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FULL-LENGTH ORIGINAL RESEARCH

Mutations of the *SCN1A* gene in acute encephalopathy

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Summary

Purpose: Acute encephalopathy is the most serious complication of pediatric viral infections, such as influenza and exanthema subitum. It occurs worldwide, but is most prevalent in East Asia. Recently, there have been sporadic case reports of epilepsy/febrile seizure and acute encephalopathy with a neuronal sodium channel alpha 1 subunit (*SCN1A*) mutation. To determine whether *SCN1A* mutations are a predisposing factor of acute encephalopathy, we sought to identify *SCN1A* mutations in a large case series of acute encephalopathy including various syndromes.

Methods: We analyzed the *SCN1A* gene in 87 patients with acute encephalopathy, consisting of 20 with acute necrotizing encephalopathy (ANE), 61 with acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), and six with nonspecific (unclassified) acute encephalopathy.

Key Findings: Three patients had distinct point mutations. Two of them had epileptic seizures prior to acute encephalopathy. Clinical and neuroradiologic findings of acute encephalopathy were diverse among the three patients, although all had a prolonged and generalized seizure at its onset. The first patient with V982L had partial epilepsy and AESD. The second patient with M1977L had febrile seizures and nonspecific acute encephalopathy. The third patient with R1575C had no seizures until the onset of ANE. M1977L was a novel mutation, whereas the remaining two, V982L and R1575C, have previously been reported in cases of Dravet syndrome and acute encephalopathy, respectively.

Significance: These findings provide further evidence that *SCN1A* mutations are a predisposing factor for the onset of various types of acute encephalopathy.

KEY WORDS: *SCN1A*, Ion channel gene defect, Acute encephalopathy status epilepticus, Seizure susceptibility.

Acute encephalopathy (AE) refers to brain dysfunction of acute onset that usually follows an infectious disease with fever. Pathologic substrate of AE is diffuse, noninflammatory brain edema. AE is most common in infants and young children, and is manifested clinically with stupor/coma and a febrile seizure, which is often severe and prolonged.

Based on clinical and neurologic findings, AE is classified into multiple syndromes, such as Reye's syndrome, acute necrotizing encephalopathy (ANE) (Mizuguchi et al., 1995), and acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) (Takanashi et al., 2006). These syndromes show distinct computed tomography/magnetic resonance imaging (CT/MRI) features: diffuse brain edema in Reye's syndrome; bilateral, symmetric thalamic lesions in ANE; and cerebral cortical edema of subacute onset (usually appearing on the third to ninth day of illness, and sparing the perirolandic region) in AESD (Mizuguchi et al., 2007); however, about one-third of patients with AE show no such features and are unable to be classified into these syndromes (nonspecific AE). Pathogenesis of AE is complex, and much remains to be elucidated. The main pathomechanism differs among syndromes: metabolic disorder in Reye's syndrome, cytokine storm in ANE, and excitotoxicity in AESD (Mizuguchi et al., 2007). Delayed neuronal death after a severe/prolonged febrile seizure may play a major role in the pathophysiology of AESD (Mizuguchi et al., 2007; Takanashi et al., 2009).

Mutation of the neuronal sodium channel alpha 1 subunit (*SCN1A*) is the most common cause of hyperthermia-induced seizure susceptibility in patients with generalized epilepsy with febrile seizure plus (GEFS+) and Dravet syndrome (Escayg et al., 2000; Claes et al., 2001; Escayg et al., 2001; Wallace et al., 2001, 2003; Ohmori et al., 2002; Sugawara et al., 2002; Nabbout et al., 2003; Fukuma et al., 2004; Mantegazza et al., 2005; Escayg & Goldin, 2010). By contrast, *SCN1A* mutations are rare in febrile seizures other

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than GEFS+ and Dravet syndrome (Malacarne et al., 2002). Recently, there have been sporadic case reports of epilepsy/febrile seizure and AE with an *SCN1A* mutation (Sakakibara et al., 2009; Kobayashi et al., 2010; Takayanagi et al., 2010). In addition, children with Dravet syndrome occasionally have AE, which often causes death (Sakauchi et al., 2011). These cases suggest the role of *SCN1A* mutations in the pathogenesis of AE. To validate the hypothesis that *SCN1A* mutations are a predisposing factor of AE, we conducted *SCN1A* gene analysis in a large case series of AE, including various syndromes.

Methods

Patients

The Ethics Committees of the University of Tokyo approved this study. The parents or legal guardians of participants signed an informed consent form as approved by the ethics committees. Eighty-seven patients, 48 female and 39 male, who were diagnosed with AE and treated by 29 hospitals in Japan between September 2008 and August 2010, participated in this study. All the patients were of Japanese ethnicity. Diagnosis of AE was based on the following criteria: (1) impairment of consciousness showing acute onset, rapid progression and duration for more than 24 h, with or without seizures; (2) onset during the course of a febrile and/or infectious disease; and (3) exclusion of similar conditions, such as postictal stupor/coma, effect of anticonvulsants, meningitis, encephalitis, toxic encephalopathy, and metabolic errors. In addition, the patients were divided to three subgroups. Diagnosis of ANE and AESD was based on the criteria described previously (Hoshino et al., 2011). According to syndromic classification, 20 patients had ANE, 61 had AESD, and 6 had nonspecific AE (Table 1). There was no case of classical Reye's syndrome. Seven patients had preexisting febrile seizures and one patient had partial epilepsy before the onset of acute encephalopathy (Table 1). One hundred healthy adult Japanese volunteers without a history of AE served as control subjects.

Genetic analysis

Genomic DNA of patients with AE was prepared from ethylene diamine tetraacetic acid (EDTA)–treated whole blood samples using the QuickGene DNA whole blood kit (Fujifilm Corporation, Tokyo, Japan). *SCN1A* was screened by a direct sequencing method with an automatic sequencer, as described previously (Kobayashi et al., 2010). Reference sequence of mRNA was based on information available from GenBank (accession number: Human SCN1A. AF117907.1).

