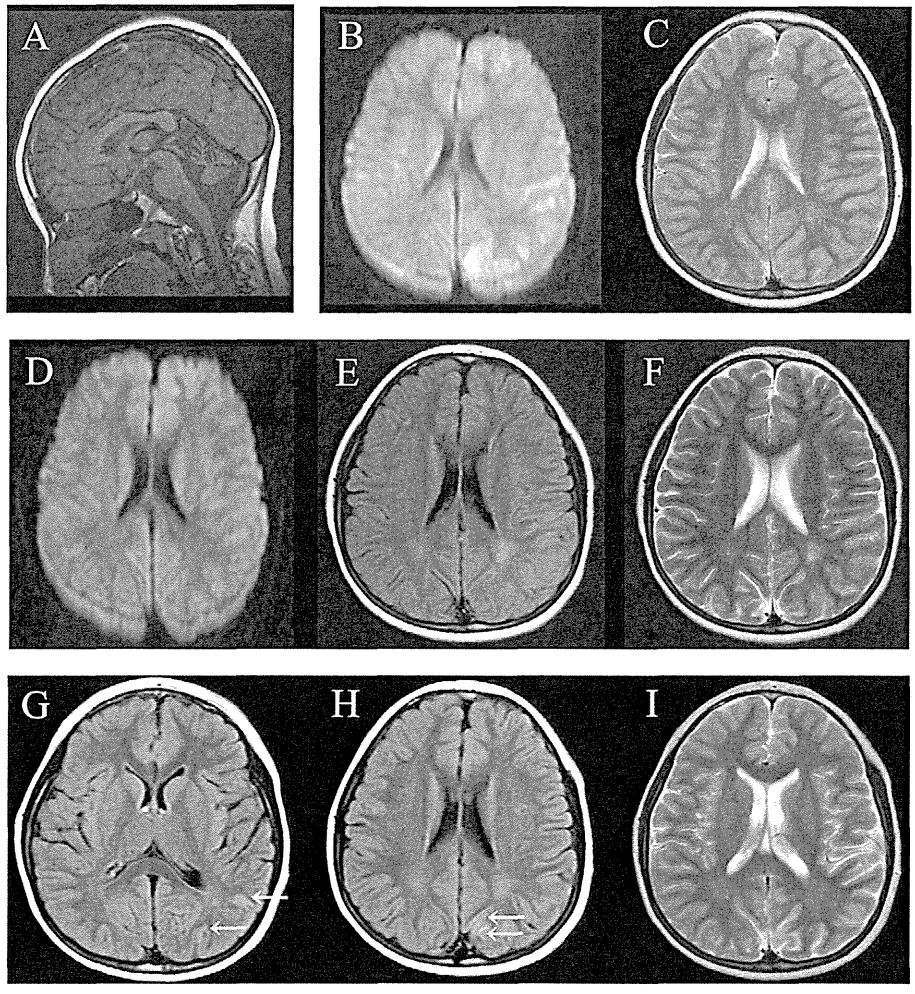

Fig. 1. Brain magnetic resonance imaging of the patient on day 1 (A), day 3 (B and C), day 14 (D–F), and day 35 (G–I) after admission (A: sagittal view, T1-weighted image; B–I: axial view, B and D: diffusion-weighted images; E, G, and H: fluid-attenuated inversion recovery images; C, F, and I: T2-weighted images) at 10 years of age.

developed progressive ataxia. At 5 years of age, magnetic resonance imaging (MRI) showed cerebellar vermis atrophy. The patient actively joined in with the usual school activities, although he had borderline intelligence and motor clumsiness. He had no history of episodic headache or hemiplegia attack before admission. None of his family members had neurological disorders including migraine.

The patient experienced dysesthesia on the right arm and leg when he was having dinner, evolving to right hemiplegia. On admission to our hospital, he manifested with vomiting, fluctuating consciousness, intermittent left-sided deviation of both eyes, and right flaccid hemiplegia. Deep tendon reflexes were attenuated on the right extremities, and Babinski's sign was negative on both toes. No meningeal signs were noted, and his body temperature was 36.4 °C. Laboratory examination of the blood showed normal results including blood gas, cell counts, electrolytes, glucose level, and coagulation profiles. Findings on computed tomography, MRI, and magnetic resonance angiography of the brain were unremarkable, apart from the vermian atrophy as observed previously (Fig. 1A). Twenty hours after the onset, the patient showed a fever of 39.0 °C. Since the acute symptoms persisted, the diagnosis of acute encephalopathy was suspected. Therefore, treatment with mannitol and acyclovir was initiated on the second day of illness. Routine cerebrospinal fluid analysis result was normal (cell count 3/μL, protein 23 mg/dL). Serum and cerebrospinal fluid interleukin-6 levels were elevated to 16.6 (normal < 4.0) and 130 pg/mL (normal < 0.2), respectively. Cerebrospinal fluid neuron-specific enolase (72 ng/mL) and lactate (21.4 mg/dL) levels were also raised. On the 3rd day of illness, electroencephalogram showed slow delta activity over the left hemisphere (Fig. 2), and MRI revealed restrictive diffusivity (Fig. 1B) and regional swelling (Fig. 1C) of the cerebral cortex at the left temporo-occipital areas. ^{99m}Tc-ethyl cysteinate dimer single photon emission computed tomography (SPECT) revealed cortical hyperperfusion

