# Congenital Infiltrating Lipomatosis of the Face with Ipsilateral Hemimegalencephaly, Band Heterotopia, and Hypertrophy of Brainstem and Cerebellum

Authors

K. Maruyama[1], A. Okumura[2], T. Negoro[3], K. Watanabe[4]

Affiliations

[1] Department of Pediatric Neurology, Central Hospital, Aichi Prefectural Colony, Kasugai, Japan
[2] Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan
[3] Department of Human Welfare, Okazaki Women's Junior College, Okazaki, Japan
[4] Faculty of Medical Welfare, Aichi Shukutoku University, Nagoya, Japan

Key words
- congenital infiltrating lipomatosis of the face
- hemimegalencephaly
- band heterotopia
- epilepsy

## Abstract

The simultaneous appearance of congenital infiltrating lipomatosis of the face that causes facial hemihypertrophy and ipsilateral hemimegalencephaly is extremely rare. We report a 4-year-old boy with congenital facial asymmetry and infantile-onset epilepsy. Magnetic resonance imaging (MRI) results led to the diagnosis of infiltrating lipomatosis of the face; the diagnosis was confirmed on the basis of the results of pathological examinations. Additionally, brain MRI revealed ipsilateral hemimegalencephaly, associated with band heterotopia and the hemihypertrophy of the ipsilateral brainstem and cerebellum. He had no nevi or other skin abnormalities suggesting neurocutaneous syndrome. His seizures were so intractable that they necessitated functional hemispherectomy. The lipomatous lesion was successfully resected without relapse. Psychomotor delay and left hemiplegia were observed at the last follow-up.

received 15.02.2010
accepted 09.08.2010

Bibliography
DOI http://dx.doi.org/10.1055/s-0030-1263165
Neuropediatrics 2010; 41: 147–150

ISSN 0174-304X

Correspondence
***Koichi Maruyama, MD***
Department of Pediatric Neurology
Central Hospital
Aichi Prefectural Colony
713-8 Kagiya-cho
Kasugai
Aichi 480-0392
Japan
Tel.: +81/568/88 0811
Fax: +81/568/88 0828
maruyama@aichi-colony.jp

## Abbreviations

| | |
|---|---|
| ACTH | adrenocorticotropic hormone |
| CILF | congenital infiltrating lipomatosis of the face |
| CMV | cytomegalovirus |
| EEG | electroencephalogram |
| ENS | epidermal nevus syndrome |
| HM | hemimegalencephaly |
| MRI | magnetic resonance imaging |

## Introduction

Congenital infiltrating lipomatosis of the face (CILF) is a rare disorder characterized by a congenital fatty mass located on one side of the cheek. This mass infiltrates the adjacent tissues, causing facial hemihypertrophy [8]. The simultaneous appearance of CILF and ipsilateral hemimegalencephaly (HM) is extremely rare; thus far, only 5 patients have been reported [1,2,4,9]. The etiology, symptoms and outcomes in patients with these 2 abnormalities have not been completely elucidated. Here, we present the radiological, electrophysiological, and pathological findings in the case of a patient with CILF and the unique association of the brain lesions: ipsilateral HM, band heterotopia, and hypertrophy of brainstem and cerebellum.

## Case Report

The patient was a 4-year-old boy who was the third child of unrelated Japanese parents. Fetal ultrasonography revealed a porencephalic cyst in his right cerebral hemisphere. His birth weight was 2.73 kg; length, 50.8 cm; and occipitofrontal circumference, 31.5 cm. Facial asymmetry was noted at birth. Since 31 days of age, he had experienced repetitive episodes of hemiconvulsions on the left side. Subsequently, since 46 days of age, he exhibited clusters of spasms. His seizures could not be controlled by daily clobazam administration.

Physical examination at 2 months of age revealed a large, elastic subcutaneous mass in his right cheek. The color and texture of the overlying skin was normal. Hemihypertrophy on the right side of the tongue and another small subcutaneous mass on his right clavicle were noted. He had no other skin anomaly such as nevi or epidermal nevi. His occipitofrontal circumference was 41.3 cm (◎ **Fig. 1a**). Social smile was observed, but his facial expressions were asymmetric. He had no difficulty in sucking and swallowing. His posture,

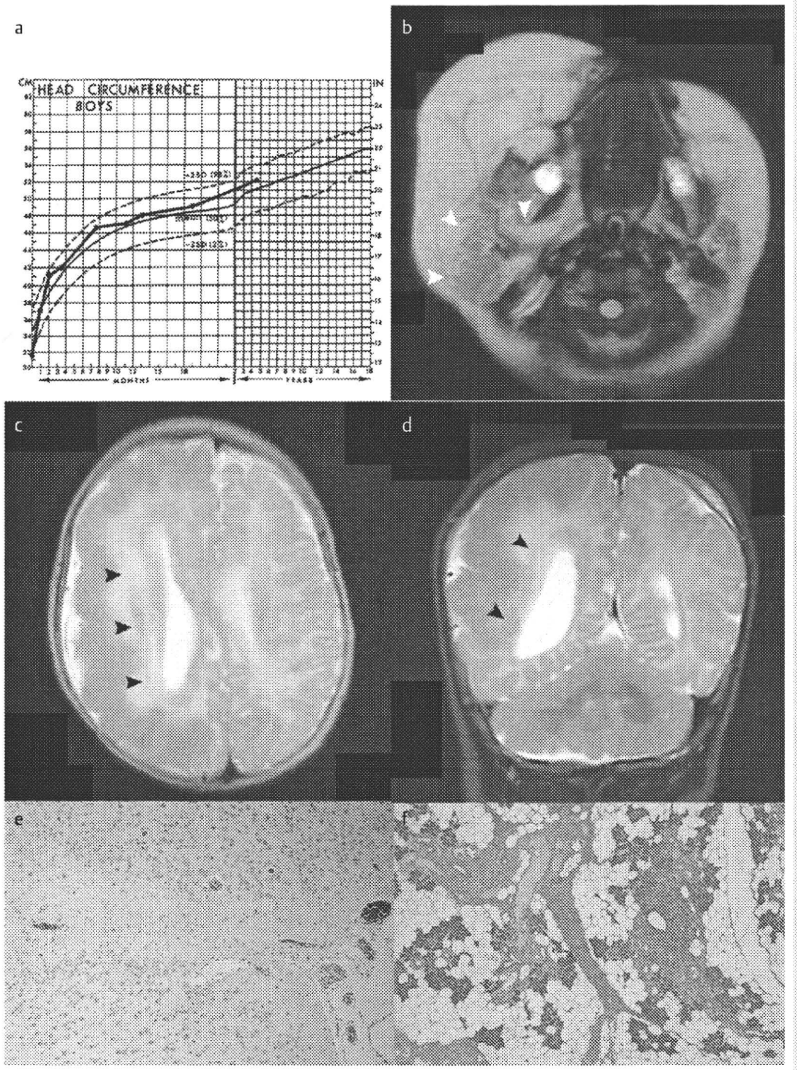



**Fig. 1** **a** Head circumference chart of the patient. The occipitofrontal circumference was always within normal limits. **b** $T_2$-weighted magnetic resonance (MR) image of the face in the axial plane. An overgrowth of the subcutaneous fatty tissue infiltrated the right parotid gland, masseter muscle, and parapharyngeal spaces on the right side (white arrow head). **c**, **d** $T_2$-weighted MR images of the brain in the axial (**c**) and coronal (**d**) planes. The right cerebral hemisphere was enlarged. The cortices of the frontal, parietal, and occipital lobes were thick with broad gyri, shallow sulci, and poorly demarcated cortical-white matter junctions. Irregular subcortical band heterotopia was noted (black arrow heads). The lateral ventricle was dilated and surrounded by heterogeneous intensity in the periventricular white matter. Ipsilateral enlargement of the cerebellum and an abnormal architecture of the folia were noted. **e** Histological examination of the biopsy specimens of the right cerebral cortex (Klüver-Barrera stain; original magnification, ×114). Disoriented, irregularly arranged, abnormal immature neurons of various sizes without distinct layering were observed. **f** Histological examination of the resected lipomatous lesions in his right cheek (hematoxylin-eosin stain; original magnification, ×40). Hyperplastic mature adipose tissues infiltrating the salivary gland were noticed.

muscle tone, and spontaneous movements were normal for his age. An ophthalmological examination did not reveal any abnormalities. Anti-cytomegalovirus (CMV) IgM antibody and CMV DNA were not detected in his serum. Chromosome analysis revealed a normal male karyotype.