Results

Of the 87 AE cases studied, three had missense mutations—V982L, M1977L, and R1575C—none of which were found in the 100 controls. The *V982L* mutation was found in case 1 with partial epilepsy and AESD. The valine 982 residue is located on the transmembrane segment 6, domain II of SCN1A protein, is highly conserved among vertebrates, and shares homology with other types of sodium channels (Fig. 1). This mutation was previously reported in a patient with Dravet syndrome without myoclonic seizures and ataxia (Singh et al., 2009). The M1977L mutation was found in case 2 with GEFS+ and nonspecific AE. The methionine 1977 residue is located on near the

Table 1. Clinical data of 87 patients with acute encephalopathy (AE)

Diagnosis	Sex	Age at onset of AE (mean)	Family history of FS/epilepsy	Preexisting seizures	Preceding infection	Status epilepticus or cluster of seizures within 2 days after the onset of AE	Prognosis: Neurologic sequelae
ANE	Male 7	8 months to 9 years	FS 2	FS 1	HHV-6 3	Yes 3	Severe 9
(n = 20)	Female 13	7 months	Epilepsy 0	Epilepsy 0	Flu 4	No 2	Mild or none 9
		(2 years 4 months)	None 18	None 19	RSV 2	NA 15	NA 2
					Rota 1		
					NI 10		
AESD	Male 28	5 months to 6 years	FS 6	FS 3	HHV-6 18	Yes 33	Severe 14
(n = 61)	Female 33	(1 year 9 months)	Epilepsy 1	Epilepsy 1	Flu 8	No 23	Mild or none 41
			None 50	None 53	RSV 2	NA 5	NA 6
			NA 4	NA 4	Others 4		
					NI 29		
Nonspecific AE	Male 4	1 year 9 months to	FS 1	FS 3	Flu 2	Yes 5	Severe 0
(n = 6)	Female 2	6 years 1 month	None 5	None 3	NI 4	No 1	Mild or none 5
		(3 years 2 months)					NA 1

Patients were classified into three syndromes: acute necrotizing encephalopathy (ANE), acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), and nonspecific AE. FS, febrile seizures; NA, not available; HHV-6, human herpesvirus 6; Flu, influenza virus; RSV, respiratory syncytial virus; Rota, rotavirus; NI, not identified.

	1.V982L	2.M1977L	3.R1575C
SCN1A	VIGNLVVLNLF	KTDLTMSTAAC	TTILSRINLVF
CHIMPANZEE	----------	----------	----------
RAT	--R-------	----------	-S--------
MOUSE	----------	----------	-S--------
DROS	----------		
SCN2A	----------	---M-P--TSP	-N--YW-----
SCN3A	----------	---GSS--TSP	
SCN8A	----------		EN--YW-----

Figure 1.
Alignment of the amino acids surrounding the missense mutations in *SCN1A* of three acute encephalopathy cases. CHIMPANZEE (accession no. XP_515872), *Pan troglodytes* sodium channel α subunit; RAT (NP_110502), rat sodium channel α1 subunit; MOUSE (CAM17350), mouse sodium channel α1 subunit; DROS (NP_523371), *Drosophila melanogaster* sodium channel α subunit. *Drosophila* gene shares no homology with human *SCN1A* (BAC21101) at M1977 and R1575 locations. All other amino acid sequences are from human sodium channel α subunit expressed in the brain. SCN8A (NP_055006) shares no homology with SCN1A at the C-terminal end of the protein. Accession nos. of SCN2A and SCN3A are Q99250 and NP_008853.

C-terminus, and is conserved through mammalians (Fig. 1). The R1575C mutation was found in case 3 with ANE. This mutation has been reported previously in a patient with acute encephalitis with refractory, repetitive partial seizures (AERRPS) (Kobayashi et al., 2010), as well as in a patient with Rasmussen encephalitis with an autoantibody against the glutamate receptor GluR3 (Ohmori et al., 2008), and markedly alters the electrophysiologic properties of the sodium channel. The arginine 1575 residue is highly conserved among vertebrates (Fig. 1). The clinical course of these three patients is described briefly below.

Case 1: AESD with V982L mutation

This patient, a 2-year-old girl, was born small-for-date weighing 2,008 g, after gestation of 39 weeks. There was no family history of epilepsy or seizure disorders. From the age of 3 months, she had recurrent, afebrile complex partial seizures. There was no febrile seizure, myoclonic seizure, mental delay, or ataxia. The diagnosis of partial epilepsy was made, and prophylaxis with carbamazepine was begun. From 1 year and 11 months, she also had bronchial asthma. At 2 years and 3 months of age, she underwent treatment with intravenous theophylline for an asthma attack. She then had a respiratory infection with fever and vomiting, and developed myoclonic seizures, which evolved into prolonged generalized tonic convulsion. Status epilepticus was refractory to anticonvulsants and lasted 2 hours, requiring general anesthesia and mechanical ventilation. Although cranial CT was normal on day 2, coma persisted. Serum levels of aminotransferases and lactic dehydrogenase were very high. On day 5, she had clusters of partial seizures. CT revealed diffuse cerebral cortical edema. Based on the biphasic clinical course and serial CT findings, the diagnosis of AESD was made. She was treated with continuous infusion of thiopental (until day 21) and methylprednisolone pulse therapy. CT and MRI thereafter showed severe atrophy of the cerebral cortex with sparing of bilateral perirolandic regions (Fig. 2). She was eventually left with spastic quadriplegia and severe mental deficit.

Case 2: Nonspecific AE with M1977L mutation

This patient, a 3-year-old boy, was born uneventfully to nonconsanguineous parents. His uncle had had febrile convulsions during infancy. From the age of 1 year 6 months, he had recurrent febrile seizures. At 3 years of age, he had a respiratory infection with fever, and then had his sixth attack consisting of repeated generalized convulsions, six times during 24 h. Each convulsion lasted from several seconds to 5 min. Phenytoin (15 mg/kg) was given intravenously to prevent their recurrence. Consciousness disturbance (Glasgow Coma Scale score, E4V4M5) persisted for 24 h, and was explained neither by postictal stupor nor by sedative effects of phenytoin. Cranial CT revealed mild diffuse edema. Electroencephalography (EEG) on day 1 showed high-voltage slow activity in the right parietal area. He was diagnosed with nonspecific AE and recovered completely; however, he developed a cluster of afebrile seizures 1 month later. EEG showed bilateral frontal spike-waves. Valproate treatment successfully prevented seizures. He had neither mental delay nor ataxia.

