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Original article

# Late-onset epilepsy in children with acute febrile encephalopathy with prolonged convulsions: A clinical and encephalographic study

Takashi Saito [a,*], Yoshiaki Saito [a], Kenji Sugai [a], Eiji Nakagawa [a], Hirofumi Komaki [a], Tetsuya Okazaki [a], Yusaku Ishido [a], Yuu Kaneko [b], Takanobu Kaido [b], Akio Takahashi [b], Taisuke Ohtsuki [b], Hiroshi Sakuma [c], Masayuki Sasaki [a]

[a] *Department of Child Neurology, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan*
[b] *Department of Neurosurgery, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan*
[c] *Department of Immunology, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan*

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**Abstract**

The aim of this study is to analyze the characteristics of epilepsies as the sequelae of acute febrile encephalopathy with prolonged convulsions during childhood. Sixteen patients (M:F = 9:7) aged 2–13 years (mean 6.1 years) with history of febrile acute encephalopathy were retrospectively reviewed. These patients experienced febrile encephalopathy at the age of 11 months to 4 years, with 11 individuals presenting with findings of a biphasic clinical course ($n = 5$), frontal predominant ($n = 8$) lesions, and/or reduced diffusivity in the cerebral white matter on magnetic resonance imaging (MRI; $n = 3$). The remaining 5 patients had unilateral lesions that manifested the phenotype of hemiconvulsion–hemiplegia–epilepsy syndrome (HHES). Epilepsy emerged with a latent period of 2 months to 2 years after the acute phase of febrile encephalopathy. Head nodding or spasm with subsequent motion arrest and brief tonic seizures were the main seizure phenotypes. Ictal records of epileptic seizures were available in 9 patients. Epileptiform discharges with a focal or uneven distribution appeared at the seizure onset and lasted less than 1 s in all patients; these were followed by either generalized attenuation or fast activity in 8 patients with head nodding, spasm, or brief tonic seizures, and by localized fast activity in 1 patient with versive tonic seizures. Notably, the seizure onset area was often located outside the severe lesions on MRI, i.e., in the parietal areas in patients with frontal predominant lesions, and in the spared hemisphere of HHES. Although phenobarbital, zonisamide, carbamazepine, clobazam, clonazepam, and clorazepate were partially effective in some patients, daily seizures persisted in 11 patients. Callosotomy was performed in 2 patients, and beneficial effects were observed in both. These characteristics suggested a broad distribution of augmented excitability in these patients, resulting in the rapid propagation of epileptic activity in the initial phase of ictal phenomena. Thus, this study investigates the most severe subgroup of epilepsy following febrile acute encephalopathy and provides the basis for further exploration of the pathogenesis and treatment of characteristic seizures in this population.


*Keywords:* Acute encephalopathy; Acute infantile encephalopathy predominantly affecting the frontal lobes; Acute encephalopathy with biphasic seizures and late reduced diffusion; Head nodding

## 1. Introduction

Acute encephalopathy is a condition defined as rapid deterioration of brain function, and is caused by various etiologies. This condition is often provoked by febrile

* Corresponding author. Address: Department of Child Neurology, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo 187-8551, Japan. Tel.: +81 42 341 2711; fax: +81 42 346 1705.
*E-mail address:* stakashi@ncnp.go.jp (T. Saito).