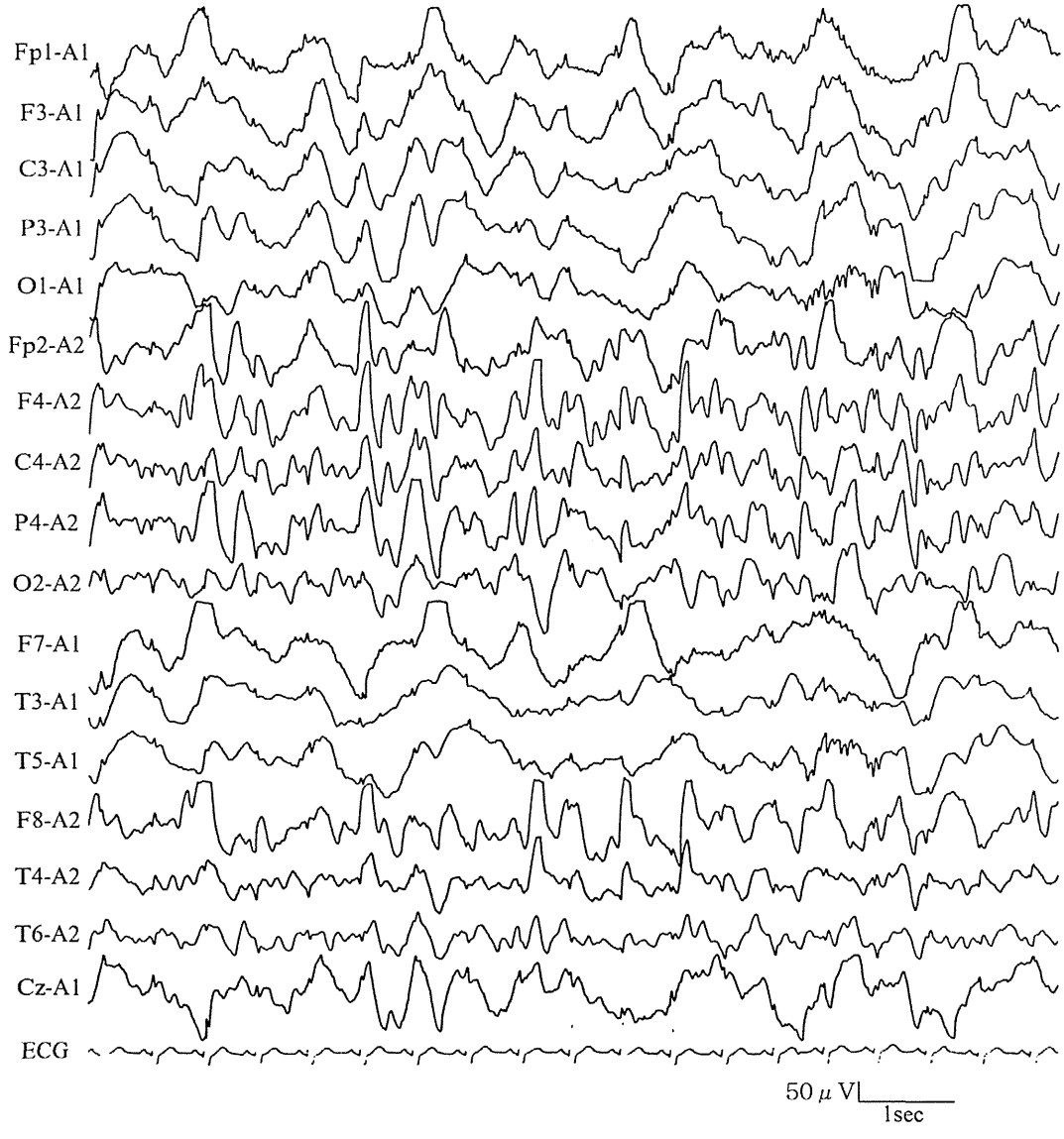

Fig. 2. Electroencephalogram on day 3 of illness.

over the left cerebral hemisphere (Fig. 3A). The fever subsided after the initiation of high-dose methylprednisolone therapy at 30 mg/kg/day for 3 days, but focal seizures with twitching of the right corner of the mouth appeared recurrently on the 6th day of illness. Edaravone (0.9 mg/kg/day) was administered after obtaining informed consent from his parent. The consciousness disturbances were ameliorated within several hours thereafter and the background laterality on electroencephalogram resolved on the same day. He could utter meaningful words, and could sit without support by the next morning. The right hemiplegia also resolved gradually, and he had recovered completely without sequelae by 3 weeks after the onset.

Viral and bacterial screenings were all negative, and urinary analysis of amino acids showed unremarkable results. The restricted diffusivity on MRI disappeared on day 14 (Fig. 1D), but cortical swelling still persisted in this period (Fig. 1E and F). On day 35, mild cortical atrophy appeared at the affected left posterior areas (Fig. 1I), accompanied by regional linear high signal intensity at the bottom of sulcus (arrows in Fig. 1G and H) on fluid-attenuated inversion recovery images. Follow-up SPECT showed hypoperfusion in the left hemisphere on day 35 (Fig. 3B), in contrast to the hyperperfusion on day 7. The changes on MRI disappeared 5 months later, but left hemispheric hypoperfusion on SPECT persisted. Seven months after the first admission, the patient developed transient left hemiplegia with visual aura and headache that lasted less than an hour. Thereafter, recurrent headache attack occurred once a month. Genetic analysis of blood DNA yielded negative results in mitochondrial 3243, 3252, 3256, 3291, and 13,513 nucleotides, but revealed a mutation

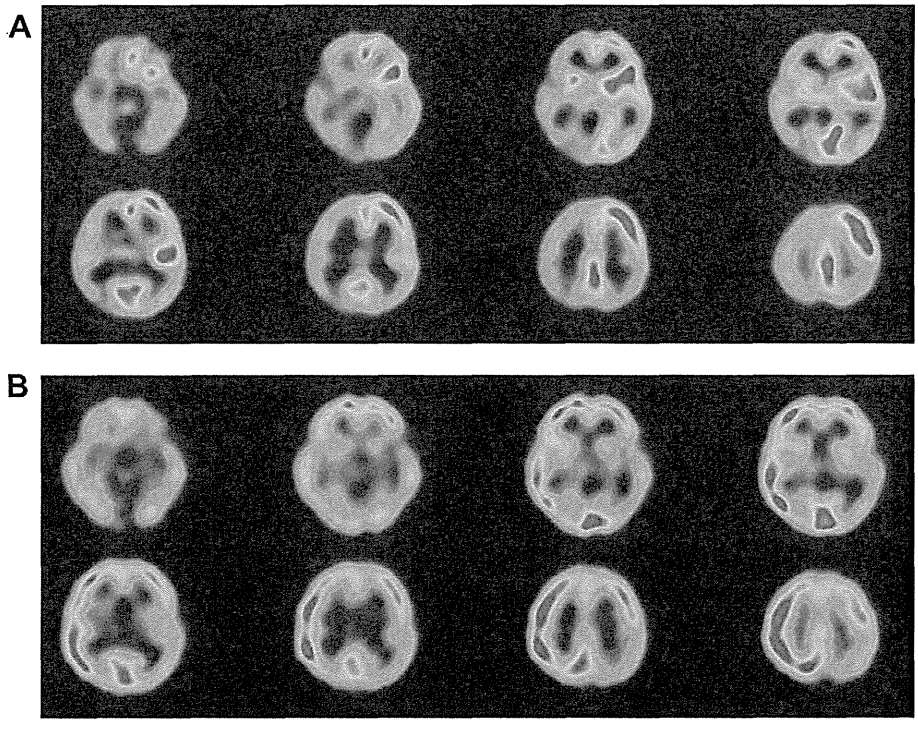

Fig. 3. Single photon emission computed tomography using ^{99m}Tc-ethyl cysteinate dimer 7 (A) and 35 (B) days after the onset of encephalopathy.

of c.1997C > T (p.T666M) in the *CACNA1A* gene. This mutation was not present in the parents.