Magnetic resonance imaging (MRI) of the face revealed a prominent overgrowth of the subcutaneous fatty tissues infiltrating the parotid gland, masseter muscle, and parapharyngeal spaces (◎ **Fig. 1b**). Brain MRI revealed enlargement of the right cerebral hemisphere (◎ **Fig. 1c, d**). The cortices had a thick and abnormal gyral pattern with shallow sulci and a poorly demarcated boundary with the subcortical white matter. In addition, the band of ectopic gray matter was arranged between the cerebral cortex and the lateral ventricle in the frontal, parietal, and occipital lobes. The lateral ventricle was mildly dilated and surrounded by heterogeneous intensity in the periventricular white matter. Moreover, ipsilateral enlargement of the brainstem and cerebellum and an abnormal architecture of the cerebellar folia were noted.

His seizures were complex and followed in a specific sequential pattern: generalized tonic posturing lasting for several seconds, partial seizures with clonic convulsions extending from left upper extremity, and clusters of spasms. Ictal electroencephalogram (EEG) of each type of seizures showed brief slow wave bursts followed by diffuse attenuation; rhythmic spike-and-wave bursts dominant in the right frontal region; and repetitive, periodic high-voltage polyphasic sharp waves dominant in the right hemisphere, respectively. Interictal EEG showed episodic bursts of high-voltage irregular sharp or slow wave activities during wakefulness and sleep predominantly in the right hemisphere.

Although adrenocorticotropic hormone (ACTH) therapy was partially effective, it was discontinued after 10 days because of rotavirus enterocolitis. In order to prevent progression to catastrophic epilepsy, a functional hemispherectomy was performed at 4 months of age. Microscopic examination of the specimen of the right cerebrum revealed disoriented, immature, irregularly arranged abnormal neurons without layering in the gray matter (◎ **Fig. 1e**), and nodular heterotopic neurons in the white matter.

The infiltrating lipomatosis in his lip, hypoglottis, and right cheek was excised at 3 years of age. Microscopic examination of the resected lesion revealed hyperplastic, mature adipose tissue infiltrating the adjacent tissues such as the parotid gland, lymphatic tissue, and masseter muscle (◎ **Fig. 1f**).

At 4 years of age, his psychomotor development was retarded. He understood some simple sentences but did not speak any

**Table 1** Patients with congenital infiltrating lipomatosis of the face with hemimegalencephaly.

| Case | Authors | Age | Sex | Subcutaneous mass | Brain malformation | Other findings | Developmental Delay | Convulsions/Seizures | Interictal EEG findings | Treatment of epilepsy | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Donati et al. | 3 months | M | left cheek | left HM | hepatomegaly and jaundice, anti-CMV antibodies (+) | NA | convulsions | slow and widespread high voltage anomalies of the left side | AED | died at 20 months due to pulmonary infection |
| 2 | Unal et al. (case 1) | 2 years | M | left cheek and scalp | left HM | pigmented navi in left cheek, neck and chest | – | – | NA | – | NA |
| 3 | Unal et al. (case 2) | 3 months | M | left cheek | left HM, agenesis of corpus callosum | – | NA | Iitractable seizures | NA | NA | died at 7 months due to status epilepticus |
| 4 | Aydingoz et al. | 3 months | M | left cheek and scalp | left HM | right esotopia | + | intractable seizures | diffuse high voltage irregular bursts and multifocal spikes | ACTH | seizure free |
| 5 | Alkan et al. | 1.5 years | M | left cheek | left HM | – | – | – | normal | – | NA |
| 6 | our case | 2 months | M | right cheek and supraclavicle region | right HM with ipsilateral band heterotopia and hemihypertrophy of brainstem and cerebellum | – | + | intractable seizures (PS + spasms) | right dominant episodic high voltage irregular sharp or slow bursts | ACTH, functional hemispherectomy | seizure free, left hemiplegia |

ACTH: adrenocorticotropic hormone; AED: antiepileptic drug; CMV: cytomegalovirus; EEG: electroencephalogram; HM: hemimegalencephaly; NA: not available; PS: partial seizure



Maruyama K et al. Congenital Infiltrating Lipomatosis of the Face with Ipsilateral ... Neuropediatrics 2010; 41: 147–150

meaningful words. Left spastic hemiplegia became apparent. He could stand with support but could not walk. There was no obvious sign of ataxia or cranial nerve involvement. Although the EEG of the right hemisphere continued to show a suppression-burst pattern, his seizures disappeared after the operation. Relapse of the lipomatosis was not observed. The subcutaneous mass on his right clavicle did not enlarge. His occipitofrontal circumference was within the normal range (◎ **Fig. 1a**).

## Discussion

In 1983, Slavin et al. reported that CILF is a rare but distinct clinical entity [8]. Pathologically, the lesions are non-capsulated congenital proliferation of mature adipose tissue with fibrous tissues, nerve bundles and vessels. They infiltrate adjacent muscles and soft tissues, although lipoblasts and signs of malignancy are absent. Subjacent bones are hypertrophic. Facial asymmetry is invariably noted at birth. Other findings on the affected side include early eruption of the teeth, macroglossia, mucosal neuroma, and capillary stain [5]. Skin lesions such as nevi or epidermal nevi are not observed. The etiology still remains unclear.

Occasionally, the patients with CILF simultaneously have ipsilateral HM. ◎ **Table 1** presents a summary of the reported patients with CILF and HM [1,2,4,9]. Our patient is the sixth one. All the patients were boys. 5 of the 6 patients exhibited hemihypertrophy on the left side of the face. 3 patients exhibited other ipsilateral subcutaneous masses. In 1 patient, nevi were observed in the skin overlying the lesion. In another patient, agenesis of the corpus callosum was observed.

Our patient had particular brain MRI findings. The white matter of the classic HM is usually enlarged and shows heterogeneous signal intensity representing heterotopia [3]. In our patient, however, an irregular band of ectopic gray matter was seen midway between the cerebral cortex and the lateral ventricle, appearing subcortical band heterotopia. Additionally, the concomitant hemihypertrophy of the brainstem and cerebellum ipsilateral to HM, known as "total hemimegalencephaly" [7], was detected. These findings were quite unique and might have an implication for the pathogenetic mechanism of HM associated with CILF.

Some neurocutaneous syndromes are associated with HM, such as epidermal nevus syndrome (ENS), Proteus syndrome, hypomelanosis of Ito, neurofibromatosis type 1, Klippel-Trenaunay-Weber syndrome, and tuberous sclerosis [3]. Especially, ENS is associated with facial hemihypertrophy and ipsilateral HM. According to Pavone et al., 17 of 63 patients (27%) with ENS exhibited HM, and 9 (14%) exhibited both HM and facial hypertrophy in the areas that were always ipsilateral to facial nevi [6]. They concluded that this association comprises a neurological variant of ENS. The patient with CILF and HM reported by Unal et al. (case 1) had pigmented nevi in his left cheek, neck and chest [9]. He could be considered as having the neurological variant of ENS. Most patients with CILF and HM, including our case, however, had no nevi or other skin abnormalities. Therefore it is reasonable to consider that CILF with HM is a distinct entity from ENS [1,2,4,7,9].

4 patients developed epilepsy with a variable prognosis. The age at onset was <3 months in all of them. In patient 1, seizures and EEG abnormalities improved on antiepileptic treatment, but a pulmonary infection resulted in death at 20 months of age. Patient 3 died at 7 months of age because of status epilepticus. Although the seizures of patient 4 were controlled by ACTH, developmental delay was observed. Our patient (patient 6) required functional hemispherectomy for controlling the intractable seizures. Psychomotor delay and left hemiplegia were noted at the last follow-up. In contrast, developmental delay was not observed in the 2 patients without epilepsy.

## Conclusion

A patient with congenital facial asymmetry and infantile-onset epilepsy is reported. He was diagnosed as having CILF from MRI findings, and confirmed by the pathological examinations. Brain MRI revealed HM associated with band heterotopia and hemihypertrophy of the brainstem and cerebellum; all of those anomalies were ipsilateral to the lipomatosis. He had no nevi or other skin abnormalities suggesting a neurocutaneous syndrome. Functional hemispherectomy was necessitated to control the intractable seizures. Although he presented left hemiplegia and mental retardation, the lipomatosis had not relapsed and seizures were stopped at 4 years of age.

## Acknowledgements

The authors thank Dr. Taisuke Otsuki and Dr. Kunimasa Arima (National Center of Neurology and Psychiatry) for providing the histopathological data of the brain biopsy specimens; Prof. Yoko Yoshimura, Dr. Masato Abe and Dr. Yoshikazu Mizoguchi (Fujita Health University) for providing the histopathological data of the lipomatous lesions of the face.