Case 3: ANE with R1575C mutation

The patient is now a 12-year-old boy who was born uneventfully and showed normal development. At the age 9 months, he had acute gastroenteritis with fever (tempera-

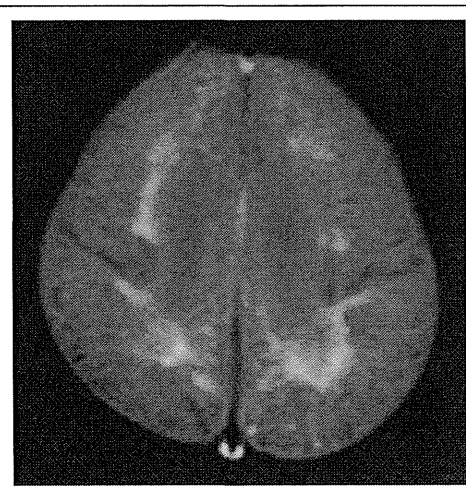

Figure 2.
Cranial MRI of a patient (case 1) with acute encephalopathy with biphasic seiaures and late reduced diffusion (AESD). Imaging at 4 years after AE (fluid-attenuated inversion recovery, FLAIR) showed cerebral atrophy, high signal intensity of the white matter, and sparing of the bilateral perirolandic regions.

ture 38°C) and diarrhea. Four days later, he was taken to hospital because of generalized seizure after several bouts of vomiting. On admission, he was afebrile and mentally obtunded, and had recurrent generalized tonic–clonic seizures. Blood examination showed slight elevation of C-reactive protein, and cerebrospinal fluid examination showed an increased protein level (370 mg/dl). MRI revealed abnormal signals in the bilateral thalamus and subcortical white matter on T_2-weighted images (Fig. 3A). Contrast T_1-weighted imaging showed medullary streaks in the white matter (Fig. 3B). Based on the clinical and imaging findings, the diagnosis of ANE was made. He was treated with intravenous anticonvulsants and gammaglobulin, and recovered without any sequelae. Two years later, his younger sister was also affected by ANE at the age of 8 months, and was eventually left with severe motor and cognitive impairment. She did not have the R1575C mutation.

Discussion

AE is a complex disorder in which multiple factors, both genetic and environmental, are involved. Environmental factors include not only infectious agents, such as influenza virus and human herpesvirus 6 (HHV-6), but also drugs, such as aspirin and theophylline (Mizuguchi et al., 2007). With regard to genetic factors, single nucleotide polymorphisms (SNPs) of carnitine transpalmitoyl transeferase II (*CPTII*) and Toll-like receptor 3 (*TLR-3*) have been identified as predisposing factors of AE (Chen et al., 2005; Hidaka et al., 2006; Shinohara et al., 2011). In our previous study on the *CPT II* gene, we found in two of the present cases (cases 2 and 3) thermolabile SNPs associated with susceptibility to AE (Shinohara et al., 2011). The relationship of these SNPs and AE is complex. For example, *CPTII* SNPs occur in association with two syndromes: AESD and ANE (Shinohara et al., 2011). For each syndrome, unidentified genes other than *CPTII* are likely to be also involved. On the other hand, there is one syndrome of AE caused by mutations of a single gene: *ANE1* (familial recurrent variant of ANE) due to mutation of the Ran-binding protein 2 (*RANBP2*) gene (Neilson et al., 2009).

In this study, we tested the possibility that mutation of another gene, *SCN1A*, is a genetic predisposition for the onset of AE. We performed *SCN1A* gene analysis in 87 Japanese patients with AE, and found point mutations, V982L, M1977L, and R1575C, in three (3.4%) of them. These results are comparable to those of a previous study, which found an *SCN1A* mutation in one of 15 AE patients (Kobayashi et al., 2010). Our study dealt with a large case series of AE, and found multiple patients with *SCN1A* mutations, thereby establishing the association between *SCN1A* mutations and AE.

In addition to our three patients, three additional patients with AE and a *SCN1A* mutation have been reported previously. Clinical and neuroradiologic findings of these six patients are variable (Table 2). With regard to epilepsy, two patients had Dravet syndrome, one had GEFS+, one had partial epilepsy, one had febrile seizures, and the remaining one had none. On the other hand, *SCN1A* missense mutations have been identified not only in patients with Dravet syndrome and GEFS+, but also in unaffected subjects without a seizure disorder (Ohmori et al., 2008). Therefore, their contribution to epilepsy and AE requires critical evaluation and further investigation.

With regard to AE, three had AESD, one had AERRPS, one had ANE, and one had nonspecific AE. Clinical features varied among the cases, although all had either prolonged seizures (status epilepticus; four cases) or a cluster of brief seizures (three cases), mostly with fever (five cases), on day 1 or 2, in contrast to mutation-negative patients in whom such seizures were absent in about 40% (Table 1). Prognosis also varied largely from severe psychomotor deficit to complete recovery. Notably, two patients with the same *SCN1A* mutation, R1575C, showed clinical phenotypes quite different from each other. Case 3 in this study had no

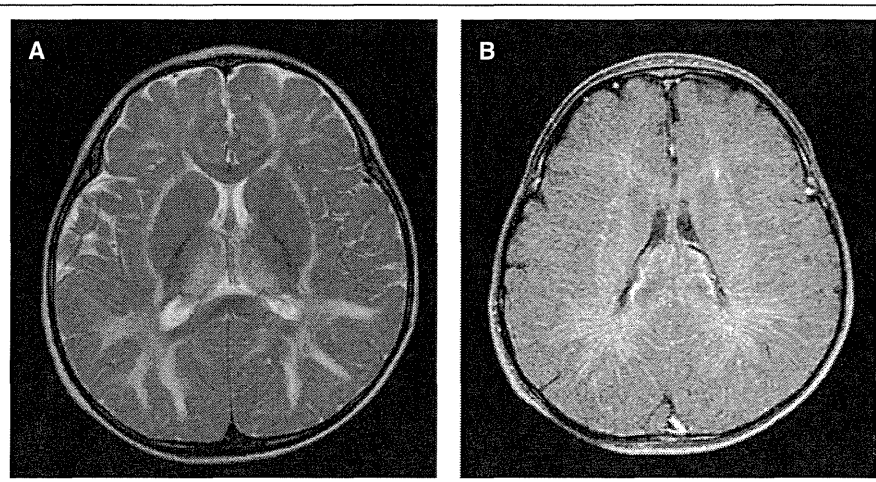

Figure 3.
Cranial MRI of a patient (case 3) with acute necrotizing encephalopathy (ANE). (**A**) T_2-weighted axial section shows high-intensity areas of bilateral thalami and the cerebral white matter. (**B**) Gadolinium-enhanced T_1-weighted axial image shows medullary streaks in the affected white matter lesions.