3. Discussion

Several cases of acute encephalopathy accompanying familiar or sporadic hemiplegic migraine have been reported [2–4]. However, these patients had a family history of hemiplegic migraine or had experienced recurrent attacks of headache and/or hemiplegia before the onset of acute encephalopathy. In contrast, our patient had neither a family history of hemiplegic migraine nor a history of migraine or hemiplegia before the onset, which made the proper diagnosis quite difficult. However, presence of cerebellar vermis atrophy [5,6], quite sudden onset of hemiplegia and unconsciousness that was unusual for infectious encephalopathy, and late-onset pyrexia prompted us to examine the *CACNA1A* gene. This led to the identification of a de novo mutation, T666M, which is one of the most common aberrations of this gene in familial and sporadic hemiplegic migraine [5,6]. The encephalopathy has been thought to be related to the essential pathophysiology of hemiplegic migraine on the basis of the recurrent [4] or familial [2] occurrence of such episodes, and the evolution of encephalopathy that was heralded by hemiplegia as the onset symptom. Our neuroradiological findings, including hemispheric or lobar gyral swelling and restricted diffusivity on MRI, as well as hyperperfusion on SPECT during prolonged hemiplegia, are consistent with those of the reported cases [2,3]. After recurrent headache and hemiplegia attacks occurred during the follow-up period, we reconfirmed that the initial acute encephalopathy of our patient was associated with hemiplegic migraine.

Prolonged neuronal depolarization, due to excessive release of neuroexcitatory amino acids [4], and vasogenic edema [7] have been hypothesized in the pathogenesis of acute neuroradiological changes in hemiplegic migraine. This depolarization is thought to result in the initial hypoperfusion and subsequent hyperperfusion in the affected hemisphere, which is a common finding accompanying various types of prolonged neurologic symptoms in migraine including hemiplegic aura [8–10]. On the other hand, the change in diffusivity is not usually observed in the cases with prolonged aura of visual, aphasic, and hemiplegic symptoms [8–12], but is often identified in severe attacks, manifesting with unconsciousness, seizures, and/or pyrexia [3,4,7]. Residual hypoperfusion in the region of diffusivity change supports the presence of irreversible damage due to inflammation in this area. Recently, interleukin-6 and other inflammatory mediators were found to be elevated in the plasma of patients with migraine [13]. Our patient also had fever and increase in serum and cerebrospinal fluid interleukin-6. This elevated interleukin-6 may play an essential role in the symptogenesis. Regional activation of inflammation induced by cytokines would result in the disruption of the blood–brain barrier, which causes brain edema and affects the neuronal excitability

in both of these conditions. In these regards, the hemiplegic migraine-related encephalopathy may represent a further augmented inflammatory process within the spectrum of intrinsic symptoms in this entity. The discrepancy in regional distribution between the left anterior hyperperfusion and the left posterior restricted diffusivity in the present case may suggest that this inflammatory process affecting the diffusivity is not directly linked to the neuronal depolarization leading to the cortical spreading depression and the perfusion changes in migrainous aura [1]. The exact differential pathomechanism in these two processes remains to be elucidated.

Although hemiplegic migraine-related encephalopathy appears to be self-limited in most cases, signs and symptoms of hemiplegic migraine-related encephalopathy do not necessarily completely recover, or can even be fatal in some patients [14]. In addition to the transient appearance of cortical atrophy and linear high signal on MRI, our patient showed an elevated cerebrospinal fluid neuron-specific enolase value, suggesting that neurotoxic insults are actually present in this encephalopathy.

In summary, this is the first case where sporadic hemiplegic migraine manifested with acute encephalopathy as an initial symptom in a subject without preceding history of headache or hemiplegia. In such situations, lack of fever at the onset of symptoms, hemiplegia and coma with quite sudden onset, and the presence of vermian atrophy are the signs suggestive of hemiplegic migraine. It is unclear whether mutations or polymorphism in the *CACNA1A* gene can act as a predisposing factor for infection-related encephalopathy, but this point may be worthy of investigation considering the activated inflammation process in the hemiplegic migraine-related encephalopathy of the present case.

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Original article

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

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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.
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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

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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

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Table 1
Characteristics of patient.

Patient	Age	Sex	Past history	Family history	Onset of encephalopathy	Viral infection at the onset of encephalopathy	Frontal predominance	Biphasic course	Bright-tree appearance	Onset of epilepsy
Bilateral group (n = 11)										
1	10y	M			1y7m		+			1y9m
2	5y	M		FC	1y3m	Exanthema subitum	+			1y4m
3	13y	F	FC	FC	1y11m		+			4y8m
4	7y	M		FC	10m		+	+		1y6m
5	8y	F			1y3m		+		+	1y10m
6	7y	M		Epilepsy	1y3m			+		1y8m
7	9y	M			11m		+			1y2m
8	4y	F		FC	1y2m		+	+	+	3y6m
9	5y	M			1y10m		+		+	2y3m
10	3y	M	FC	FC	11m	HHV-6		+		1y10m
11	2y	F	FC		10m	HHV-6	+	+		1y4m
Unilateral group (HHES; n = 5)										
12	5y	F	Epilepsy	FC	1y4m	Rotavirus				7m
13	4y	F			1y1m	Exanthema subitum			+	1y3m
14	4y	M			1y8m					1y10m
15	4y	M	Birth asphyxia		1y4m	HHV-6				1y5m
16	8y	F	Neonatal hypoglycemia	FC	1y6m					2y

FC, febrile convulsion.

patients in the HHES group with a history of neonatal asphyxia or neonatal hypoglycemia, exhibited normal psychomotor development until the onset of encephalopathy. A family history of convulsive disorders was present in 6 patients (5 patients with febrile convulsion and 1 patient with epilepsy) in the bilateral group and 2 patients (2 patients with febrile convulsion) in the HHES group.

The patients experienced febrile encephalopathy at the ages of 11 months to 1 year and 10 months. HHV-6 and rotavirus were identified as causative pathogens for febrile illness in 3 and 1 patient, respectively, and an additional 2 patients presented with exanthema subitum at the onset of encephalopathy. Two patients had been administered theophylline for the treatment of asthmatic bronchitis. As previously mentioned, all of the patients manifested with prolonged febrile convulsion and subsequent impaired consciousness lasting longer than 48 h, and were diagnosed with acute encephalopathy. The duration of the initial seizure was longer than 30 min in 15 patients and 15 min in the remaining patient. The 5 patients with HHES presented with hemiconvulsions during this acute phase.