## References

1 *Alkan O, Yildirim T, Seyhan T et al.* Congenital infiltrating lipomatosis of the face with hemimegalencephaly. Neuropediatrics 2009; 40: 141–143
2 *Aydingoz U, Emir S, Karli-Oguz K et al.* Congenital infiltrating lipomatosis of the face with ipsilateral hemimegalencephaly. Pediatr Radiol 2002; 32: 106–109
3 *Barcovich A.* Hemimegalencephaly (Unilateral megalencephaly). In: Pediatric Neuroimaging 4th edn. Philadelphia: Lippincott Williams & Wilkins; 2005; 337–341
4 *Donati L, Candiani P, Grappolini S et al.* Congenital infiltrating lipomatosis of the face related to cytomegalovirus infection. Br J Plast Surg 1990; 43: 124–126
5 *Padwa BL, Mulliken JB.* Facial infiltrating lipomatosis. Plast Reconstr Surg 2001; 108: 1544–1554
6 *Pavone L, Curatolo P, Rizzo R et al.* Epidermal nevus syndrome: a neurologic variant with hemimegalencephaly, gyral malformation, mental retardation, seizures, and facial hemihypertrophy. Neurology 1991; 41: 266–271
7 *Sener RN.* MR demonstration of cerebral hemimegalencephaly associated with cerebellar involvement (total hemimegalencephaly). Comput Med Imaging Graph 1997; 21: 201–204
8 *Slavin SA, Baker DC, McCarthy JG et al.* Congenital infiltrating lipomatosis of the face: clinicopathologic evaluation and treatment. Plast Reconstr Surg 1983; 72: 158–164
9 *Unal O, Cirak B, Bekerecioglu M et al.* Congenital infiltrating lipomatosis of the face with cerebral abnormalities. Eur Radiol 2000; 10: 1610–1613

Epilepsy Research (2010) 91, 143–152

journal homepage: www.elsevier.com/locate/epilepsyres

# Genetic seizure susceptibility underlying acute encephalopathies in childhood

**Katsuhiro Kobayashi[a,1], Mamoru Ouchida[b,1], Akihisa Okumura[c], Yoshihiro Maegaki[d], Itsuko Nishiyama[a], Hideki Matsui[e], Yoko Ohtsuka[a], Iori Ohmori[e,*]**

[a] *Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Shikatacho 2-chome 5-1, Kita-ku, Okayama 700-8558, Japan*
[b] *Department of Molecular Genetics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Shikatacho 2-chome 5-1, Kita-ku, Okayama 700-8558, Japan*
[c] *Department of Pediatrics, Juntendo University, School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan*
[d] *Division of Child Neurology, Institute of Neurological Sciences, Faculty of Medicine, Tottori University, 36-1 Nishi-Cho, Yonago 683-8504, Tottori, Japan*
[e] *Department of Physiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Shikatacho 2-chome 5-1, Kita-ku, Okayama 700-8558, Japan*

Received 18 March 2010; received in revised form 10 June 2010; accepted 4 July 2010
Available online 2 August 2010

**KEYWORDS**
Acute encephalopathy;
Childhood;
Seizure susceptibility;
SCN1A;
Febrile seizure;
Genetics

**Summary** We herein investigated risk factors of pediatric acute encephalopathy (AE) regarding the hitherto uncharacterized genetic background of seizure susceptibility underlying the pathogenesis of AE. The study included 15 patients with a history of various types of AE in childhood. We undertook the mutational analysis of the neuronal sodium channel alpha 1 subunit (*SCN1A*) gene which is the most representative gene for hyperthermia-induced seizure susceptibility.

Six patients (40%) had a positive family history of seizures or AE, especially febrile seizures, in first- or second-degree relatives. The *SCN1A*-R1575C mutation was detected in a patient with a history of acute encephalitis with refractory, repetitive partial seizures (AERRPS) and also in the patient's apparently healthy father.

In the present study, dense familial seizure predisposition was present in the patients with AE. Although the presence of seizure susceptibility alone is insufficient to cause AE, it can exacerbate seizures and the subsequent development of inflammatory reactions in the brain when environmental factors are included. Genetic seizure susceptibility may contribute to some types of AE in childhood.


* Corresponding author. Tel.: +81 86 235 7109; fax: +81 86 235 7111.
*E-mail address:* iori@md.okayama-u.ac.jp (I. Ohmori).
[1] Both these authors contributed equally to this work.

0920-1211/$ – see front matter. 
doi:10.1016/j.eplepsyres.2010.07.005

## Introduction

Some normally developing children unexpectedly experience a catastrophe of acute encephalopathy (AE) showing consciousness impairment, seizures, and other neurological symptoms. These neurological calamities are serious clinical problems in childhood. The pathophysiological mechanisms of acute encephalopathy (AE), however, are not yet thoroughly understood.

There are mounting reports of several types of AE in addition to the well-defined Reye syndrome, which is classically caused by metabolic dysregulation. The currently recognized AE types with characteristic clinical and neuroimaging findings include acute necrotizing encephalopathy of childhood (ANE) (Mizuguchi, 1997), which is associated with a cytokine storm; acute encephalopathy with febrile convulsive status epilepticus, or AEFCSE (Mizuguchi et al., 2007) which is related to excitotoxicity; and clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) (Tada et al., 2004). AEFCSE is a collective term and includes a spectrum of subtypes, such as acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF) (Yamanouchi et al., 2006), acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) (Takanashi et al., 2006; Takanashi, 2009; Okumura et al., 2009), and hemiconvulsion-hemiplegia syndrome.

Acute encephalitis with refractory and repetitive partial seizures (AERRPS) (Awaya and Fukuyama, 1986; Saito et al., 2007) is remarkable due to a unique combination of findings, including the acute onset of seizures and/or consciousness impairment in the absence of underlying neurological abnormalities, extraordinary frequent and refractory partial seizures, and a continuous switchover to refractory epilepsy without a latent period (Sakuma, 2009). There are reports of encephalopathies with somewhat similar clinical characteristics including devastating epileptic encephalopathy in school-aged children (DESC) (Mikaeloff et al., 2006), idiopathic catastrophic epileptic encephalopathy presenting with acute onset intractable status (Baxter et al., 2003), and cryptogenic new onset refractory status epilepticus (NORSE) (Wilder-Smith et al., 2005; Costello et al., 2009). These types of encephalitis or encephalopathies attract attention because of their close relationship with seizures or epilepsy.

Experimental studies in rodent models have also uncovered the close relationship between inflammatory reactions and seizures (Vezzani and Granata, 2005). For instance, inflammatory cytokines can directly induce seizures in young rodents, and an increased blood brain barrier (BBB) permeability may occur after seizures and inflammation. We speculate that intrinsic seizure susceptibility may contribute to the occurrence of AE. Therefore, we herein investigated the family history of convulsive disorders in patients with AE. We have particular interest in febrile seizures because they are often provoked during the clinical course of AE patients. Therefore we undertook a mutational analysis of the *SCN1A* gene, which is the most representative gene for hyperthermia-induced seizure susceptibility and febrile seizure-related epileptic syndromes such as generalized epilepsy with febrile seizure plus (GEFS+).

## Subjects and methods

### Patients

Between July of 2007 and October of 2009, all patients, who had a history of AE of obscure origin in childhood, and who visited either Okayama University Hospital, Juntendo University Hospital, or Tottori University Hospital, were eligible for this study. We selected 15 patients (eight male and seven female subjects) who met the following criteria. The inclusion criteria in the study included a normal development before the onset of AE, an age of AE onset 10 years of age or younger, an acute onset and rapid progression of consciousness impairment with or without seizures, and the association of these symptoms with fever or a preceding infectious disease. The exclusion criteria included meningitis, toxic encephalopathy, possible metabolic errors, and encephalitis caused by a direct infection of the brain, or by a well-defined secondary immunological reaction to infectious disease.

The ages at the onset of AE ranged from 10 months to 9 years of age (mean age 5 years), and the ages at the time of follow-up ranged from 3 years to 27 years of age (mean age 12 years). The clinical diagnoses regarding the types of AE were as follows: AERRPS in seven patients, influenza encephalopathy with otherwise no specific findings in five subjects, and AESD in three subjects. The clinical findings at the acute phase of these patients are summarized in Table 1.

The study was approved by the Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. Written informed consent was obtained from the parents.

### Genetic analysis

The family history of each patient with respect to neurological disorders, especially seizure disorders and encephalopathy, was investigated by interviews and the examination of medical records. *SCN1A* mutations were analyzed by the previously reported methods (Ohmori et al., 2002). In brief, genomic DNA was extracted from peripheral blood cells. Twenty-six exons of the *SCN1A* gene were amplified with intronic primers. All PCR products were purified with a PCR product presequencing kit (Amersham Biosciences, Little Chalfont, Buckinghamshire, United Kingdom), reacted with the Big Dye Terminator FS ready-reaction kit (Applied Biosystems, Foster City, CA, U.S.A.), and analyzed on an ABI PRISM3100 sequencer (Applied Biosystems).

