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Genetic seizure susceptibility underlying acute encephalopathies in childhood

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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.

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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).