Table 2. Characteristic of AE and preceding epilepsy in the [a]present (cases 1, 2 and 3) and previously reported cases

Case no.	Age	Gender	*SCN1A* mutation	Antecedent infection	Other etiologic factors	Precedimg eplilpsy or seizure dieorder	AE	Seizure at acute stage of AE	Neuroimaging findings	Prognosis	Reference
1[a]	2 years 3 months	F	V982L/ missense	Upper respiratory infection	Theophylline	Partial epilepsy	AESD	Status, febrile, on day1	CT/day 2, unremakable; CT/day 5, diffuse brain edema; follow-up MRI, central sparing	Spastic quadriplegia, severe MR	This study
2[a]	3 years	M	M1977L/ missense	Upper respiratory infection		GEFS+	Nonspecific AE	Cluster, febrile, on day1	CT/day 2, unremakable	Complete recovery	This study
3[a]	0 year 9 months	M	R1575C/ missense	Acute gastroenteritis	Family history of AE	None	Mimiking ANE	Cluster, afebrile, on day 1	MRI/day 2, bilateral thalamic lesions	Complete recovery	This study
4	1 year 4 months	F	R1892X/ nonsense	Rotavirus gastroenteritis		Dravet syndrome	AESD (HH)	Status, febrile, on day1	MR/day 6, left hemispheric edema	Mild MR (DQ = 71), right spastic heniplegia	Sakakibara et al., 2009
5	0 year 9 months	F	D43fs/ truncation	Fever of unknown etiology		Suspected Dravet syndrome	Atypical AESD	Status, febrile, on day1	MRI/day ×3, diffuse high signal intesity in cortex and subcortical white matter	Spastic quadriplegia, severe MR	Takayanagi et al., 2010
6	6 years 5 months	M	R1575C/ missense	Fever of unknown etiology		Febrile seizure	AERRPS	Cluster and status, febrile on day 2	CT and MRI, unremarkable	Mild MR	Kobayashi et al., 2010

Cases 4, 5, and 6 were reported in references.

GEFS+, generalized epilepsy with febrile seizure plus; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AE, acute encephalopathy; ANE, acute necrotizing encephalopathy; HH, hemiconvulsion-hemiplegia syndrome; AERRPS, acute encephalitis with refractory, repetitive partial seizures.

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epilepsy and ANE, whereas case 6 reported previously had febrile seizure and AERRPS (Kobayashi et al., 2010). This difference suggests the involvement of factors other than *SCN1A* mutation in the pathogenesis of AE.

The family history of case 3 deserves attention. The younger sister of this patient also had the same type of AE, despite the absence of *R1575C* mutation, which strongly suggests the involvement of another, as yet unidentified factor in this familial ANE. Comparison between the siblings revealed a longer duration of status epilepticus in the brother (case 3), and a worse prognosis in the sister. Plausibly, the *SCN1A* mutation contributed more to the evolution of status epilepticus, and the unidentified factor more to the development of bithalamic lesions and the overall neurologic damage.

In summary, we found *SCN1A* mutations in 3 of 87 cases of AE, and identified them as a predisposing genetic factor of AE. As for both epilepsy and AE, clinical phenotypes were variable among patients with *SCN1A* mutations. This variability, together with the family history of one patient (case 3), suggested that factors other than *SCN1A* mutations are also involved in the pathogenesis of AE.

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Disclosures

None of author has any conflict of interest to disclosure.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Original article

Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes

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Abstract

A research committee supported by the Japanese government conducted a nationwide survey on the epidemiology of acute encephalopathy in Japan using a questionnaire. A total of 983 cases reportedly had acute encephalopathy during the past 3 years, 2007–2010. Among the pathogens of the preceding infection, influenza virus was the most common, followed by human herpesvirus-6 (HHV-6) and rotavirus. Among syndromes of acute encephalopathy, acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) was the most frequent, followed by clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS), acute necrotizing encephalopathy (ANE) and hemorrhagic shock and encephalopathy syndrome (HSES). Influenza virus was strongly associated with ANE and MERS, HHV-6 with AESD, and rotavirus with MERS. Mortality was high in ANE and HSES, but was low in AESD, MERS and HHV-6-associated encephalopathy. Neurologic sequelae were common in AESD and ANE, but were absent in MERS.

Keywords: Acute encephalopathy; Epidemiology; Acute necrotizing encephalopathy; Acute encephalopathy with biphasic seizures and late reduced diffusion; Clinically mild encephalitis/encephalopathy with a reversible splenial lesion

1. Introduction

Acute encephalopathy is a severe complication of common infections of childhood, such as influenza, exanthem subitum and acute viral gastroenteritis. It usually affects children who have previously been healthy, and often causes death or severe neurological handicaps. There are two classifications of acute encephalopathy [1]. One is based on the pathogen of the preceding infection, such as influenza encephalopathy, human herpesvirus-6 (HHV-6) encephalopathy and rotavirus encephalopathy, whereas the other is based on clinical, laboratory, imaging and pathological findings of encephalopathy. With recent advances in this syndrome classification,

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many novel syndromes, such as acute necrotizing encephalopathy (ANE) [2], acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [3] and clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) [4], have been established.

At present, epidemiologic data on acute encephalopathy are limited. In the United States, the California Encephalitis Project has collected a large number of cases of central nervous system infection since 1988; however, this study focused primarily on encephalitis, not on encephalopathy [5]. In Japan, several attempts have previously been made to estimate the morbidity and mortality of acute encephalitis/ encephalopathy [6–10]; however, none has used syndrome classification of acute encephalopathy.

In 2010, supported by a grant from the Ministry of Health, Labour and Welfare of Japan, we started the Committee for the Research on the Etiology, Diagnosis and Treatment of Severe and Intractable Acute Encephalopathy, and conducted a nationwide survey of acute encephalopathy in Japan. This study used for the first time both classifications, pathogenic (virological) and syndrome (clinico-pathological) [1], and elucidated the relationship between viruses and syndromes.

2. Material and methods

In this study, we defined acute encephalopathy based on the following criteria: (1) acute onset of impaired consciousness after a preceding infection, and (2) exclusion of well-defined intracerebral inflammation. According to the second criterion, we excluded meningitis/ encephalitis, such as herpes simplex virus (HSV) encephalitis and acute disseminated encephalomyelitis, in which inflammatory pathology is clearly established. On the other hand, we included several conditions in which the distinction between encephalitis and encephalopathy is unclear, such as MERS [4] and acute encephalitis with refractory, repetitive partial seizures (AERRPS) [11]. We also included cases even if the respondent inadvertently failed to answer a single item.

In June 2010, we mailed a questionnaire to the heads of the Department of Pediatrics of 520 hospitals that had been qualified as institutions for training pediatric specialists by the Japanese Pediatric Society. The hospitals included all the pediatric referral centers in Japan, and were distributed all over the country.

The questionnaire items were (1) the number of cases of acute encephalopathy treated by each hospital during the last 3 years (from April 2007 to June 2010), (2) date

Table 1
Diagnostic criteria for three major syndromes.