During the data collection period, the developmental quotient was below 20 in all 11 patients with bilateral AEFCSE, whereas it ranged 8–75 (mean 43) in the HHES patients. Four patients were ambulant, and an additional 4 individuals could maintain a sitting position or shuffle in the bilateral group; one individual was ambulant, and the other 3 could maintain a sitting position in the HHES group. The remaining patients were bedridden. One patient in the bilateral group was tube-fed; however, all of the other individuals could consume meals orally.

3.2. Seizure manifestations of late-onset epilepsy

In the bilateral AEFCSE group, epilepsy emerged at the ages of 1 year and 2 months to 4 years and 8 months, with an interval of 2 months to 3 years (7.8 months; mean) after resolution of the initial convulsions during the acute phase of illness. Multiple seizure types were observed in 4 patients. Seizure phenotypes in this group included head nodding with motion arrest ($n = 3$), spasm involving the trunk and extremities ($n = 2$), and versive ($n = 2$), brief tonic ($n = 5$, including 1 patient manifesting startle seizures provoked by auditory stimuli), myoclonic ($n = 1$), and complex partial ($n = 1$) seizures.

The onset of postencephalopathy epilepsy in the HHES group was between 1 year and 3 months and 2 years of age, with a latent period of 2–6 months after the acute phase, including 1 patient with a history of epilepsy with onset at the age of 6 months. Seizure manifestations in the 5 patients varied: hemitonic, head nodding with atonia/unilateral myoclonus, head nodding with fencing posture/brief tonic seizure provoked by startle, and generalized myoclonus/generalized tonic–clonic and complex partial seizures.

Overall, the duration of these seizures was less than 1 min. Seizures occurred daily, weekly, and monthly in 12, 1, and 1 patient, respectively, despite treatment with antiepileptics during the data collection period.

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3.3. Interictal and ictal EEG findings

At the onset of epilepsy, diffuse polyspike bursts with repetitive/periodic appearance characterized the interictal EEG of 5 patients in the bilateral AEFCSE group (Fig. 1A). Focal spikes were recorded in the other 11 patients, and the distribution was described as multifocal in 6 of them. The diffuse polyspikes were attenuated and evolved into rather localized epileptiform paroxysms during the follow-up period in all of the 5 patients (Fig. 1B). Among these patients, 3 patients showed the identical seizure manifestation of head nodding, spasm, or brief tonic seizures throughout the course despite the change in epileptiform activity. Myoclonus and complex

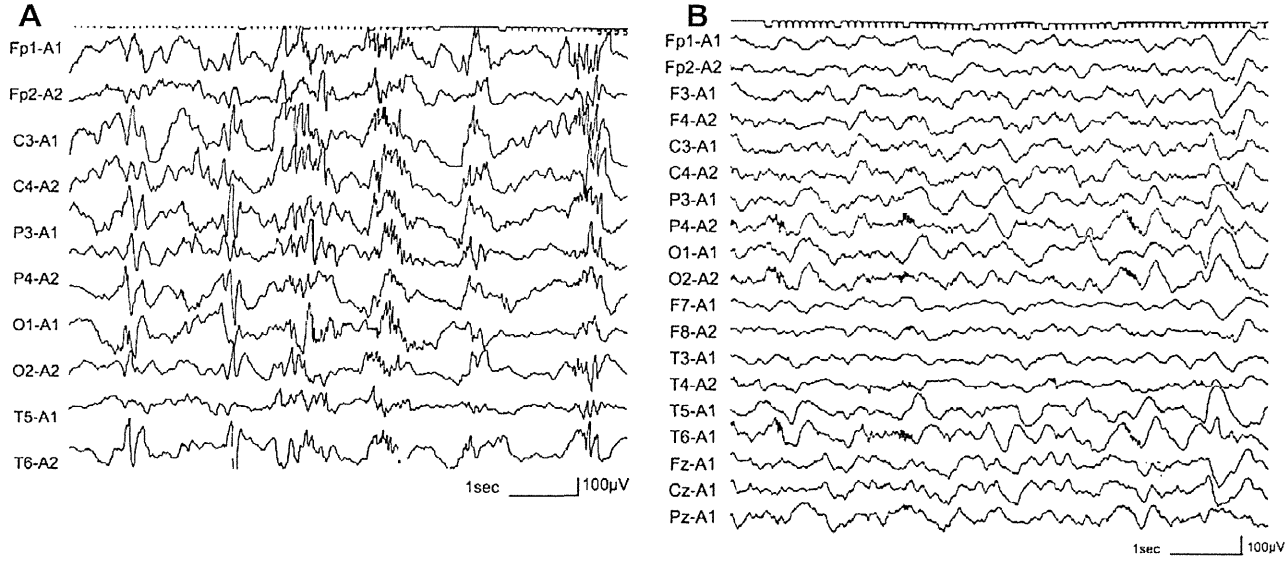

Fig. 1. Interictal electroencephalography (EEG) of a patient with bilateral acute encephalopathy with febrile convulsive status epilepticus (AEFCSE). The patient developed AEFCSE at the age of 1 year and 3 months and exhibited periodic bursts of diffuse polyspike activity at the onset of epilepsy (A). This pattern had disappeared at the age of 3 years and 4 months, and residual right posterior low-amplitude fast activity was observed (B).