## Results

Six of the 15 patients (40%) had a family history of seizure disorders and/or AE in first- or second-degree relatives (Table 2). Of these, five patients had a family history of febrile seizures (FS), and two had a family history of epilepsy or seizures with or without FS (Fig. 1B–D). The remaining patient #8 with influenza encephalopathy had a sister with acute disseminated encephalomyelitis (ADEM); both of these siblings exhibited hypopituitarism after the AE episodes, and may harbor unknown genetic abnormalities other than seizure susceptibility. The proportion of patients with a positive family history, excluding this sibling patient, was high (5/14, 35.7%, regarding the positive family history including both first- and second-degree relatives; 4/14, 28.5%, regarding the positive family history including only the first-degree relatives).

**Table 1** Characteristics of acute encephalopathy.

| Patient no. | Acute encephalopathy | | | | | | |
|---|---|---|---|---|---|---|---|
| | Age | Gender | Type | Infection or etiology | Acute seizure | Acute neuroimaging | Acute EEG findings |
| 1 | 6 years 5 months | M | AERRPS | Preceding fever of unknown etiology | Generalized convulsive seizures and hemiseizures involving either side | CT: unremarkable | Diffuse HVS |
| 2 | 6 years 1 month | M | AERRPS | Preceding fever of unknown etiology | Clustering CPS with multifocal origins and evolution to SE | CT and MRI: unremarkable | Diffuse HVS |
| 3 | 5 years 7 months | M | AERRPS | Acute enterocolitis of unknown etiology | Focal seizures evolving to SE | MRI: unremarkable | Diffuse HVS and spike-waves |
| 4 | 8 years 1 month | F | AERRPS | Common cold | Frequent CPS | MRI: unremarkable (day 7) | Mild slow wave dysrhythmia, widespread spiky theta |
| 5 | 8 years | M | AERRPS | Common cold | Repeated generalized convulsions | CT and MRI: unremarkable | Diffuse low voltage slow |
| 6 | 7 years | F | AERRPS | Common cold | Initial frequent generalized tonic convulsions and subsequent repetitive partial seizure | CT: unremarkable; MRI: enhancement in bilateral parieto-temporal cortex (day 32) | Periodic pattern |
| 7 | 5 years | M | AERRPS | Common cold | Frequent generalized tonic convulsions | CT and MRI: unremarkable (day 1), high intensity in claustrum on T2 and FLAIR (after day 11) | HVS (days 2 and 3), periodoc pattern (day 8) |

**Table 1** (*Continued*)

| Patient no. | Acute encephalopathy | | | | | | |
|---|---|---|---|---|---|---|---|
| | Age | Gender | Type | Infection or etiology | Acute seizure | Acute neuroimaging | Acute EEG findings |
| 8 | 2 years 4 months | M | IE | Influenza | None | Brain edema in CT | Information not available |
| 9 | 2 years 3 months | M | IE | Influenza A | Clustering focal seizures | MRI: unremarkable | Diffuse HVS and PLEDs |
| 10 | 5 years 9 months | F | IE | Influenza A | Generalized convulsive SE with left side dominance | Mild brain edema in CT | Right hemisphere dominant HVS |
| 11 | 9 years 7 months | F | IE | Influenza | Generalized convulsion (day 1) | Brain edema in CT (day 2) | Flat (day 2) |
| 12 | 5 years 8 months | F | Probable IE | Probable influenza | Right hemiconvulsive SE | CT: unremarkable | HVS |
| 13 | 10 months | F | AESD | HHV-6 | Generalized convulsion (day 1), CPS cluster (day 5) | MRI: unremarkable (day 3), bright tree appearance in DWI (day 5) | Mild generalized slowing |
| 14 | 1 year 5 months | M | AESD | Common cold | Generalized convulsion (day 1), CPS cluster (day 5) | MRI: unremarkable (day 3), bright tree appearance in DWI (day 5) | Diffuse HVS (day 5) |
| 15 | 1 year 1 month | F | AESD | Influenza A | Generalized convulsions (days 1 and 6) | MRI: bright tree appearance in DWI (day 7) | Frontal dominant mild slowing (day 6) |

SE, status epilepticus; IE, influenza encephalopathy; AERRPS, acute encephalitis with refractory, repetitive partial seizures; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; HVS, high-voltage slow waves; PLEDs, periodic lateralized epileptiform discharges; SW, spike-and-wave complex; ND, not detected; DWI, diffusion-weighted image; HHV-6, human herpes virus 6; MR, mental retardation.

**Table 2** Genetic and neurological findings.

| Patient no. | Age at genetic analysis | Family history | SCN1A mutation | Sequel | |
|---|---|---|---|---|---|
| | | | | Mental and neurological state (neuroimaging) | Seizure or epilepsy (EEG findings) |
| 1 | 25 years | Negative | None | Severe mental deficit, no neurological abnormalities (brain atrophy in MRI) | Intractable seizure persisting from the acute phase of encephalopathy with no interval (multifocal SW) |
| 2 | 21 years | Seizures in a grandfather and FS in a niece | R1575C | Mild mental deficit (MRI unremarkable) | Intractable CPS persisting from the acute phase with no interval (multifocal spikes, disappearing from 15 years 11 months) |
| 3 | 6 years | Negative | None | Mild mental deficit with hyperkinetic behaviors (IQ 69), no neurological abnormalities (diffuse brain atrophy in MRI) | Intractable CPS (multifocal spike-waves) |
| 4 | 9 years | FS in the mother brothers and an aunt, epilepsy in an uncle | None | Normal development (left temporal gliotic changes in MRI) | Intractable focal seizures with short interval from acute phase |
| 5 | 24 years | Negative | None | Mild MR (mild diffuse brain atrophy in MRI) | Intractable seizure persisting from the acute phase |
| 6 | 15 years | Negative | None | Severe MR (moderate diffuse brain atrophy in MRI) | Intractable seizure persisting from the acute phase |
| 7 | 0 year | Negative | None | Mild MR (mild diffuse brain atrophy in MRI) | Intractable frequent seizures (frontal and temporal spikes) |
| 8 | 7 years | ADEM in a sister | None | Hypopituitarism, no mental or neurological abnormalities (MRI) | No seizures (mild dysrhythmia of background with no spikes) |
| 9 | 18 years | FS in a sister | None | Severe mental deficit (brain atrophy in MRI) | Intractable CPS and periodic spasms from 2 years 5 months of age (multifocal SW) |
| 10 | 7 years | An episode of LOC in a maternal uncle (not counted as a seizure) | None | Borderline intelligence (IQ 75), no neurological abnormalities (MRI unremarkable) | Intractable focal seizures (multifocal spikes) |
| 11 | 15 years | Negative | None | Clinical brain death (not available) | No seizure (flat EEG) |
| 12 | 15 years | Negative | None | Severe mental deficit with behavior disorders, no neurological abnormalities (MRI unremarkable at 8 years of age) | Intractable CPS of left frontal origin with occasional generalization from 6 years 6 months of age (slow alpha rhythm with rare multifocal) |
| 13 | 3 years | FS in the mother, an aunt and a cousin | None | Moderate MR, no motor impairment (mild atrophic change in MRI) | No seizure (EEG unremarkable) |
| 14 | 3 years | FS in the father and an aunt | None | Moderate MR, no motor impairment (mild atrophic change in MRI) | No seizure (EEG unremarkable) |
| 15 | 3 years | Negative | None | Normal development (MRI unremarkable) | No seizure (EEG unremarkable) |

CPS, complex partial seizure(s); LOC, loss of consciousness; SW, spike-and-wave complex; MR, mental retardation; FS, febrile seizure(s); ADEM, acute disseminated encephalomyelitis.