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infections during infancy and early childhood, and several subtypes with distinct clinical features have been classically recognized: Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and acute necrotizing encephalopathy [1]. In addition, a category of acute encephalopathy that is characterized by the initial manifestation of prolonged febrile convulsions, biphasic clinical course, emergence of restricted diffusivity on magnetic resonance imaging (MRI) in the cerebral white matter at 3–8 days of illness ("bright tree appearance"), and a propensity for frontal lobe involvement has been recently proposed by Japanese child neurologists. This category has been termed acute encephalopathy of obscure origin with biphasic clinical course [2], acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF) [3], and acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [4]. Either of these terms may be applied to individual patients, depending on which of the aforementioned characteristics predominate or are lacking in their manifestations; however, these conditions are likely to represent the same entity. In addition, hemiconvulsion–hemiplegia–epilepsy syndrome (HHES) has as its onset prolonged febrile hemiconvulsion. Apart from patients with structural brain lesions due to vascular, infectious, and dysplastic etiologies [5], this clinical syndrome is characterized by residual epilepsy after a latent period, signal change on diffusion-weighted imaging, and genetic predisposition, which are similar to the characteristics of the aforementioned acute encephalopathy. Thus, many cases of HHES in Japan can be also regarded as hemispheric variants of this entity [6,7]. An inclusive concept of acute encephalopathy with febrile convulsive status epilepticus (AEFCSE) has also been proposed [1]. With hundreds of identified cases, this entity has been recognized as the most prevalent subgroup in acute febrile encephalopathy in Japan, and is becoming a social burden. The higher predominance of this condition in Japanese populations than in other countries, the family history of febrile convulsion in many cases, and the identification of *SCN1A* mutations in rare instances suggest a genetic predisposition for this type of acute encephalopathy [8,9], which may involve increased neuronal excitation and/or augmented inflammatory process in the central nervous system.

Despite the pertinent characterization of AEFCSE during the acute phase, the clinical features of this condition during the chronic phases have not been well delineated. Residual epilepsy as the sequela of AEFCSE is reported to complicate 65% of cases [10], but details are not available in terms of seizure phenotype, findings of electroencephalography (EEG), and response to antiepileptic treatment. We herein summarize the clinical and electrophysiological findings in post-AEFCSE epilepsy, which would provide a basis for the management of this patient population.

## 2. Subjects and methods

We identified 21 patients with a history of febrile acute encephalopathy who were admitted to our hospital between September 2007 and October 2011, mainly for evaluating residual epilepsy. All patients had disease onset with prolonged febrile seizures but no evidence of meningoencephalitis, including elevation of cerebrospinal fluid (CSF) cell counts and detection of pathogenic microorganisms in the CSF culture. Patients with Reye syndrome ($n = 1$), acute necrotizing encephalopathy ($n = 1$), severe anoxic episode during the course of encephalopathy ($n = 2$), and a preceding history of West syndrome/Lennox–Gastaut syndrome ($n = 1$) were excluded, and the clinical data of the remaining 16 patients were retrospectively reviewed through their medical charts (Table 1). These patients experienced encephalopathy with onset at the age of 11 months to 1 year and 10 months, and 11 individuals developed one or more of the findings of a biphasic clinical course ($n = 5$), frontal predominance ($n = 8$) and reduced diffusivity in the cerebral white matter on MRI ($n = 3$). The other 5 patients had unilateral lesions that manifested the phenotype of HHES. Thus, we could divide the patients into 2 groups: AEFCSE with bilateral hemisphere involvement ($n = 11$) and HHES ($n = 5$). None of these patients exhibited dysplastic lesions on MRI. The clinical findings of 1 HHES patient with an *SCN1A* mutation have been reported previously [11]. None of other patients had been examined by specific gene analysis.

To analyze epilepsy in these patients, data were collected with regard to the family history of convulsive disorders, past history of the patients, seizure phenotypes of residual chronic epilepsy, and developmental quotient assessed by either the Enjoji Developmental Assessment Scale or Kinder Infant Development Scale. We also reviewed the MRI findings on admission, ictal ($n = 12$) and interictal EEG, and magnetoencephalography (MEG; $n = 7$). Video EEG monitoring for ictal EEG recording was conducted using a standard 10–20 system. MEG was performed using a 204-channel MEG system (VectorView; Neuromag Co., Helsinki, Finland). Dipole sources with a goodness of fit greater than 80% were accepted and overlaid on the MRI results.

## 3. Results

### 3.1. Patient characteristics (Table 1)

The 16 patients (M:F = 9:7) were aged 2–13 years (mean 6.1 years) at the time of data collection. Two patients in the bilateral AEFCSE group had a history of febrile convulsions, and 1 patient in the HHES group had a history of epilepsy. All patients, including 2