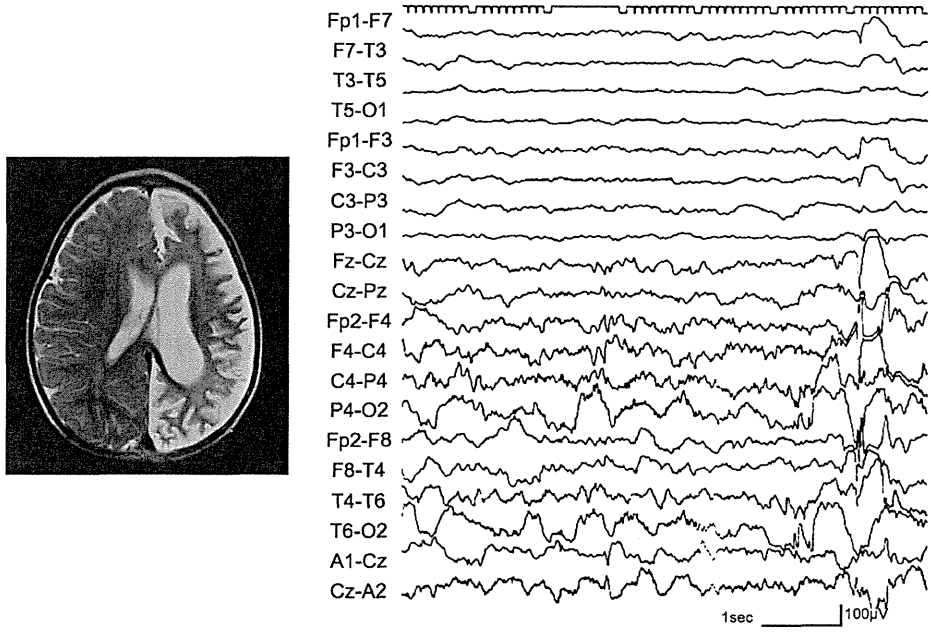

Fig. 2. T2-weighted magnetic resonance imaging (MRI) and interictal EEG of a patient with hemiconvulsion–hemiplegia epilepsy syndrome (HHES). The patient developed acute encephalopathy with hemiconvulsion–hemiplegia at the age of 1 year and 5 months. Atrophy of the left cerebral hemisphere, left-sided attenuated activity, and right-sided high-voltage slow waves with spike components were observed at the age of 2 years and 4 months.

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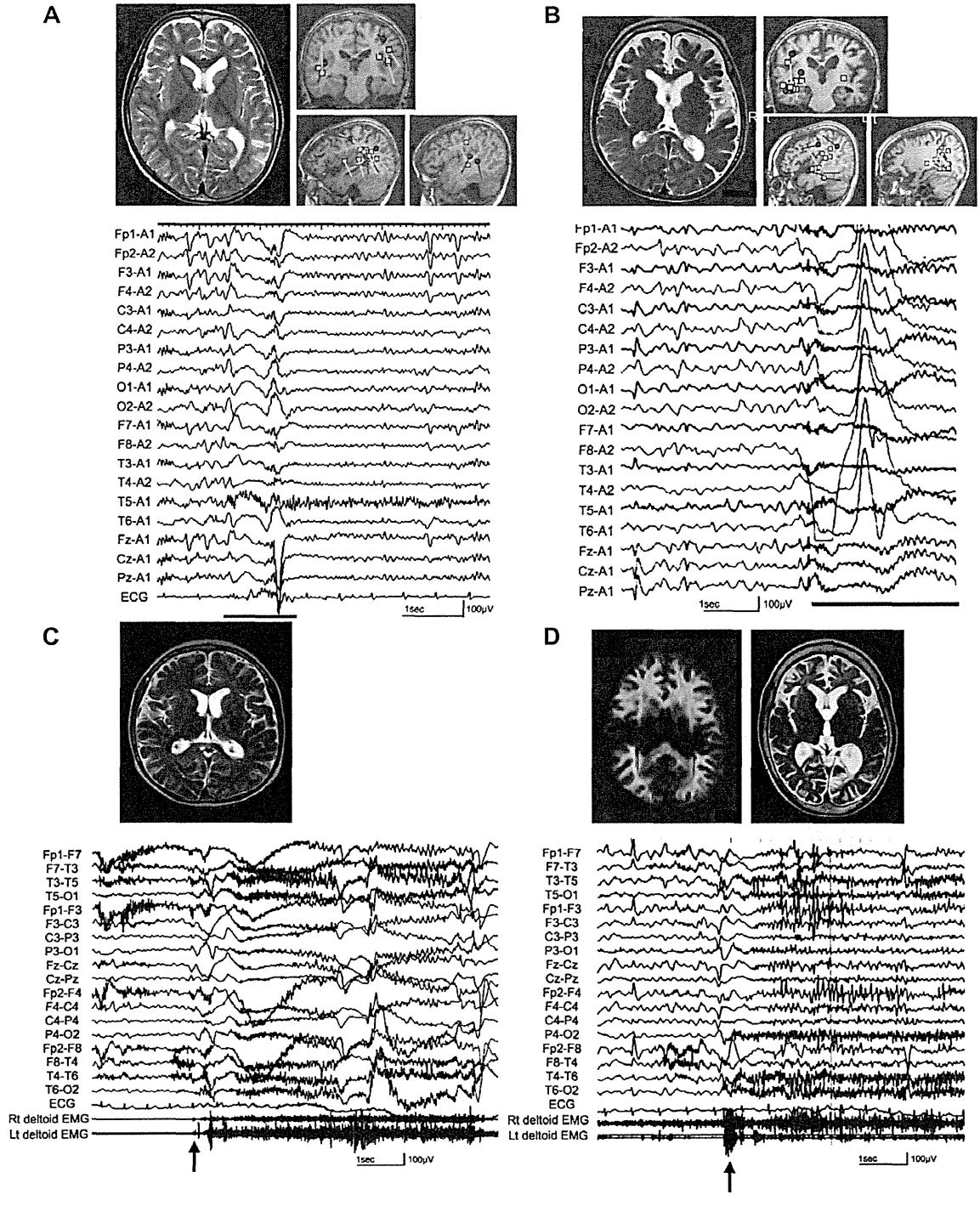