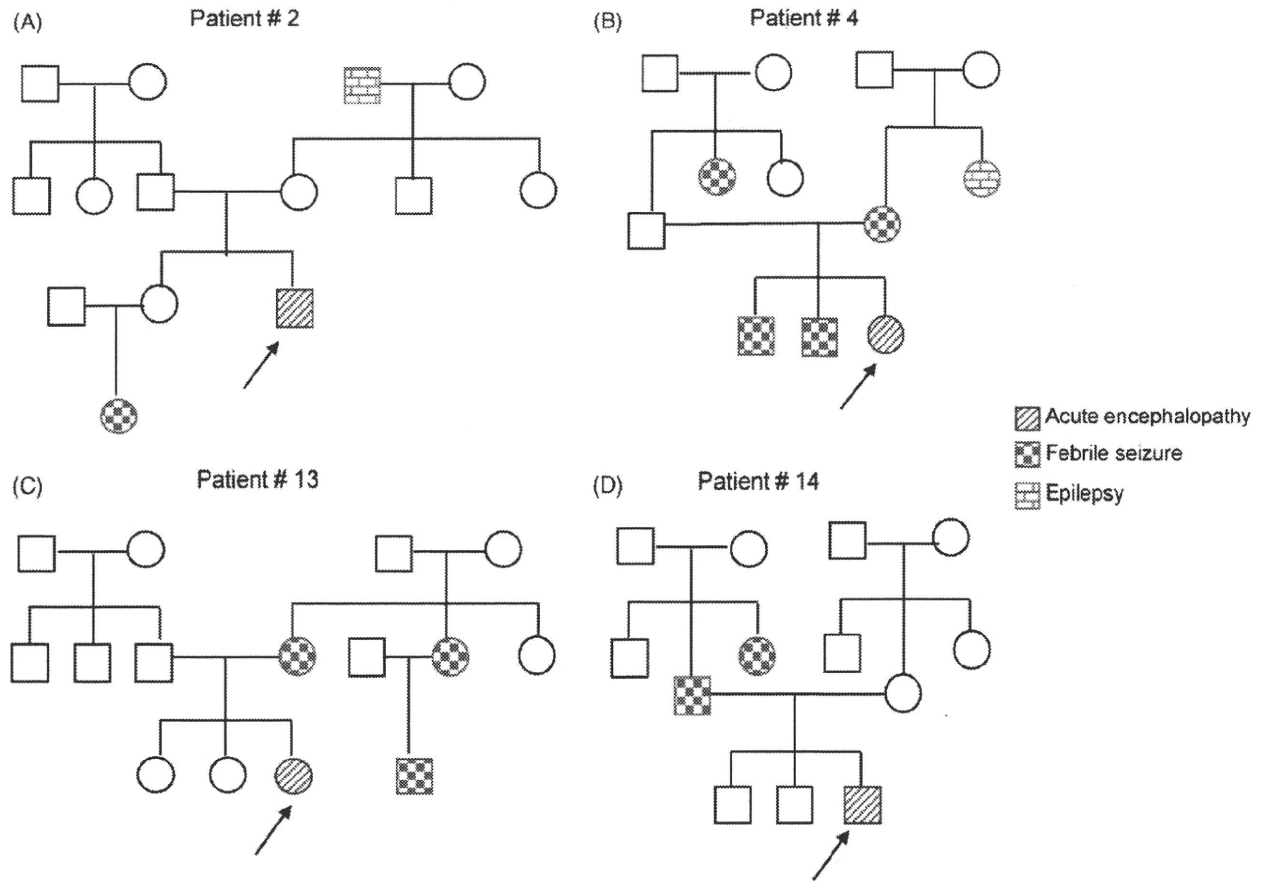



**Figure 1** Pedigrees of representative families with convulsive disorders and a family with the *SCN1A*-R1575C mutation.

The DNA analysis revealed that the *SCN1A*-R1575C mutation was present in patient #2 clinically diagnosed with AERRPS. This mutation was twice confirmed by independent PCR amplification and sequencing with forward and reverse primers. *SCN1A*-R1575C mutation was found in this patient's healthy father, but not in his mother; this case is reported in detail as following (Figs. 1A and 2). This mutation was not detected in the 96 healthy individuals. The remaining 14 patients had no mutations in the *SCN1A* gene.

## Case report of patient #2

The participant with the *SCN1A*-R1575C mutation is a male subject, and has a maternal grandfather who had seizures starting in old age and a niece who experienced a febrile seizure at 1 year of age. The patient was born after an uneventful 40-week gestation with a birth weight of 3460 g. He developed normally with no seizures during infancy or young childhood.

At 6 years and 1 month of age, the patient had a fever for 3 days, and after an uneventful 1-day interval he experienced the first complex partial seizure (CPS), which lasted for several minutes. On the same day following a temporary recovery, the patient had another seizure that evolved to secondary generalization, and he was then admitted to a local hospital. At the time of admission, the patient exhibited fever again, became irritable with impaired consciousness, and walked unsteadily.

On the second day of admission, the patient suffered from very frequent CPSs that often led to generalization, and his seizures culminated into status epilepticus, which caused a sustained loss of consciousness between apparent seizures; during this status epilepticus, the patient had a respiratory insufficiency that necessitated artificial ventilation for 3 days. After being weaned from the artificial ventilation, the patient continued to suffer from almost daily seizures. The patient could talk, but was forgetful and had slow responses and visual hallucinations.

The examination of blood cell counts, liver function, ammonia, glucose, and electrolyte levels in the acute phase were all unremarkable. The CSF cell count was 6 per $mm^3$ and was hence slightly higher than the normal limit of 5 per $mm^3$ (Maegaki et al., 2006); the CSF was otherwise unremarkable with a protein level of 21 mg/dl, glucose levels of 79 mg/dl, and negative results for myelin basic protein, an oligoclonal IgG band, and viral titers for Japanese encephalitis, measles, and herpes simplex virus. The CT and MRI scans revealed no brain pathology. The EEG analysis showed a marked increase of irregular 1.5–3 Hz slow waves in the background with no spikes (Fig. 3).

The patient continued to have almost daily CPS with a duration of under 1 min, exhibiting eye-deviations to either side, hypersalivation, oral automatisms, and occasional generalization with no seizure-free intervals after the acute phase. The patient was moved to the Okayama University Hospital on the 50th day of encephalopathy.

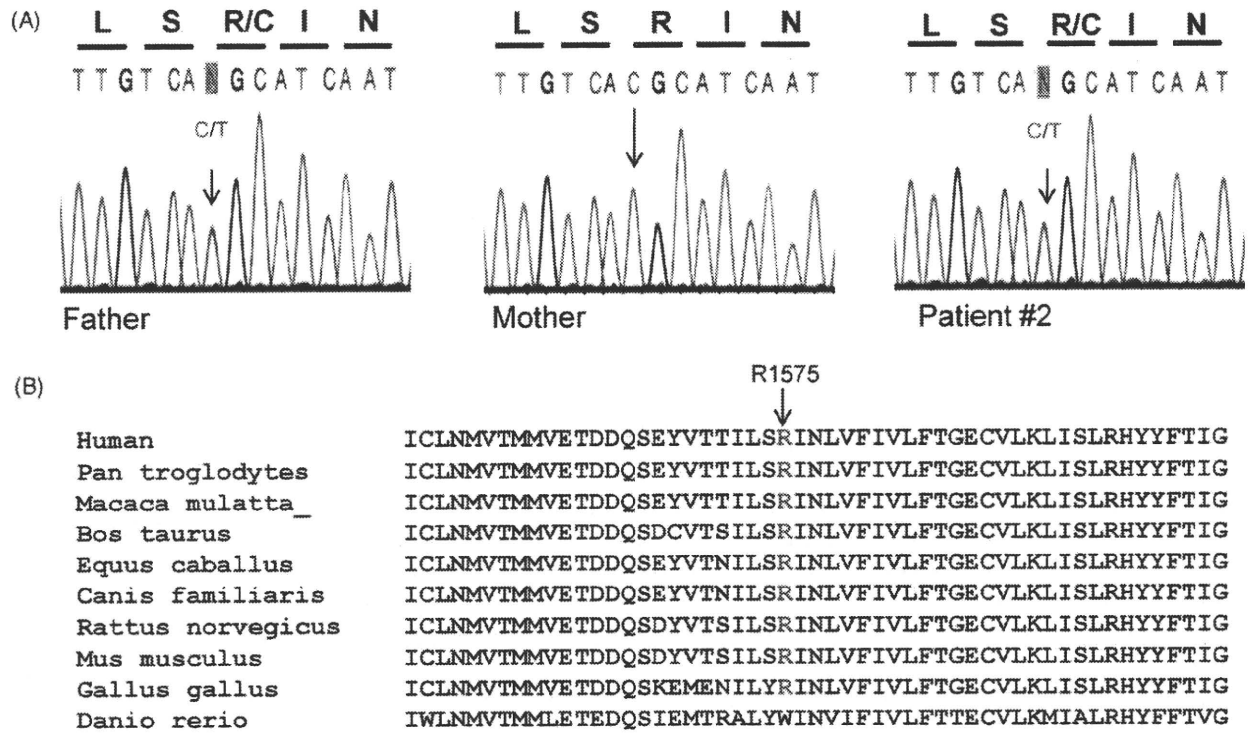



**Figure 2** A mutational analysis of the *SCN1A* gene. Patient #2 and his father both exhibited the R1575C mutation. The numbering of amino acids is described in the GenBank accession number AB093548 (A). The amino acid sequence alignment of the region near R1575 in the sodium channel α-subunit genes (B). R1575 is highly conserved throughout various animal species. GenBank accession numbers, from top to bottom, are AB093548, XP_515872, XP_001101023, XP_001252668, XP_001916728, XP_858797, NP_110502, NP_061203, XP_001233839, and NP_956426.

