* mRNA is highly expressed in the thalami, deep cerebral nuclei, pons, medulla, and spinal cord (Ogiwara et al., 2007). The involvement of the caudate nuclei and putamen may be explained by high expression of the mutant *SCN1A*. Reduced diffusion in the subcortical white matter was observed in two of our patients. The distribution of diffusion abnormalities resembled that of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), proposed by Takanashi et al. (2006; Takanashi, 2009). However, biphasic clinical course, that is an outstanding feature of AESD, was not recognized in any of our patients. The different clinical manifestations despite similar MRI findings are difficult to explain at present.

The precise incidence of acute encephalopathy among children with Dravet syndrome is not easy to determine. In our study, 13 of approximate 170 children with Dravet

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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Oxidative stress in patients with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)

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Abstract

We examined oxidative stress markers, tau protein and cytokines in the cerebrospinal fluid (CSF) in six patients with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). In the CSF, 8-hydroxy-2′-deoxyguanosine (8-OHdG) and hexanoyl-lysine adduct levels increased over the cutoff index in four and one out of six MERS patients, respectively. The CSF IL-6 and IL-10 levels were increased in three out of six patients, two of which had extended lesion of the cerebral white matter. The CSF value of tau protein, marker of the axonal damage, was not increased, and neuron specific enolase (NSE) in the CSF was not increased. The increased 8-OHdG levels in the CSF, DNA oxidative stress marker, in four MERS patients, suggesting involvement of oxidative stress in MERS. MERS is occasionally accompanied with hyponatremia, although our patients lacked hyponatremia. It is possible that the disequilibrium of systemic metabolism including electrolytes may lead to facilitation of oxidative stress and reversible white matter lesion in MERS. The increase of cytokine production seems to be involved in the distribution of lesions in MERS.

Keywords: Encephalitis; Encephalopathy; Corpus callosum; Splenium; Oxidative stress; Tau; Cytokine

1. Introduction

The patients with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) showed the magnetic resonance imaging (MRI) findings of a reversible lesion in the central portion of the splenium of corpus callosum (SCC) with transient reduced diffusion, and had mild clinical courses and recovered completely without sequelae [1,2]. Intramyelinic edema, hyponatremia and axonal damage have been hypothesized for pathogenesis in MERS [2–4]. However, the detailed reasons for the transiently reduced diffusion are unknown. Levels of oxidative stress markers [5] and tau protein [6], a marker of axonal injuries, have been examined in the cerebral spinal fluids (CSF) in the patients with

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developmental brain disorders. We reported the involvement of oxidative stress in a patient with limbic encephalopathy [7]. Here we examined the oxidative stress markers, tau proteins and neuron specific enolase (NSE) in CSF in six MERS patients to clarify the pathogenesis.

2. Materials and methods

Six patients (four female and two male, age 1–13 years) diagnosed as MERS with clinical course and MRI findings were included (Table 1). Six controls aged from 11 months to 8 years, in which the CSF was tested for the examination of fever, and no neurological symptoms such as convulsions were observed. Parent consent was obtained in all subjects in accordance with the Helsinki Declaration and all protocols were approved by the institutional ethics committee of the Tokyo Metropolitan Institute of Neuroscience. Viral infection was preceded in four out of six patients, and patient 5 demonstrated an increase in serum level of CRP (Table 1). The amount of DNA oxidative stress marker, 8-hydroxy-2′-deoxyguanosine (8-OHdG), and the early stage lipid peroxidation marker, hexanoyl-lysine adduct (HEL), were examined using ELISA kits (Japan Institute for the Aging, Shizuoka, Japan) [5]. Tau protein and NSE were determined using ELISA kit (BioSource International, Inc., CA) [6], and radioimmunoassay, respectively. Cytokine levels were evaluated by multiplex bead-based assay (BioPlex 200 system) (Bio-Rad Laboratories, CA). The comparison of averaged CSF values of each marker between the MERS patients and controls was analyzed by t-test, respectively, and $p < 0.05$ was evaluated as significant.

3. Results

There were no abnormalities in serum levels of sodium (136–141 mmol/l) and other electrolytes. Patient 5 showed delirium, whereas other five patients did not. Five patients except patient 6 had generalized tonic seizures, and anticonvulsants were given temporally. Patient 1 subsequently developed cluster of the similar convulsion, and continuous intravenous infusion of midazolam. Patients 2 and 4 were given antibiotics for a few days. Hyponatremia or hypoglycemia was not seen in patients. Patients 2 and 4 demonstrated the additional signal changes in the cerebral white matters on diffusion-weighted MRI (extended lesion). Patients 1, 2 and 4 showed transient mild increase of liver transaminase. In the CSF, no patients demonstrated abnormalities in protein level or cell count (Table 2). We calculated the mean + 2SD value in controls to set up a cutoff index for 8-OHdG, HEL, tau protein NSE and cytokines. In the CSF, 8-OHdG levels increased over the cutoff index in four out of six MERS patients. HEL level was increased over the cutoff index in patient 6, in which the 8-OHdG value was not increased. IL-6 and IL-10 were increased in three out of six patients, patients 2 and 4 of which had extended lesion of the cerebral white matter. Patient 6 showed increased levels of cytokines in the absence of extended lesion, but the distribution pattern of splenial lesions did not differ from that in patient 1, not showing increased levels of cytokines. There were no patients showing abnormal levels of tau protein and NSE. The CSF 8-OHdG values were significantly increased in the MERS patients ($p = 0.029$). There were no significant differences in CSF values of other markers between the patients and controls.