Fig. 3. MRI, magnetoencephalography (MEG), and ictal EEG of patients with bilateral AEFCSE. Dipoles with a goodness of fit exceeding 90% are drawn in yellow, and those with a goodness of fit of 80–90% are drawn in green. (A) A 5-year-old boy with a history of AEFCSE at 1 year and 3 months of age. MRI revealed diffuse cerebral atrophy, and dipole sources were identified bilaterally in the parietotemporal areas. The bar under the EEG tracing indicates the period of head nodding and forward bending of the trunk on sitting; an irregular train of sharp waves of less than 1 s preceded this event, and the waves were followed by diffuse attenuation or slow waves and subsequently by widespread slow waves superimposed by fast activity. Subsequently, diffuse, low-amplitude 10-Hz activity lasted several seconds, during which the patient appeared vacant with motion arrest. (B) Another 5-year-old boy with a history of AEFCSE at 11 months of age. Frontal predominant brain atrophy and bilateral dipoles over parietotemporal areas were observed. Brief tonic seizure (bar) was initiated by a parietal-predominant spike, followed by fast activity with left-sided predominance. (C) A 3-year-old boy with AEFCSE at 11 months of age. MRI revealed diffuse and mild brain atrophy. A tonic seizure was provoked by a handclap (arrow); EEG revealed diffuse slow waves superimposed by right-sided fast activity in the initial startle phase, followed by diffuse attenuation/10-Hz activity during the tonic phase of the seizure. (D) A 5-year-old boy with AEFCSE at 1 year and 10 months of age. A seizure emerged as a spasm at the beginning that was preceded by a parietal sharp wave (arrow), followed by fast activity in the T6 area, and subsequently followed by sharp wave bursts with bifrontal predominance during the tonic phase, accompanied by versive movement to the right side. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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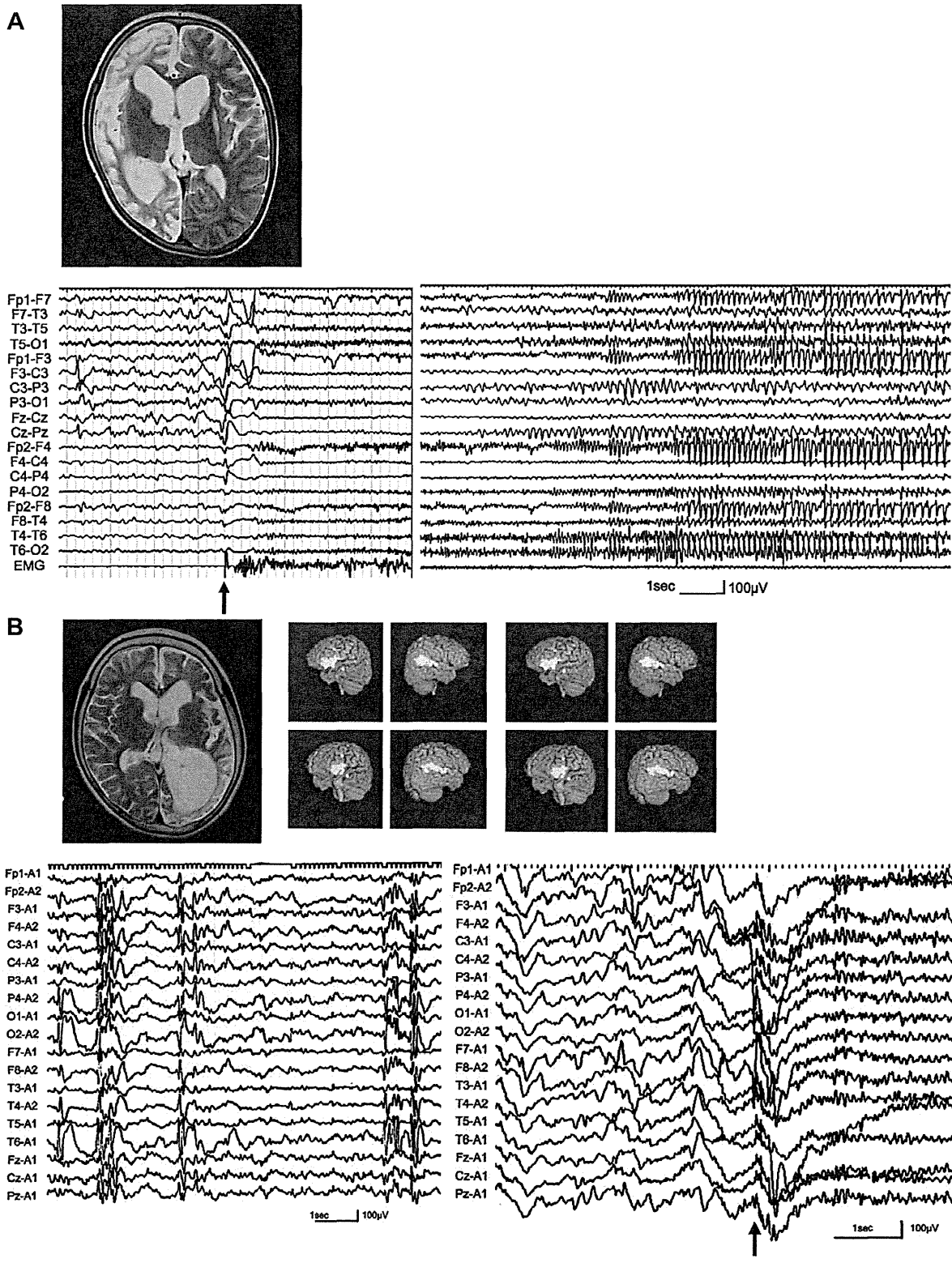

Fig. 4. MRI, MEG, and EEG of patients with HHES. (A) A 4-year-old boy with a history of HHES at the age of 1 year and 4 months. The right cerebral hemisphere was severely atrophic (top). On ictal EEG (bottom), an isolated spike in the C3/Cz areas (arrow) initiated a sudden tonic extension of the right extremities during sleep with bending of the head to the right. This was successively followed by diffuse attenuation, recruitment of 6–7-Hz activity with left centroparietal predominance, and then bursts of bifrontal spikes. (B) An 8-year-old girl with HHES at the age of 4 years. The left posterior hemisphere was severely atrophied. Dipole sources were clustered at the right supramarginal and superior temporal gyri and the left inferior frontal gyrus. On interictal EEG, epileptic discharges appeared with right-sided predominance (bottom left). Ictal EEG of head nodding with subsequent tonic extension of extremities revealed polyspikes with probable right frontal predominance (arrow) and subsequent generalized fast activity (bottom right).

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partial seizures in the other two 2 patients were replaced by spasm and brief tonic seizures a few years after the onset of epilepsy. The patients with HHES commonly exhibited attenuated background activity over the affected hemisphere, and polymorphic epileptic activity with spikes, polyspikes, sharp waves, and high-voltage slow waves predominantly over the spared hemisphere (Fig. 2).

Ictal EEG of epileptic seizures was available for 6 bilateral AEFCSE and 3 HHES patients. Regardless of the seizure manifestations, the ictal EEG data in the bilateral AEFCSE group were characterized by the onset with brief discharges with focal or uneven distribution (Fig. 3). In 5 patients, head nodding and spasm appeared during or just after these initial discharges. This initial phase was also present in the seizures regarded as brief tonic (Fig. 3B–D), where short-lasting muscle contraction at their beginning was identified. Another phase of motion arrest (Fig. 3A) or tonic phase (Fig. 3B–D) ensued, during which generalized attenuation or fast activity persisted on EEG (Fig. 3A–D), accompanied by brief bursts of sharp waves with bifrontal predominance in 1 patient (Fig. 3D). In the remaining patient with brief tonic seizures and subsequent automatism, focal fast activity remained localized to the frontal areas at its onset. The initial discharges presented as irregular trains of sharp waves (Fig. 3A) or a complex of spikes, slow waves, and fast activity with an uneven distribution (Fig. 3B–D). Notably, the regional predominance of this initial activity migrated to other areas during its brief duration of less than 1 s in a few patients, e.g., frontal to right hemispheric predominance (Fig. 3A) or parietal to right temporal areas (Fig. 3D). We also noted similar brief initial discharges of spikes (Fig. 4A) and sharp waves (Fig. 4B) with uneven distributions and subsequent generalization in the HHES group. Hemispheric lateralization of these initial discharges appeared with predominance on either the affected side (not shown) or the less affected side (Fig. 4A and B).