I. *Acute necrotizing encephalopathy of childhood (ANE)*
1. Acute encephalopathy following a viral febrile disease. Rapid deterioration in the level of consciousness. Convulsions
2. No CSF pleocytosis. Increase in CSF protein commonly observed
3. CT or MRI evidence of symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brain stem tegmentum and cerebellar medulla. No involvement of other CNS regions
4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia
5. Exclusion of resembling diseases.
A. Differential diagnosis from clinical viewpoints.
Overwhelming bacterial and viral infections, and fulminant hepatits; toxic shock, hemolytic uremic syndrome and other toxin-induced diseases; Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.
B. Differential diagnosis from radiological viewpoints.
Leigh encephalopathy and related mitochondrial cytopathies; glutaric acidemia, methylmalonic acidemia, and infantile bilateral striatal necrosis; Wernicke encephalopathy, and carbon monoxide poisoning; acute disseminated encephalomyelitis, acute hemorrhagic leucoencephalitis, other types of encephalitis and vasculitis; arterial or venous infection, and the effects of severe hypoxia or head trauma

II. *Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)*
1. Onset with convulsion (status epilepticus convulsivus in most cases) within 24 hours from the onset of fever
2. Subsequent, transient improvement in consciousness
3. Recurrence of convulsions (clustering partial seizures in most cases) on the fourth to sixth day of illness, followed by impairment of consciousness
4. Pathogens of precedent infection: influenza virus and HHV-6, 7 in many cases
5. Variable prognosis: mild to severe psychomotor retardation. Typical cases show impaired speech and voluntariness
6. Normal MRI on the first to second day of illness
7. High signal intensity lesions in the cerebral subcortical white matter on diffusion-weighted images on the third to ninth day of illness. T2-weighted and FLAIR images may show high signal intensities along U-fibers

III. *Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)*
1. Onset with neuropsychiatric symptoms, such as abnormal speech and/or behavior, and impaired consciousness and convulsion, within one week after the onset of fever
2. Complete recovery without sequelae, mostly within ten days after the onset of neuropsychiatric symptoms
3. High signal intensity lesion in the splenium of corpus callosum, in the acute stage. T1 and T2 signal changes are mild
4. Lesion may involve the entire corpus callosum and the cerebral white matter in a symmetric fashion
5. Lesion disappears within a week, with neither residual signal changes nor atrophy

(year/month) and age at onset of each case, (3) sex, (4) syndrome of acute encephalopathy (e.g. ANE, AESD, MERS and others), (5) pathogen of preceding infection (e.g. influenza virus, HHV-6, unknown and others), and (6) prognosis. With regard to syndrome diagnosis (item #4), we also sent the diagnostic criteria of three major syndromes, ANE [12], AESD [13,14] and MERS [13] (Table 1), together with their typical neuroimaging findings. Diagnosis of hemorrhagic shock and encephalopathy syndrome (HSES) and other syndromes was based on previously published criteria [1,11,15]. As for prognosis (item #6), sequelae were judged as severe if the patient was unable either to walk independently or to utter meaningful words. Responses were sent back either by mail or by fax.

Statistical data were compared among the three syndromes, ANE, AESD and MERS. For numerical data (age), statistical significance was evaluated with one-way ANOVA. The homogeneity of the variances was analyzed by the Levene test; in case of P less than 0.05, pairwise comparisons were made and corrected by Bonferroni method. For categorical data (outcome), we used chi square tests with residual analysis.

This study was based on the Ethical Guideline for Epidemiological Researches published by Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare, Japan.

3. Results

3.1. Acute encephalopathy as a whole

Of the 520 hospitals, 265 (51.0%) responded. The total number of cases of acute encephalopathy was 983. The calculated annual incidence was 302 cases per year.

There were 497 males (51.0%) and 477 females (49.0%); no gender difference was noted.

Age at onset ranged from infancy to puberty. The incidence was most high in infancy and early childhood (Fig. 1). The average/standard deviation was 4.0 ± 3.7 years, and the median was 3 years.

Syndrome classification revealed that AESD was the most common (282 cases, 28.7%), followed by MERS (153 cases, 15.6%), ANE (39 cases, 4.0%), HSES (20 cases, 2.0%), limbic encephalitis (15 cases, 1.5%), Reye-like syndrome (7 cases, 0.7%), AERRPS (6 cases, 0.6%), Reye syndrome (4 cases, 0.4%) and posterior reversible encephalopathy syndrome (PRES) (4 cases, 0.4%). Thirteen cases (1.3%) had other syndromes, and 431 cases (43.8%) remained unclassified.

Among pathogenic viruses of preceding infection, influenza virus was the most common (263 cases, 26.6%), followed by HHV-6 (168 cases, 17.0%), rotavirus (40 cases, 4.0%), respiratory syncytial virus (RSV) (17 cases, 1.7%), mumps virus (9 cases, 0.9%), adenovirus (7 cases, 0.7%), HHV-7 (6 cases, 0.6%), HSV (6 cases, 0.6%), norovirus (5 cases, 0.5%), Epstein Barr virus (3 cases, 0.3%), varicella-zoster virus (3 cases, 0.3%), human parechovirus (2 cases, 0.2%) and measles virus (1 case, 0.1%). Bacterial pathogens, such as enterohemorrhagic *Escherichia coli* and *Salmonella*, were detected in 16 cases (1.6%), and *Mycoplasma pneumoniae* in 9 cases (0.9%). Concomitant infections, such as HHV-6/RSV and rotavirus/*Campylobacter jejuni* or *coli*, were found in 5 cases (0.5%). Pathogens remained unidentified in 401 cases (40.8%).

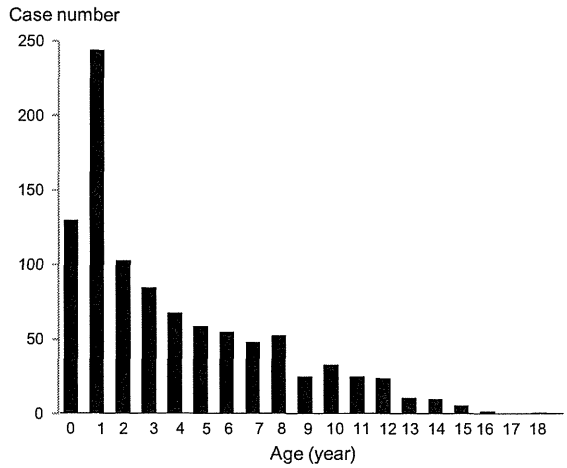

Fig. 1. Age distribution of acute encephalopathy.

The outcome of acute encephalopathy varied. Full recovery was noted in 552 cases (56.2%), mild to moderate sequelae in 218 (22.1%), severe sequelae in 133 (13.5%), and death in 55 (5.6%).

3.2. Major syndromes of acute encephalopathy

3.2.1. AESD

AESD was the most frequent syndrome (282 cases), with 114 male (40.4%) and 167 female (59.6%) patients. Age distribution showed a high incidence in infancy (average/standard deviation 1.7 ± 2.2 years, median 1 year) (Fig. 2).