At this time, the EEG analysis still showed diffuse high-amplitude irregular slow waves with no alpha rhythms in the background, and multifocal spikes emerged involving the bilateral frontal, centrotemporal, and parietooccipital regions. The EEG recording captured one of the patient's CPS with eye-deviations to the left and a duration of 30 s, and showed rhythmic multiple spike-wave activity originating from the right parietooccipital region. There were 10 episodes of subclinical ictal EEG patterns with multiple different origins involving either hemisphere (Fig. 4).

The frequency of seizures gradually decreased and the spikes on the EEG analysis also gradually diminished upon treatment. The follow-up MRI analysis, undergone when the patient was 17 years and 11 months of age, disclosed no brain pathology. At 22 years 7 months of age, the patient had a rare brief CPS that was precipitated by a fever, while on a combination therapy of phenytoin, sodium valproate, clonazepam, and lamotrigine.

## Discussion

AE includes a variety of pathological processes with more or less inflammatory reactions in the CNS. The relationship between seizures and inflammatory reactions has received increasing attention in recent years. A seizure induced by chemicals or hyperthermia increases the levels of cytokines such as interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF) alpha in the rodent brain (Vezzani and Granata, 2005). In humans, prolonged seizures or a single seizure is sufficient to cause activation of a cytokine cascade and the associated inflammatory signals (Lehtimäki et al., 2007). Conversely, the intracerebral application of IL-1 beta reduces the seizure threshold in an experimental mouse model (Dubé et al., 2005). In addition, under conditions of hyperexcitability, circulating leukocytes extravasate through the BBB, where they produce local inflammation. This event induces leakage of the BBB, spilling plasma constitutions such as proteins and excess potassium into the neuronal environment, which leads to status epilepticus and the subsequent development of recurrent seizures (Fabene et al., 2008). Considering the findings of these experimental and clinical studies, seizures and inflammatory reactions seem to be mutually interacting responses.

Many studies have been performed regarding inflammatory processes involved in the pathophysiological mechanisms of AE, especially acute encephalitis (Mizuguchi et al., 2007). The role of seizure susceptibility in AE, however, has been so far scarcely investigated. Considering the above-mentioned close link between seizures and inflammatory reactions, we speculate that intrinsic seizure susceptibility may have detrimental effects in the process of AE. Given this speculation, familial seizure predispositions might be greater in patients with AE. Of the 15 patients with various types of AE, a high proportion had a family history of seizures or AE, especially FS (five patients, 33.3%). In the 14 selected patients, excluding the sibling case, the proportion of patients with a family history of seizures in the

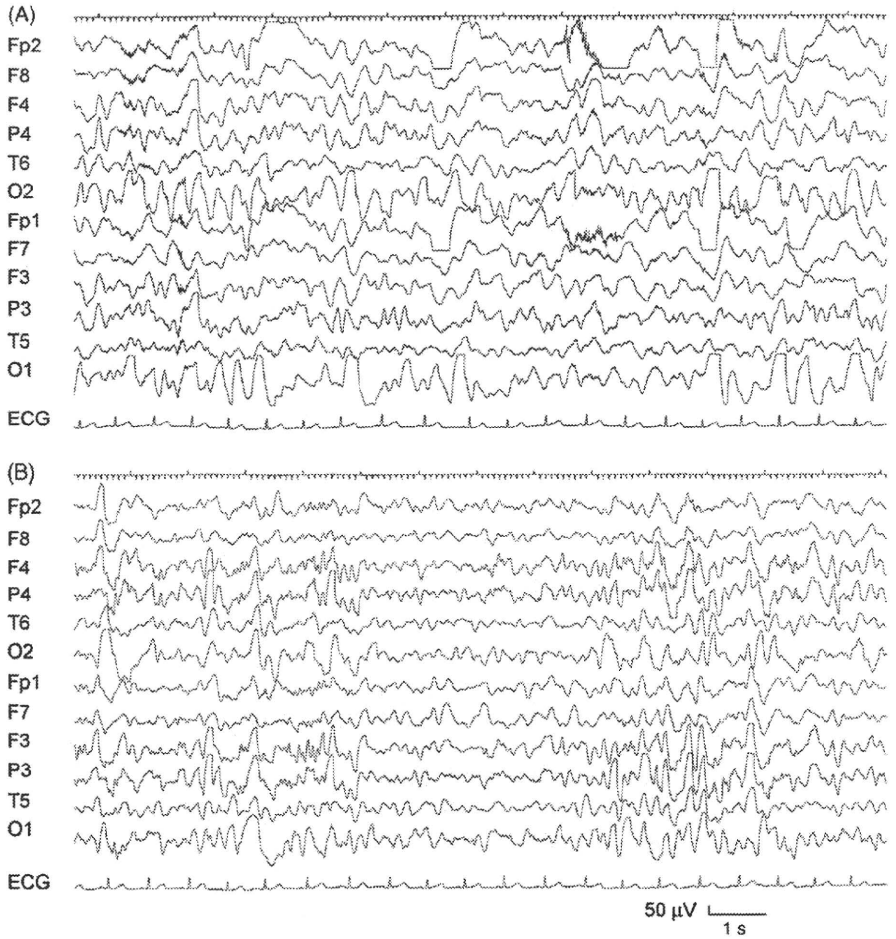



**Figure 3** The interictal EEGs recorded during the subacute phase of disease in patient#2 with AERRPS and the *SCN1A*-R1575C mutation. The EEG that was recorded on the 23rd day of disease showed diffuse high-amplitude slow waves with no alpha rhythms during the waking state (A), and revealed no epileptic discharges in either the waking (A) or sleep state (B). These EEG traces were recorded at the Kurashiki Central Hospital.

first-degree relatives was 28.6% (4/14), as mentioned above, and this rate was much higher than in healthy children (9.3%, or 98/1057) according to a study on EEG abnormalities in healthy Japanese children. In this normative study, a family history of seizures in the first-degree relatives was noted in seven children with EEG abnormalities and in 91 children without EEG abnormalities (Okubo et al., 1994). This difference in the family history of seizure disorders was statistically significant ($p=0.037$) according to Fisher's exact test. Therefore, some, if not all, patients with AE have a genetic susceptibility to seizure. The seizures were intrinsically involved in the pathogenesis of AE in most patients. Previous reports on individual types of AE thus far have not examined the relationship between AE and seizure susceptibility (Mizuguchi, 1997; Yamanouchi et al., 2006; Mikaeloff et al., 2006; Sakuma, 2009).

The *SCN1A* mutations are linked to febrile seizure-related epileptic syndromes such as GEFS+ and severe myoclonic epilepsy in infancy. Febrile seizures were the most frequently observed in family histories in this study and as we anticipated this finding, we planned to screen the *SCN1A* mutation in patients with AE. As a result, the heterozygous R1575C mutation was identified in a patient with AERRPS. AERRPS is thought to have an inflammatory basis because of the clinical findings of an acute fever and the common observation of CSF pleocytosis. There is a report of the detection of an autoantibody against the glutamate receptor Glu$\varepsilon$2 in serum and/or CSF (Ito et al., 2005), therefore, autoimmune mechanisms appear to underlie the pathogenesis of AERRPS (Sakuma, 2009). The patient harboring the R1575C mutation experienced a relatively mild form of AERRPS with no destructive brain lesions. AERRPS is characterized by the persistence of devastating seizures from the acute phase through the chronic phase with no latent interval, and this unique phenomenon suggests a close relationship between the pathophysiological mechanisms of encephalopathy and seizure generation. An identical *SCN1A*-R1575C mutation was also detected in a patient with Rasmussen encephalitis together with an autoantibody against glutamate receptor GluR3 (Ohmori et al., 2008). The electrophysiological properties of *SCN1A*-R1575C have exhibited greater persistent sodium currents as compared to wild-type (Ohmori et al., 2008). This may contribute to exacerbated epileptic seizures and the consequent development of inflammatory reactions in the brain. The *SCN1A*-R1575C mutation was not detected in 96 healthy individuals and it was highly