4. Discussion

The causes of transient and reduced diffusion in the SCC are unknown in MERS patients [2]. The SCC consists of commissural fibers from the occipital, temporal and parietal lobes, the changes in which tend to affect the SCC more frequently than the genu or body of corpus callosum. The difference in arterial vascularization and/or water content in the corpus callosum may lead to the frequent occurrence of SCC lesion [8,9]. Reversible diffusion changes in the SCC are also observed in patients with epilepsy receiving antiepileptic drugs, in which the involvement of focal cytotoxic edema occurring at the glial level is speculated by the absence of fiber interruption on diffusion tensor imaging [3]. However, no patients in this analysis had anticonvulsants before the onset of MERS. Intramyelinic edema may be hypothesized in pathogenesis of MERS, but the neonate showing an identical lesion in the SCC with incomplete myelination did not support such intramyelinic edema hypothesis [4]. Tau protein is reported to increase in

Table 1
Summary of clinical features. Abbreviations: GTCS, generalized tonic clonic seizure; DZP, diazepam; PB, phenobarbital; Extended, extended lesion of the cerebral white matter; GTS, generalized tonic seizure.

Patient	Age/sex	Antecedent events	CRP at admission (mg/dl)	Convulsions	Anticonvulsants	Lesions on MRI
1	1y/F	(Not determined)	0.53	Day 3, GTCS	DZP, PB, midazolam	Splenial
				Cluster of GTCS	Midazolam	Splenial
2	2y/F	Viral tonsilitis	1.28	Day 1, GTCS	DZP	Extended
3	2y/M	Influenza A virus	1.9	Day 2, GTCS	DZP,PB	Splenial
4	3y/F	(Not determined)	3.5	Day 4, GTCS	DZP,PB	Extended
5	6y/M	RS virus	8.527	Day 6, GTS	(None)	Splenial
6	13y/F	Influenza A virus	<0.3	(None)	(None)	Splenial

Table 2
Summary of data in patients and controls. Stars denote the values above the cutoff index. Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; HEL, hexanoyl-lysine adduct; NSE, neuron specific enolase; IL, interleukin; n/a, not assessed.

Patient	Cerebrospinal fluid								
	Day	Cell count	Protein (mg/dl)	8-OHdG (ng/ml)	HEL (nmol/l)	Tau protein (pg/ml)	NSE (ng/ml)	IL-6 (pg/ml)	IL-10 (pg/ml)
		Controls	Mean ± SD	0.043 ± 0.027	2.64 ± 1.72	450 ± 119	8.6 ± 4.1	3.5 ± 2.9	0.9 ± 0.8
			(Cutoff)	0.097	6.08	688	16.8	9.3	2.5
1	1	1.3	8	0.06	4.158	396	6.9	2.4	0.39
	13	2	19	0.06*	3.355	637	16	0.76*	0.03
2	2	0	13	0.173*	2.6	422	5	9.41*	6.11*
3	3	3	<10	0.174*	4.99	489	n/a	n/a	n/a
4	4	0.3	32	0.374*	n/a	48	n/a	13.96*	7.15*
5	3	1	24.9	0.328*	1.72	320	n/a	n/a	n/a
6	2	0.3	21	0.041	7.37*	281	5.1	15.56*	2.79*
			Mean ± SD	0.173 ± 0.134	4.03 ± 2	370 ± 184	8.3 ± 5.2	8.4 ± 6.7	3.3 ± 3.2
		t-test	(*p* value)	0.018	0.275	0.194	0.457	0.101	0.086

the white matter diseases including leukodystrophy and encephalopathy with reduced diffusion in the cerebral white matter. The CSF values of tau protein were not increased in the MERS patients, indicating less possible involvement of axonal injury. The absence of severe axonal damage is in good accordance with the absence of fiber interruption on diffusion tensor imaging in the aforementioned epileptic patients with a similar SCC lesion [3]. It is noteworthy that the tau protein values increased from 396 to 637 pg/ml in patient 1 (Table 2), although the consecutive assay of CSF is not practical, given good prognosis of MERS.