Pathogens of the preceding infection were HHV-6 in 108 cases (38.2%), influenza virus in 27 (9.5%), HHV-7 in 5 (1.8%), rotavirus in 4 (1.4%) and RSV in 4 (1.4%). There were no cases of bacterial infection.

Outcome of AESD was characterized by low fatality and a high incidence of neurologic sequelae. Full recovery was noted in 81 patients (28.7%), mild to moderate sequelae in 116 (41.1%), severe sequelae in 71 (25.1%) and death in only 4 (1.4%). The ratio of patients with mild to moderate sequelae was significantly higher than for ANE ($P < 0.01$) and MERS ($P < 0.01$).

3.2.2. MERS

MERS was the second most frequent syndrome (153 cases), with 80 male (52.3%) and 69 female (45.1%)

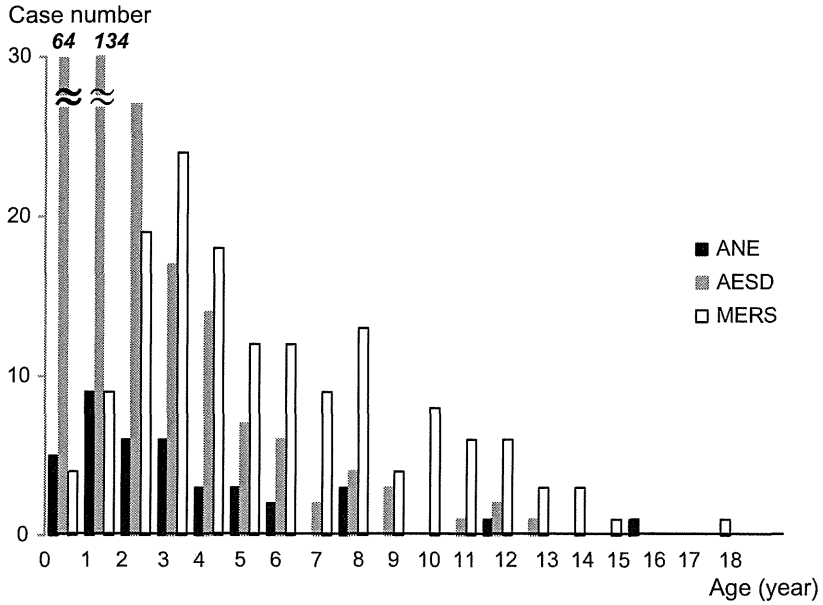

Fig. 2. Age distribution of major syndromes of acute encephalopathy. ANE, acute necrotizing encephalopathy; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; MERS, mild encephalitis/encephalopathy with a reversible splenial lesion.

patients. Age at onset varied (average/standard deviation 5.6 ± 3.7 years, median 5 years), and was significantly higher than for AESD ($P < 0.01$) (Fig. 2).

Pathogens of the precedent infection were influenza virus in 53 cases (34.4%), rotavirus in 18 (11.7%), mumps virus in 6 (3.9%), and HHV-6 in only 3 (2.0%). Notably, there were 5 cases (3.3%) following bacterial infections.

Outcome was good, with the vast majority of patients (138 cases, 90.2%) achieving a full recovery. The ratio of full recovery was significantly higher in MERS than in AESD ($P < 0.01$). In the remaining patients (11 cases, 7.1%), the sequelae were mild to moderate. There was no case resulting in severe handicap or death.

3.2.3. ANE

ANE ranked third with regard to incidence (39 cases); there were 23 male (59.0%) and 16 female (41.0%) patients. Age at onset of ANE showed the highest incidence in infancy (average/standard deviation 3.3 ± 3.4 years, median 2 years) (Fig. 2), and was significantly higher than for AESD ($P < 0.01$) and lower than for MERS ($P < 0.01$).

Pathogens of the preceding infection were influenza virus in 16 cases (41.0%) and HHV-6 in 8 (20.5%). There was no case of bacterial infection.

Outcome was poor in most patients. Full recovery was noted in only 5 patients (12.8%), mild to moderate sequelae in 9 (23.0%), severe sequelae in 13 (33.3%) and death in 11 (28.2%). Compared to AESD, the mortality of ANE was higher, whereas the probability of neurologic sequelae was comparable. The ratio of full recovery was significantly lower than for AESD ($P < 0.01$) and MERS ($P < 0.01$), and that of death significantly higher than for AESD ($P < 0.01$) and MERS ($P < 0.01$).

3.2.4. HSES

HSES was the fourth most common syndrome (20 cases), with 8 male (40.0%) and 12 female (60.0%) patients. Age at onset ranged from 0 to 8 years. The average and median age was 2.9 ± 2.9 years and 1 year, respectively.

Pathogens of the preceding infection were influenza virus in 3 cases, HHV-6 in 2, norovirus in 1, and RSV in 1.

Outcome was very poor. Eleven patients (55.0%) died, whereas only 2 (10.0%) showed full recovery. The remaining patients had neurologic sequelae, mild to moderate in 1 (5.0%) and severe sequelae in 5 (25.0%).

3.3. Major pathogens of acute encephalopathy

3.3.1. Influenza virus

Influenza virus was the most common pathogen (263 cases), with 153 male (58.2%) and 109 female (41.8%) patients. Age at onset of influenza-associated encephalopathy ranged widely from infancy to puberty (Fig. 2). The mean and median ages were 6.3 ± 3.4 and 6 years, respectively.

Syndrome classification revealed that MERS was the most common (53 cases, 20.2%), followed by AESD (27 cases, 10.3%), ANE (16 cases, 6.1%), HSES (3 cases, 1.1%), Reye, Reye-like and other syndrome (each 1 case, 0.4%). More than half of the patients (158 cases, 60.1%) were unclassified.

The outcome varied. Although many patients achieved a full recovery (199 cases, 75.7%), fatal cases were not uncommon (18 cases, 6.8%). Neurologic sequelae were mild to moderate in 22 patients (8.4%), and severe in 22 (8.4%).

3.3.2. HHV-6

HHV-6 was the second most common pathogen (168 cases), with 73 male (43.5%) and 95 female (56.5%) patients. The vast majority of patients were infants under 2 years of age (Fig. 2). Age at onset of HHV-6-associated encephalopathy (average/standard deviation 0.8 ± 1.1 year, median 1 year) was significantly lower than with influenza-associated encephalopathy ($P < 0.001$).

Among encephalopathy syndromes, AESD was by far the most common (108 cases, 64.3%). Eight patients had ANE (4.8%). Other syndromes, such as MERS (3 cases, 1.8%), HSES (2 cases, 1.2%) and limbic encephalitis (1case, 0.6%), were rare. The number of unclassified cases was smaller (39 cases, 23.2%) than for influenza.

