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FULL-LENGTH ORIGINAL RESEARCH

Acute encephalopathy in children with Dravet syndrome

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Summary

Purpose: The occurrence of acute encephalopathy in children with Dravet syndrome has been reported sporadically. This study clarified the features of acute encephalopathy in children with Dravet syndrome.

Methods: Through the mailing list of the Annual Zao Conference on Pediatric Neurology, we collected 15 patients with clinically diagnosed Dravet syndrome, who had acute encephalopathy, defined as a condition with decreased consciousness with or without other neurologic symptoms, such as seizures, lasting for >24 h in association with infectious symptoms.

Key Findings: There were seven boys and eight girls. A mutation of the *SCN1A* gene was present in nine (truncation in six and missense in three). The frequency of seizures during the 3 months before the onset of acute encephalopathy was monthly in seven children and none in three. The median age at the onset of acute encephalopathy was 44 months (range 8–184 months). All children had status epilepticus followed by coma as the initial manifestation. Two different distributions of brain lesions were observed on diffusion-weighted images during the acute phase: cerebral cortex–dominant lesions with or without deep gray matter involvement and subcortical-dominant lesions. Four children died; nine survived with severe sequelae, and two had moderate sequelae.

Significance: We must be aware that acute encephalopathy is an important complication in children with Dravet syndrome, and associated with fulminant clinical manifestations and a poor outcome.

KEY WORDS: Dravet syndrome, Acute encephalopathy, *SCN1A*, MRI.

Dravet syndrome is an epileptic syndrome characterized by the following: an onset with prolonged seizures that are often provoked by fever during early infancy, intractable seizures, repetitive episodes of status epilepticus (SE), and a subsequent decline in cognitive function (Dravet et al., 2005a). Fever sensitivity is an outstanding feature of Dravet syndrome. SE can be provoked by a febrile illness and may be followed by severe neurologic sequelae. Most patients with Dravet syndrome have a mutation in the *SCN1A* gene, which encodes the voltage-dependent sodium channel (Nav1.1) α subunit (Claes et al., 2001).

Acute encephalopathy, characterized by noninflammatory cerebral edema, implies sudden onset of severe central nervous system (CNS) symptoms such as convulsions followed by prolonged consciousness disturbance, and is often preceded by infection (Mizuguchi et al., 2007). In Japan, acute encephalopathy during influenza, exanthema subitum, and other febrile illnesses has attracted the attention of pediatric neurologists and general pediatricians since the outbreak of influenza-associated encephalopathy in the winter of 1997/1998 (Morishima et al., 2002). The occurrence of acute encephalopathy in children with Dravet syndrome has been reported sporadically in Japan (Takayanagi et al., 2010). In addition, we encountered several children with Dravet syndrome who had acute encephalopathy in association with a febrile illness. In addition, similar events have been reported from the developed countries in Europe, North America, and Oceania (Berkovic et al., 2006; Chipaux et al., 2010; Tang et al., 2011). Children with Dravet syndrome

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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.

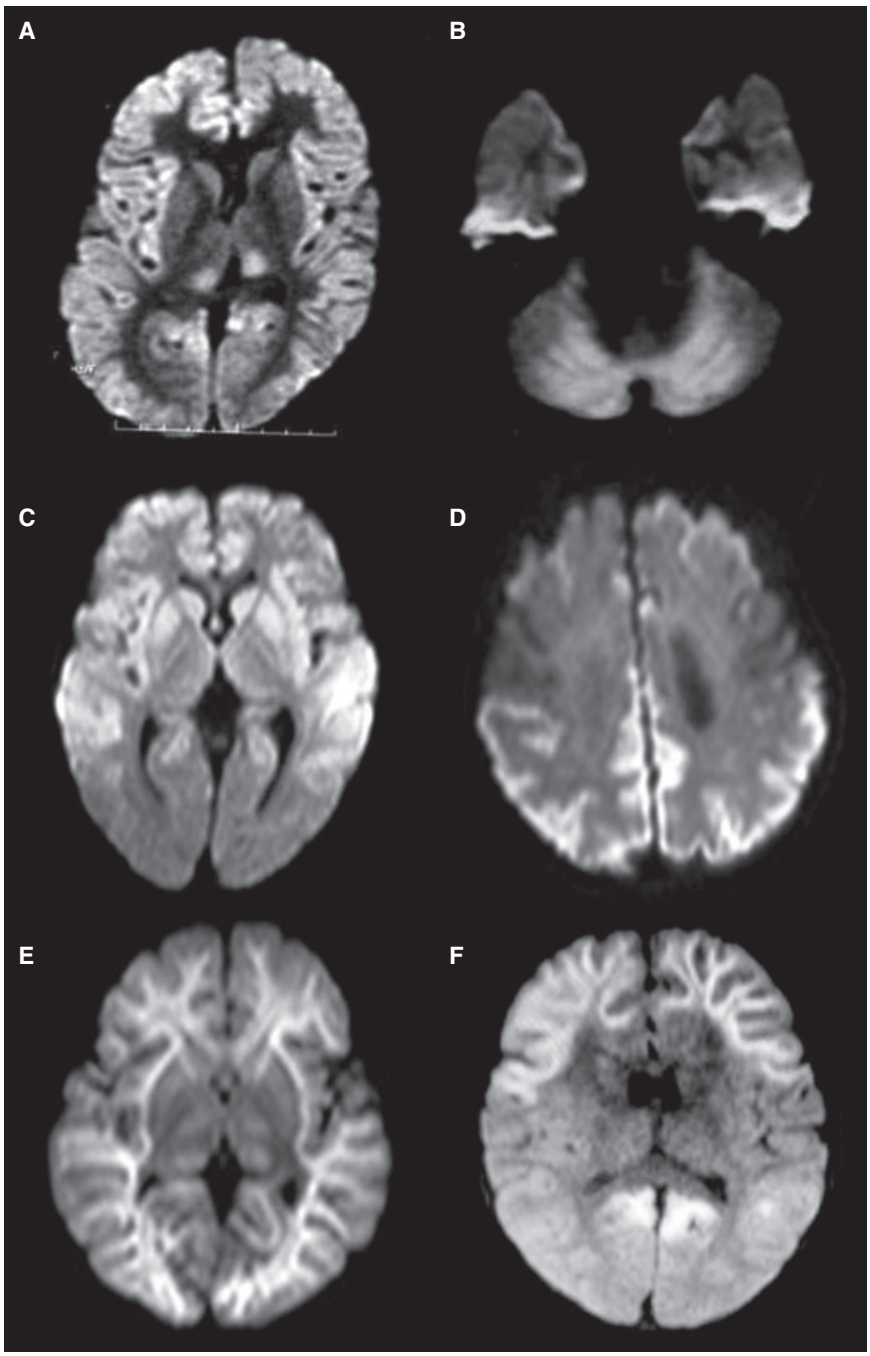

Figure 1.
Diffusion-weighted images. (**A**, **B**) Patient 15, 1 day after the onset of acute encephalopathy. Abnormal high intensities were observed in the cerebral cortex, thalami, and cerebellar hemispheres. (**C**) Patient 1, 6 days after the onset of acute encephalopathy. Abnormal high intensities 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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