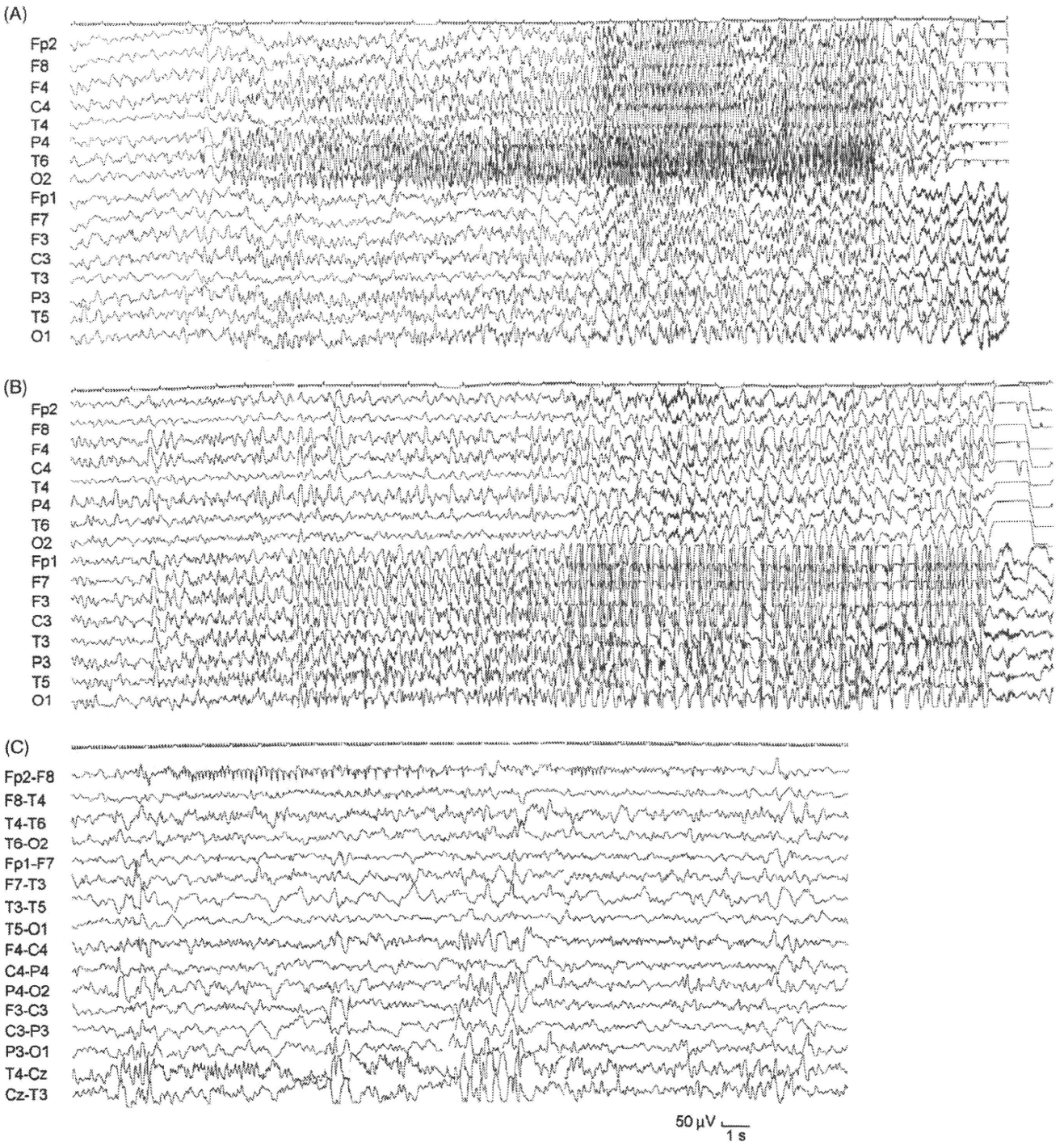



**Figure 4** The ictal and subclinical ictal EEGs recorded during the chronic phase of disease in patient #2 with AERRPS and with the *SCN1A*-R1575C mutation. The ictal EEG of a complex partial seizure with eye-deviations to the left and an origin from the right parietooccipital region was recorded at 3 months after disease onset (A). The subclinical ictal EEG patterns with different origins were also recorded (B, origin in the left hemisphere; C, origin at the right anterior temporal region). EEGs (A and B) were recorded taking reference to the bilateral earlobes.

conserved throughout various animal species, although the possibility of coincidental association of the occurrence of AERRPS and *SCN1A* mutation cannot be excluded.

The infection of pathogenic viruses including influenza, human herpes virus (HHV)-6, rotavirus, and the varicella-zoster virus preceded the onset of AE in some patients. Aspirin, non-steroidal anti-inflammatory drugs, and theophylline have been shown to be risk factors (Mizuguchi et al., 2007). Most of the previous clinical studies have been clarified the extrinsic factors. A high family incidence of convulsive disorders in this study has indicated that the intrinsic susceptibility to AE should be investigated. Some subtypes

of AE, such as AERRPS, influenza encephalopathy, HHV-6 encephalopathy, and ANE have been reported by Japanese researchers. Several epidemiological studies revealed that the prevalence of FS is approximately 2–5% in North America and Europe and 7–14% in Japan (Baulac et al., 2004). A differential genetic susceptibility to fever in Japan might contribute to the different clinical subtypes and etiology of AE. We have, however, not yet excluded the possibility of environmentally-based susceptibility to AE.

The present results were obtained with a limited number of subjects. We investigated each patient who visited one of our institutions during the study period and met the criteria, but the sample size was ultimately small with a potential bias. We do not yet have enough information to fully elucidate the relationship between the types of AE and the types of mutations or other genetic abnormalities. In the future we require more extensive familial studies regarding each specific type of AE, especially on the role of febrile seizure susceptibility and other genetic risk factors. These studies will facilitate the overall understanding of AE pathogenesis and will therefore lead to the development of rational prevention treatments for AE in childhood. We hope that the present study will encourage a comprehensive analysis in this direction.

## Acknowledgements

We thank Drs. Yoshio Arakaki and Yoshinobu Nishida of the Division of Pediatrics, Kurashiki Central Hospital, Kurashiki, Japan, for allowing us to use the clinical data of a patient obtained during his admission to their hospital.

## References

Awaya, Y., Fukuyama, Y., 1986. Epilepsy sequelae of acute encephalitis or encephalopathy (third report). Jpn. J. Psychiatry Neurol. 40, 385–387.

Baulac, S., Gourfinkel-An, I., Nabbout, R., Huberfeld, G., Serratosa, J., Leguern, E., Baulac, M., 2004. Fever, genes, and epilepsy. Lancet Neurol. 3, 421–430.

Baxter, P., Clarke, A., Cross, H., Harding, B., Hicks, E., Livingston, J., Surtees, R., 2003. Idiopathic catastrophic epileptic encephalopathy presenting with acute onset intractable status. Seizure 12, 379–387.

Costello, D.J., Kilbride, R.D., Cole, A.J., 2009. Cryptogenic new onset refractory status epilepticus (NORSE) in adults — infection or not? J. Neurol. Sci. 277, 26–31.

Dubé, C., Vezzani, A., Behrens, M., Bartfai, T., Baram, T.Z., 2005. Interleukin-1beta contributes to the generation of experimental febrile seizures. Ann. Neurol. 57, 152–155.

Fabene, P.F., Navarro, M.G., Martinello, M., Rossi, B., Merigo, F., Ottoboni, L., Bach, S., Angiari, S., Benati, D., Chakir, A., Zanetti, L., Schio, F., Osculati, A., Marzola, P., Nicolato, E., Homeister, J.W., Xia, L., Lowe, J.B., McEver, R.P., Osculati, F., Sbarbati, A., Butcher, E.C., Constantin, G., 2008. A role for leukocyte-endothelial adhesion mechanisms in epilepsy. Nat. Med. 14, 1377–1383.

Ito, H., Mori, K., Toda, Y., Sugimoto, M., Takahashi, Y., Kuroda, Y., 2005. A case of acute encephalitis with refractory, repetitive partial seizures, presenting autoantibody to glutamate receptor Glu$\varepsilon$2. Brain Dev. 27, 531–534.

Lehtimäki, K.A., Keränen, T., Palmio, J., Mäkinen, R., Hurme, M., Honkaniemi, J., Peltola, J., 2007. Increased plasma levels of cytokines after seizures in localization-related epilepsy. Acta Neurol. Scand. 116, 226–230.

Maegaki, Y., Kondo, A., Okamoto, R., Inoue, T., Konishi, K., Hayashi, A., Tsuji, Y., Fujii, S., Ohno, K., 2006. Clinical characteristics of acute encephalopathy of obscure origin: a biphasic clinical course is a common feature. Neuropediatrics 37, 269–277.

Mikaeloff, Y., Jambaqué, I., Hertz-Pannier, L., Zamfirescu, A., Adamsbaum, C., Plouin, P., Dulac, O., Chiron, C., 2006. Devastating epileptic encephalopathy in school-aged children (DESC): a pseudo encephalitis. Epilepsy Res. 69, 67–79.

Mizuguchi, M., 1997. Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev. 19, 81–92.

Mizuguchi, M., Yamanouchi, H., Ichiyama, T., Shiomi, M., 2007. Acute encephalopathy associated with influenza and other viral infections. Acta Neurol. Scand. 115 (Suppl. 186), 45–56.

Ohmori, I., Ouchida, M., Ohtsuka, Y., Oka, E., Shimizu, K., 2002. Significant correlation of the SCN1A mutations and severe myoclonic epilepsy in infancy. Biochem. Biophys. Res. Commun. 295, 17–23.