Half of the patients recovered (85 cases, 50.6%). Fatality was low (3 cases, 1.8%); however, many patients were left with neurologic sequelae, being mild to moderate (48 cases, 28.6%) or severe (28 cases, 16.7%).

3.3.3. Rotavirus

Rotavirus was the third most common pathogen (40 cases, 16 male and 23 female). The average and median ages were 2.8 ± 2.4 and 2 years, respectively. Eighteen patients had MERS (45.0%), four AESD (10.0%), and one ANE (2.5%). Full recovery was noted in 28 patients (70.0%), mild to moderate sequelae in 5 (12.5%), severe sequelae in 3 (7.5%), and death in 3 (7.5%).

3.3.4. RSV

RSV was the fourth most common pathogen (17 cases, 4 male and 13 female). The average and median ages were 1.4 ± 0.9 and 1 year, respectively. There were 4 cases of AESD, and 1 case each of MERS and HSES. Full recovery was noted in 12 patients (70.6%), mild to moderate sequelae in 3 (17.6%), severe sequelae in 2 (11.8%), and death in none.

4. Discussion

In this study, the Research Committee on the Etiology, Diagnosis and Treatment of Severe and Intractable Acute Encephalopathy, supported by the Ministry of Health, Labour and Welfare of Japan, conducted a nationwide survey on the epidemiology of acute encephalopathy. In Japan, several studies have previously been performed on the epidemiology of acute encephalitis/encephalopathy [6–10]. All these studies classified encephalitis/encephalopathy pathogenically (virologically), but not syndromically (clinico-pathologically). They paid little attention to the distinction between encephalitis and encephalopathy. Some were performed prior to the advent of clinically useful virological methods, such as immunochromatography (rapid antigen detection) for influenza virus and rotavirus [6,7], resulting in inaccurate virological diagnosis in many cases. The present study is the first to focus on acute encephalopathy, and uses both pathogenic and syndrome classifications.

Our study, however, had several limitations. First, the rate of responding hospitals was not high (51.0%), excluding accurate estimation of the nationwide incidence. Second, this survey was a multi-center study in which many and varied hospitals participated. Among them, the medical activities, including various aspects of diagnosis and treatment, are diverse. Accordingly, the quality of the data obtained in this study are not well guaranteed. For instance, most cases of MERS, as well as many cases of AESD, cannot be properly diagnosed without magnetic resonance imaging (MRI) [13]. Poor access to MRI in some hospitals may cause underdiagnosis of these conditions. In addition, some institutions may have failed to perform proper virological examination for the diagnosis of exanthema subitum. It is thus plausible that several cases of HHV-7-associated encephalopathy were misdiagnosed into HHV-6-associated encephalopathy.

Despite these limitations, this study has several strengths. First, the study area covered all prefectures in Japan. Second, a large number of cases were collected. Third, recent advances in virological examination have facilitated rapid and accurate identification of pathogens. Fourth, diagnostic criteria have recently been established for multiple syndromes [12–14], enabling proper syndrome diagnosis in many cases. Taking advantage of this, this study successfully demonstrated many important features of each syndrome as to its age distribution, relation to pathogens, and prognosis.

Among the three major syndromes, ANE, AESD and MERS, there were striking differences. With regard to age distribution, the mean age was 1.7 years in AESD, 3.3 years in ANE, and 5.6 years in MERS. Most cases of AESD occurred in infancy (0–1 years), and those of ANE in infancy and early childhood (0–5 years). By contrast, MERS was often seen in schoolchildren (Fig. 2). These findings were comparable to those of previous studies on AESD [3,16], ANE [2,12] and MERS [4].

With regard to pathogens of the preceding infection, ANE and MERS were strongly associated with influenza. In AESD, by contrast, HHV-6 was the most common pathogen. The findings of ANE in this study are comparable to those reported in 1990's [2,12]. Comparison with previous data [3,4,16] suggests an increase of influenza-associated MERS and a decrease of influenza-associated AESD in this decade. In this study, it

was noteworthy that five cases of MERS had a preceding bacterial infection. This finding is in agreement with previous data that 6 out of 54 MERS cases were infected with streptococcus and *E. coli* (3 cases each) [13]. In contrast, bacterial pathogens were identified in none of the ANE and AESD cases. Although there have previously been several reports of ANE following bacterial infections [17,18], such cases are exceptional.

The prognosis of ANE and HSES was poor. In many cases, ANE caused either death or neurologic sequelae. The findings were comparable to those in the 1980's and 1990's [2,12], indicating that the overall prognosis of ANE has not been improved substantially despite the efficacy of corticosteroids in some cases [19]. The prognosis of AESD was characterized by low mortality (1.4%) and the high possibility of neurologic sequelae (66.2%). These results are again comparable to those of previous studies [3,16], reflecting the failure of current therapies to protect patients from neurologic damage in AESD. By contrast, the prognosis of MERS was excellent, in agreement with the findings of previous reports [4,13].

A large population (43.1%) of patients remained unclassified into specific syndromes. This group may consist of (1) cases of mild encephalopathy showing no abnormal findings on cranial CT/MRI, (2) cases of unknown or uncommon types of encephalopathy, and (3) cases of MERS, AESD and other syndromes in which proper diagnosis could not be reached.

In this study, we also classified acute encephalopathy based on pathogens [1], and found differences between influenza virus and HHV-6 in age distribution, syndrome, and prognosis. With regard to age, HHV-6-associated encephalopathy was predominantly seen in infants, whereas influenza-associated encephalopathy was prevalent also in older children (Fig. 3). This difference is partially explained on the basis of age predilection of these viruses, namely the incidence of exanthem subitum and influenza in general. As to syndromes, HHV-6 was associated strongly with AESD, but not with MERS. By contrast, influenza was associated with all three major syndromes, AESD, ANE and MERS. Reasons for this discrepancy remain unclear. Multiple factors, such as neurovirulence of these viruses, the host response of inflammatory cytokines, and development of the human brain, may possibly be involved. With regard to prognosis, the number of deaths was higher with influenza-associated encephalopathy, whereas that of neurologic sequelae was higher with HHV-6-associated encephalopathy. These findings may merely reflect the difference in the proportion of syndromes.

In general, the data obtained in this study were comparable to those of previous studies for influenza-associated encephalopathy (1999–2002) [8] and HHV-6 encephalopathy (2003–2004) [10], with regard to the incidence, age distribution and sex ratio. As to the prognosis of influenza-associated encephalopathy, however, mortality has markedly decreased from 30% in 1999–2000 [8] to 7% in 2007–2010. This decline may have resulted from improved treatment and/or the altered incidence of each syndrome.