Oxidative stress is reported to relate to some neurological diseases [5,7,10]. The CSF values of 8-OHdG and HEL increased in four and one MERS patients, respectively, and the increase of 8-OHdG values was significant (Table). The CSF 8-OHdG values increased in the patients with status convulsive [10]. In our study, the patient 1 with more severe epileptic seizure lacked abnormalities in the CSF oxidative stress markers. Oxidative stress is involved in infectious and/or inflammatory white matter diseases [11]. The MERS patients did not have any common predisposing episodes (Table 1). Patient 6 aged over 10 years and lack convulsion, and such clinical features may be related to increased level of HEL but not of 8-OHdG (Tables 1 and 2), however the exact reason of discrepancy between changes of 8-OHdG and HEL in each patient remains to be investigated. Five patients with the increased CSF values of 8-OHdG or HEL showed various inflammatory changes, in which the serum CRP levels ranged from < 0.3 to 8.527 mg/dl (Table 2). There was no direct relationship of oxidative stress with infection or inflammation. However, patients 2 and 4 with the extended lesion showed increased CSF values of IL-6 and IL-10, and altered cytokine production may be involved in the distribution of lesions in MERS. The involvement of oxidative stress has been reported in non-inflammatory myeline disorders such as pontine myelinolysis due to hypoglysemia [12]. It was reported in rats that a rapid rise in serum sodium following hyponatremia potentiated oxidative stress, which subsequently damaged myelin proteins [13]. MERS is occasionally accompanied with hyponatremia [2]. Although our patients lacked hyponatremia, the disequilibrium of systemic metabolism including electrolytes may lead to facilitation of oxidative stress and reversible white matter lesion in MERS.

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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

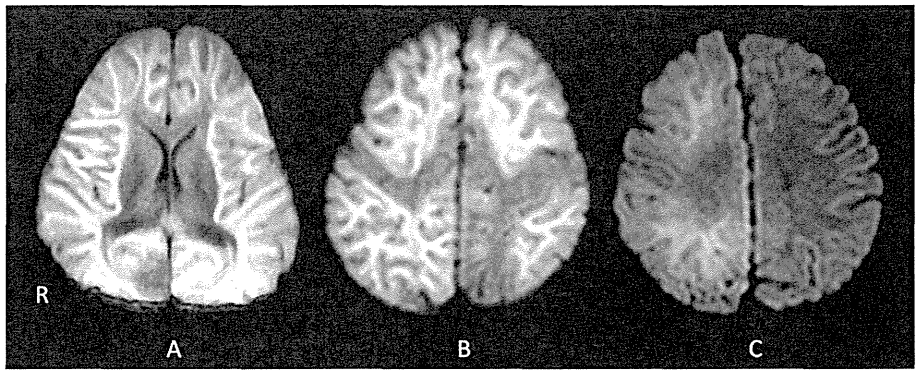

Fig. 1. Sample diffusion-weighted images of acute encephalopathy with reduced subcortical diffusion. (A) Diffuse reduced subcortical diffusion. Abnormal high intensities were observed in the whole subcortical white matter. (B) Bilateral reduced subcortical diffusion with central sparing. Abnormal high 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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Case report

Sporadic hemiplegic migraine presenting as acute encephalopathy

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Abstract

A 10-year-old boy with psychomotor developmental delay and cerebellar vermis atrophy developed right hemiplegia with vomiting, unconsciousness, convulsions, and late-onset fever. Slow delta activity was noted over the left hemisphere on electroencephalography, and neuroimaging revealed swelling of the left temporo-occipital cerebral cortex with restricted diffusivity, successive transient cortical atrophy, and hyperperfusion over the left cerebral hemisphere. Interleukin-6 was elevated in the cerebrospinal fluid. The acute symptoms resolved completely within 3 weeks after onset, but hypoperfusion persisted in the left posterior cortex thereafter. Another episode with transient left hemiplegia appeared 7 months later, followed by recurrence of migraine attacks. Analysis of the *CACNA1A* gene revealed a mutation of c.1997 C > T (p.T666M). None of his family members had migraine. This case represents an unusual evolution of sporadic hemiplegic migraine with manifestations of acute encephalopathy, for which the role of migraine-related inflammatory process is assumed.

Keywords: Hemiplegic migraine; Neuroimaging; Inflammation; Interleukin-6

1. Introduction

Hemiplegic migraine is a rare subtype of migraine with aura and shows either familial or sporadic occurrence. Patients with familial hemiplegic migraine have recurrent attacks of headache and hemiplegia with an autosomal dominant trait, while those with sporadic hemiplegic migraine have similar clinical symptoms except for family history [1]. Both familial and sporadic hemiplegic migraines are genetically heterogeneous and the majority of them are caused by mutations in *CACNA1A*, *ATP1A2*, and *SCN1A*. On rare occasions, patients with hemiplegic migraine experience hemiplegic attack with symptoms of acute encephalopathy, including fever, vomiting, unconsciousness, and convulsions [1–4]. However, little is known about the pathomechanism of this hemiplegic migraine-related encephalopathy.

We herein report a case of sporadic hemiplegic migraine with *CACNA1A* T666M mutation in which hemiplegic migraine-related encephalopathy developed without preceding history of headache or hemiplegia.

2. Case report

The patient was a 10-year-old boy who was born to nonconsanguineous parents after uneventful pregnancy and delivery. Delayed psychomotor development was noted during his infancy. Although he gained the ability to walk at the age of 2 years and 6 months, he slowly

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