Ohmori, I., Ouchida, M., Kobayashi, K., Jitsumori, Y., Inoue, T., Shimizu, K., Matsui, H., Ohtsuka, Y., Maegaki, Y., 2008. Rasmussen encephalitis associated with *SCN1A* mutation. Epilepsia 49, 521–526.

Okubo, Y., Matsuura, M., Asai, T., Asai, K., Kato, M., Kojima, T., Toru, M., 1994. Epileptiform EEG discharges in healthy children: prevalence, emotional and behavioral correlates, and genetic influences. Epilepsia 35, 832–841.

Okumura, A., Kidokoro, H., Tsuji, T., Suzuki, M., Kubota, T., Kato, T., Komatsu, M., Shono, T., Hayakawa, F., Shimizu, T., Morishima, T., 2009. Differences of clinical manifestations according to the patterns of brain lesions in acute encephalopathy with reduced diffusion in the bilateral himsipheres. Am. J. Neuroradiol. 30, 825–830.

Saito, Y., Maegaki, Y., Okamoto, R., Ogura, K., Togawa, M., Nanba, Y., Inoue, T., Takahashi, Y., Ohno, K., 2007. Acute encephalitis with refractory, repetitive partial seizures: case reports of this unusual post-encephalitic epilepsy. Brain Dev. 29, 147–156.

Sakuma, H., 2009. Acute encephalitis with refractory, repetitive partial seizures. Brain Dev. 31, 510–514.

Tada, H., Takanashi, J., Barkovich, A.J., Oba, H., Maeda, M., Tsukahara, H., Suzuki, M., Yamamoto, T., Shimono, T., Ichiyama, T., Taoka, T., Sohma, O., Yoshikawa, H., Kohno, Y., 2004. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Neurology 63, 1854–1858.

Takanashi, J., Oba, H., Barkovich, A.J., Tada, H., Tanabe, Y., Yamanouchi, H., Fujimoto, S., Kato, M., Kawatani, M., Sudo, A., Ozawa, H., Okanishi, T., Ishitobi, M., Maegaki, Y., Koyasu, Y., 2006. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. Neurology 66, 1304–1309.

Takanashi, J., 2009. Two newly proposed infectious encephalitis/encephalopathy syndromes. Brain Dev. 31, 521–528.

Vezzani, A., Granata, T., 2005. Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia 46, 1724–1743.

Wilder-Smith, E.P.V., Lim, E.C.H., Teoh, H.L., Sharma, V.K., Tan, J.J.H., Chan, B.P.L., Ong, B.K.C., 2005. The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. Ann. Acad. Med. Singapore 34, 417–420.

Yamanouchi, H., Kawaguchi, N., Mori, M., Imataka, G., Yamagata, T., Hashimoto, T., Momoi, M.Y., Eguchi, M., Mizuguchi, M., 2006. Pediatr. Neurol. 34, 93–100.

# 平成22年度班会議プログラム

厚生労働科学研究費補助金

難治性疾患克服研究事業

# 「先天性筋無力症候群の診断・病態・治療法開発研究」

# 平成 22 年度　班会議

# プログラム

研究代表者　大野　欽司（名古屋大学）

日時：平成 23 年 1 月 8 日（土）11：00～14：30

場所：名古屋大学医学部(鶴舞キャンパス)　鶴友会館 2 階

名古屋市昭和区鶴舞町 65

厚生労働科学研究費補助金
難治性疾患克服研究事業研究事業
**「先天性筋無力症候群の診断・病態・治療法開発研究」**
**平成 22 年度　班会議**
**平成 23 年 1 月 8 日**

**11:00～11:05　開会あいさつ　研究代表者　大野欽司**

**午前の部　11:00～12:25**

**I. 先天性筋無力症候群の臨床・病態・制御　座長　福留隆泰**

11:05～11:15　**Collagen Q 欠損症自験例の臨床的検討**

奥村（おくむら）　彰久（あきひさ）　10 分

順天堂大学医学部小児科　小児神経学

11:15～11:45　**先天性筋無力症候群の臨床的特徴**

苛原（いらはら）　香（かおり）　30 分

国立精神・神経医療研究センター　小児神経学

11:45～11:55　**本邦における先天性筋無力症候群の遺伝子変異解析**

東（あずま）　慶輝（よしてる）　10 分

名古屋大学　神経遺伝情報学・小児科学

11:55～12:15　Collagen Q 欠損症に対する protein anchoring therapy

伊藤（いとう）　美佳子（みかこ）　20 分

名古屋大学　神経遺伝情報学

12:15～12:25　Collagen Q 欠損症の分子病態

中田（なかた）　智彦（ともひこ）　10 分

名古屋大学　神経遺伝情報学・小児科学

**12:25～13:30　お昼休憩**

**班員会議 12：25～13：30**

**場所：名古屋大学病院　病棟 14F　ソレイユ**

**午後の部　　13:30～14:30**

**II. 神経筋接合部欠損病態の研究　　座長　大野欽司**

13:30～14:00　**神経筋接合部分子欠損モデル動物の電気生理学的研究**

福留（ふくどめ）　隆泰（たかやす）　　30 分

長崎川棚医療センター　神経内科

14:00～14:30　**次世代シークエンサーによる exome capture resequencing 解析**

大野欽司（おおのきんじ）　　30 分

名古屋大学　神経遺伝情報学

14:30　**閉会**

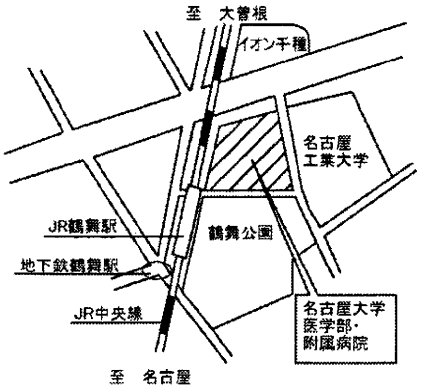
# 会場案内

鶴友会館　名古屋大学医学部（病院）内　　2階　大会議室
名古屋大学　鶴舞キャンパス

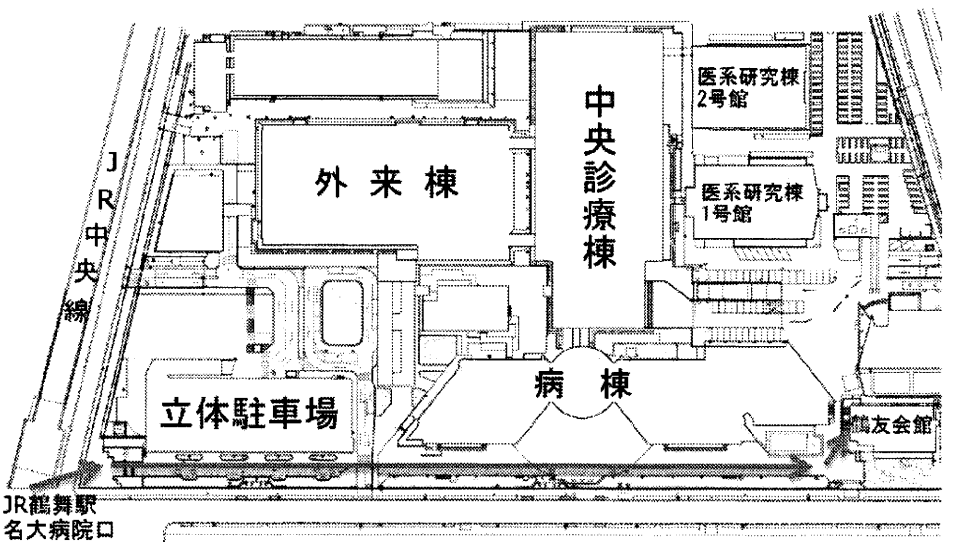
**JR 中央本線・鶴舞駅「名大病院口」すぐ**

○新幹線をご利用の場合・・・・ 東海道新幹線「名古屋」下車、JR 中央本線(7 番・8 番ホーム)
**鶴舞駅　下車**　普通・快速電車が停車します。
JR 中央線ご乗車の際は先頭車両が便利です。
下車した電車の進行方向にある出口が「名大病院口」です。

○中部国際空港をご利用の場合
→**名鉄電車・中部国際空港駅**よりミュースカイまたは、快速特急・特急電車
（この駅発のどの電車でもご利用になれます）
**金山駅**　下車
→JR 中央線下り線
（千種・大曽根方面、中津川行き・高蔵寺行きの普通又は、快速電車）
**鶴舞駅　下車**　JR 中央線ご乗車の際は先頭車両が便利です。
下車した電車の進行方向にある出口が「名大病院口」です。




**名古屋大学病院**




鶴友会館脇の階段より 2 階にお上がり下さい。