In conclusion, we conducted a national survey of acute encephalopathy in Japan during three years,

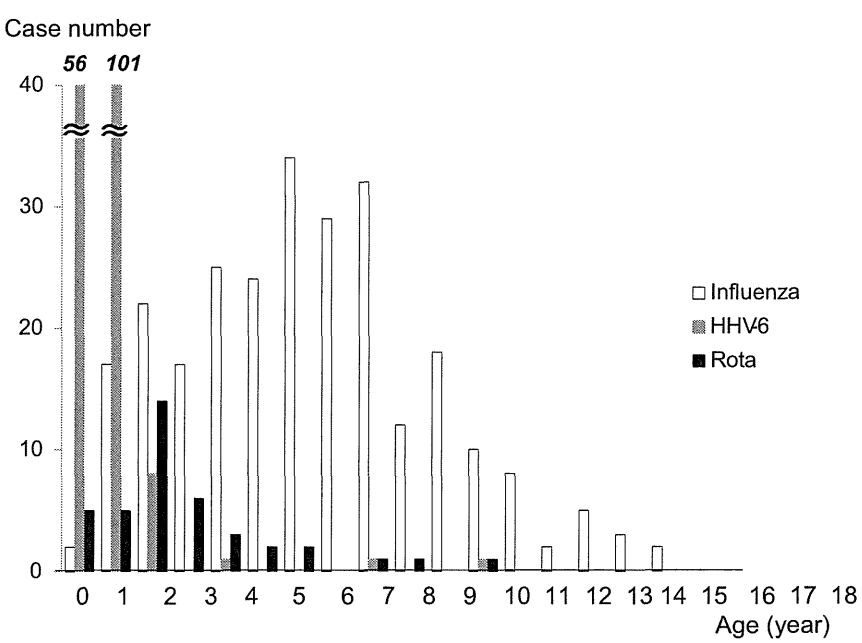

Fig. 3. Age distribution of influenza-, human herpesvirus-6- and Rotavirus-associated encephalopathy HHV-6, human herpesvirus-6; Rota, Rotavirus.

2007–2010, and revealed the epidemiology of ANE, AESD, MERS and other syndromes. These syndromes showed marked differences in their age distribution, pathogens of preceding infection and prognosis, underscoring the necessity for therapies specific to each syndrome.

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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).

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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

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.

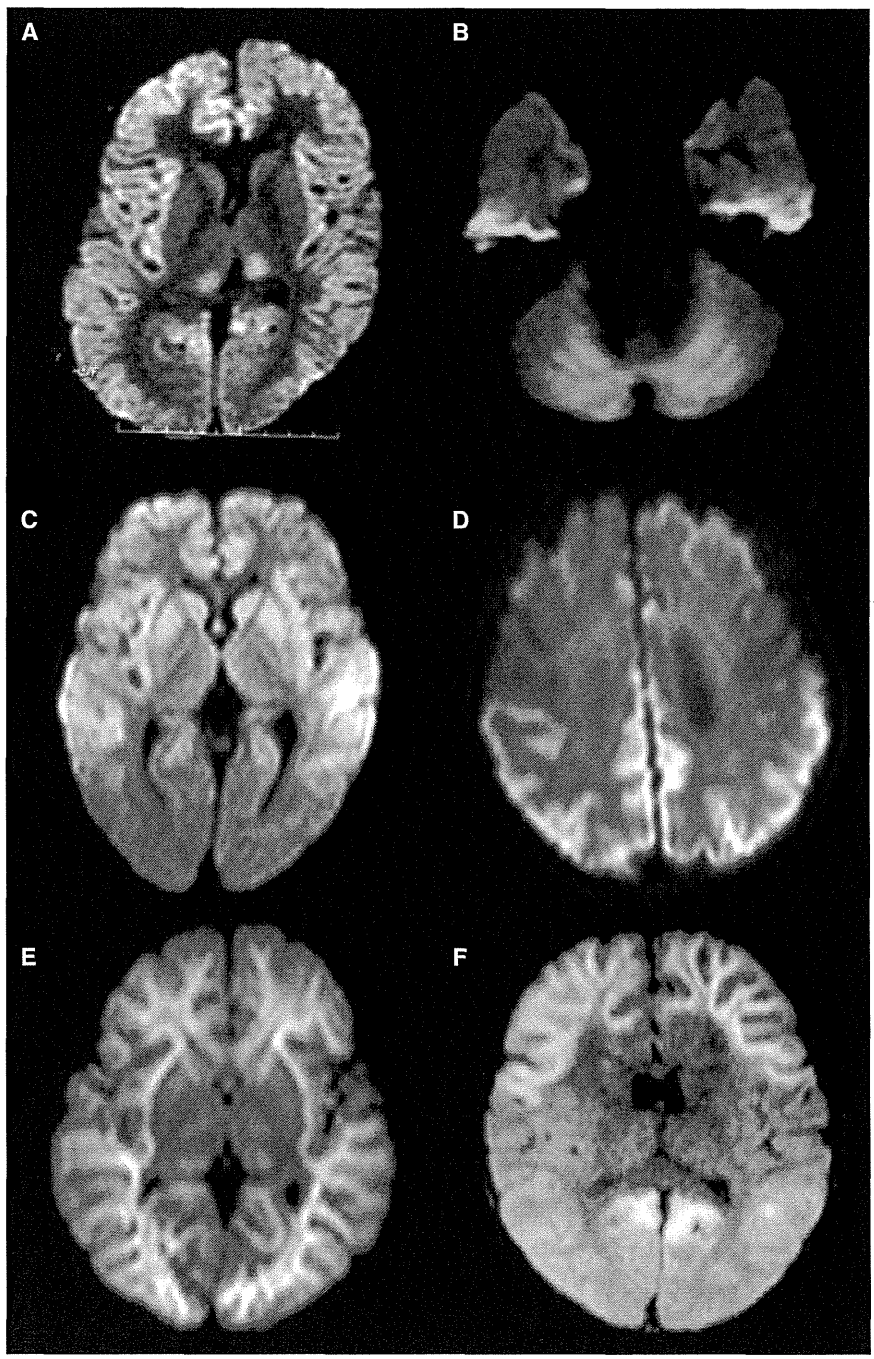

Figure 1.
Diffusion-weighted images. (**A**, **B**) Patient 15, 1 day after the onset of acute encephalopathy. Abnormal high intensities were observed in the cerebral cortex, thalami, and cerebellar hemispheres. (**C**) Patient 1, 6 days after the onset of acute encephalopathy. Abnormal high intensities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