3.4. Localization of dipole sources in the interictal MEG investigation

MEG was performed in 5 bilateral AEFCSE and 2 HHES patients. In the former group with either frontal predominance or diffuse involvement during the acute phase, the dipole sources tended to cluster in the frontoparietotemporal junction areas, including the supramarginal and angular gyri (Fig. 3A and B). In HHES, dipole sources were identified at the right parietotemporal junction and left inferior frontal gyrus in 1 patient with left hemispheric lesions (Fig. 4B) and at the left precentral gyrus in another patient with left-sided lesions. No relationship was noted between the seizure onset areas on the ictal EEG and the areas of dipole clustering.

3.5. Effect of antiepileptic treatment and surgical intervention on postencephalopathy epilepsy

The number of antiepileptics that had ever been administered for persistent epilepsy in each patient was 2–12 (mean 4.8). Two patients in the bilateral AEFCSE group were seizure-free under treatment with valproate sodium (VPA) and zonisamide (ZNS) or carbamazepine (CBZ) and ZNS. For the remaining patients, drugs that had beneficial effects in apparently reducing the frequency and intensity of seizures were clonazepam for 3 of 5 patients; clobazam for 2 of 8 patients; clorazepate dipotassium for 2 of 3 patients; ZNS for 4 of 8 patients; CBZ for 3 of 6 patients; phenobarbital for 2 of 7 patients; VPA for 1 of 8 patients; potassium bromide for 1 of 3 patients; and lamotrigine for 1 of 4 patients. Phenytoin ($n = 3$), gabapentin ($n = 3$), acetazolamide ($n = 2$), topiramate ($n = 4$) and levetiracetam ($n = 1$) did not confer any beneficial effects. Callosotomy was conducted in 2 patients; hundreds of daily head nodding seizures in 1 bilateral AEFCSE patient were completely controlled for longer than 1 year after total callosotomy, and brief tonic seizures with frequent falls in an HHES patient became limited to focal myoclonus after partial callosotomy.

4. Discussion

The outcome regarding the intellectual and motor disabilities in this series of AEFCSE patients was severer compared to the reported prognosis of AEFCSE. According to a report on 10 patients with AIEF, 9 recovered to be ambulant, and 3 regained the ability to speak in sentences [3]. In another series of AEFCSE patients at a rehabilitation center, motor and intellectual disabilities were reported to persist in less than 30% and 90% of the 68 patients, respectively [10]. As the patients in the present study were referred to our hospital for the evaluation of intractable epilepsy, they should be regarded as representing the severest subgroup of AEFCSE. This selection bias may also have relationship to the high proportion of family histories of convulsive disorders in this patient group. Thus the patients are not representative of the whole AEFCSE group; however, the data here provide considerable information for understanding and managing AEFCSE patients in the chronic phase.

The HHES group displayed a somewhat different seizure manifestation than the bilateral AEFCSE group. Although one case was accompanied by a "bright tree appearance," no patient exhibited frontal predominance or a biphasic clinical course in the present series. The diffuse polyspike activity during the chronic phase in the bilateral AEFCSE group was not observed in the HHES group. The involvement of bilateral hemispheres may be essential for these characteristics, although the

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differential pathomechanisms explaining why either of these conditions affects individual patients remain to be elucidated. It is also unclear whether the residual diffuse polyspike activity during the chronic phase itself might have a detrimental effect on the brain function of certain patients as a type of epileptic encephalopathy.

In both of these groups, the presence of a latent period before the emergence of residual epilepsy was common to those with epilepsy after viral encephalitis, and this period was reported to be 0.8 ± 1.9 years [12] or 3.82 ± 3.7 years [13]. The prevalence of residual epilepsy in patients with AEFCSE has been reported to be as high as 65% [10], whereas that in patients with viral encephalitis with early seizures was 22% [14]. The cause of this high risk of complications is unclear, but the genetic propensity of neuronal excitability leading to febrile encephalopathy might have a relationship with this late epileptogenicity in AEFCSE.

In the majority of patients with bilateral AEFCSE in this study, ictal EEG revealed that the seizures were triggered by epileptic activity with an uneven distribution that spread either rapidly or after a brief migrating period to result in diffuse desynchronization or fast activity. Short-lasting motor phenomena of head nodding and spasm accompanied the initial phase of triggering activity (Fig. 3A), lasting into the phase of desynchronization to manifest as brief tonic seizures (Figs.3B–D and 4B) in some cases. These EEG findings and the biphasic motor manifestation do not accompany tonic seizures in typical symptomatic localization-related epilepsies, but they are reminiscent of the findings in epileptic spasms [15] and some cases of startle epilepsy [16]. Presumably, these characteristics represent the wide epileptogenic zone with multiple foci of augmented excitability, located within and outside the severely affected cortical regions in each case of the present series. This assumption is also applicable to the results in the HHES group; multifocal independent foci on interictal EEG involving the both hemispheres, propagation of epileptic activity that is faster and more widespread than usual, and the onset of ictal discharge in the contralesional hemisphere have been recognized in this syndrome [5,17]. These findings may again support the idea that bilateral AEFCSE and HHES could be regarded as a spectrum of disorders with a common entity. On the other hand, the characteristics of epilepsies in these groups may represent those in children subjected to catastrophic brain insults during infancy or early childhood. In addition, it remains to be elucidated whether the genetic predisposition for these syndromes involving the less severely affected brain regions are responsible for the pathogenesis of intractable postencephalopathy epilepsy. Despite these limitations in interpretation of the findings in this series of patients, the seizure and EEG characteristics are distinct from the findings regarding medial temporal lobe epilepsy due to hippocampal sclerosis that evolves after prolonged febrile convulsion in infancy. This fact would merit worldwide recognition.

In summary, we delineated for the first time the characteristics and prognosis of late-onset epilepsy in children with acute encephalopathy with onset of febrile prolonged convulsion. These findings provide useful information for the management of this chronic illness is children as well as clues to investigate the background condition related to the propensity for febrile encephalopathy.

Disclosure

None of the authors have any conflict of interest to disclose. Dr. Saito Y was supported for conduction of this study by Grant-in-Aid for Research on Measures for Intractable Diseases, No. H23-Nanji-Ippan-78, from the Ministry of Health, Labour and Welfare, Japan.

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Short communication

Kawasaki disease complicated by mild encephalopathy with a reversible splenial lesion (MERS)

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ABSTRACT

We reported four patients (2 to 10 years) with Kawasaki disease complicated by clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). All were treated with γ-globulin (2 to 6 g/kg) after the diagnosis of Kawasaki disease, the fever being alleviated between day 6 and 25. One of two patients exhibiting a poor response to γ-globulin had a cardiac aneurysm as a sequela. Their neurological manifestations (delirious behavior and drowsiness), laboratorial hyponatremia, and radiological abnormalities completely disappeared. It is important for pediatricians to acknowledge that MERS can be observed in patients with Kawasaki disease, especially in older children, and that they might be at high risk for cardiac abnormalities.
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1. Introduction

Kawasaki disease (KD) is an acute febrile, systemic vasculitis of unknown pathogenesis, most often affecting young children under 5 years old. The most important complication of KD is coronary arterial aneurysms (in 15-25% of untreated children), which may cause ischemic heart disease and sudden death [1,2]. Irritability, lethargy, transient unilateral facial nerve palsy are sometimes observed, and pleocytosis in the cerebrospinal fluid (CSF) is found in around 40% [1–4], however, febrile convulsions and acute encephalopathy are extremely rare [5–7].

Magnetic resonance imaging (MRI) finding of a reversible lesion with transiently reduced diffusion in the splenium of the corpus callosum has been reported in patients with clinically mild encephalitis/encephalopathy, leading to a new clinical-radiological syndrome, clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) [8,9]. We present here four patients with KD complicated by MERS, which suggest that MERS is a more common neurological complication than previously considered.

2. Methods

Information on patients with KD who developed MERS was collected retrospectively after approval by the institutional review board of the Kameda Medical Center. The diagnosis of KD and MERS were established according to diagnostic criteria [1,2,8], respectively. We reviewed the clinical charts of the patients in order to accrue information on symptoms, medication, treatment, outcome, and results of CSF analysis, MRI, and electroencephalography (EEG).

3. Results

Four previously healthy Japanese patients (1 male and 3 females, aged from 2 to 10 years) met the criteria for enrollment in this study, with the onset from March 2010 to February 2011. The clinical and radiological records of the four patients are summarized in Table 1. All were treated with γ-globulin (2 to 6 g/kg) after the diagnosis of KD, the fever being alleviated between day 6 and 25. Two patients exhibiting a poor response to γ-globulin were additionally treated with cyclosporine and infliximab (patient 1), and prednisolone

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Table 1
Data for Kawasaki disease with MERS.

Pt.	Age/Sex	Tx for KD γ-globulin	Other therapies	End of fever	Na level (lowest) follow up	Coronary sequelae	Consciousness disturbance	Duration delirium
1	8/M	2 g/kg × 3 (D5, D7, D9)	cyclosporine infliximab	D21	119 (D6) 137 (D40)	AN (5 mm)	Mild drowsiness D1-8	D1-8
2	7/F	2 g/kg (D5)		D6	129 (D3) 139 (D9)	No	Drowsiness D3-5	D3-5
3	10/F	2 g/kg × 2 (D3, D5)		D6	127 (D4) 138 (D13)	No	Drowsiness D3-5	D3-5
4	2/F	2 g/kg × 2 (D9, D20)	prednisolone	D25	134 (D9) 139 (D45)	No	Drowsiness D10-14	D10-12
	14/F	1.8 g/kg (D5)		D13	128 (D6) 142 (D25)	AN (8 mm)	Mild drowsiness D5-7	D5-7
	7/F	2 g/kg (D4)		D5	131 (D3) 141	No	Drowsiness D2-3	D2-3

ABBREVIATIONS
Pt, patient; Tx, therapy; M, male; F, female; D, day; AN, aneurysm; CC, cell count; WM, white matter; CR, complete recovery.

Delirious behavior Components	Seizure	CSF study	MRI results	EEG results	Neurological outcome	
Incoherent speech, unresponsiveness	No	Normal (D6)	Splenium (D7) Normal (D15)	Frontal slow (D6) Normal (D14)	CR	
Impulsive behavior, visual hallucinations, incoherent speech	No	Normal (D3)	Splenium (D4) Normal (D10)	Diffuse slow (D4) Normal (D9)	CR	
Emotional changes (laughter, weeping, fear), visual hallucinations, incoherent speech	No	Normal (D3)	Splenium + WM (D3) Normal (D7)	Diffuse slow (D3) Normal (D6)	CR	
Visual hallucinations, misperceptions	No	Normal (D10)	Splenium (D10) Normal (D17)	Normal (D10)	CR	
Visual hallucinations	No	CC 16/mm^3 (D7)	Splenium (D10) Normal (D14)	Normal (D11)	CR	[10]
Impulsive behavior, visual hallucinations, incoherent speech	No	Normal (D3)	Sp (D3) Normal (D11)	Diffuse slow (D3)	CR	[11]

(patient 4). One patient (patient 1) had a cardiac aneurysm (5 mm) as a sequela.

All four patients presented with fluctuating delirium with onset between day 1 and 10, and a duration of 3 to 8 days, and all showed mild to moderate drowsiness between the episodes of delirious behavior. The results of neurological examinations were unremarkable except for the delirium and drowsiness. CSF analysis was normal in all patients. The Na level during neurological symptoms decreased to 119–134 mEq/l, which had become normal at the time of follow-up. MRI performed during their neurological manifestations (day 3 to 10) revealed homogenously reduced diffusion in the splenium (patients 1, 2, and 4) (Fig. 1-A) or the splenium and symmetrical subcortical white matter (patient 3), which had completely disappeared by the time of follow-up (day 7 to 17) with an interval of 4 to 8 days (Fig. 1-B). No specific treatment for MERS was performed for any patient; however, their neurological manifestations disappeared completely. EEG showed slow waves in three patients (became normal on follow-up EEG), and normal in another.

4. Discussion

Encephalitis or encephalopathy is an extremely rare complication of KD. Actually, none of 540 patients with KD presented with encephalitis/encephalopathy [4]. As far as we know, there have been only six patients with KD complicated by MERS (Table 1) [10,11], including the present four patients, their onset ranging from March 2010 to February 2011. The number of KD patients in 2010 in Japan has been reported to be 12,755, and that over 6 years being 466 [12]. The incidence of MERS in KD over 6 years, therefore, seems to be at least 1% (5/466).

All six patients (mean age, 8.0 years) presented with delirious behavior and drowsiness with hyponatremia (119–134 mEq/l); and a homogenously reduced diffusion in the splenium, all of which completely recovered or disappeared. These clinical, laboratorial, and radiological findings are typical of MERS (mean age, 9.0 years; serum sodium level, 131.8 ± 4.1 mEql/l) [8,13]. MERS has been reported to be an encephalitis or encephalopathy associated with infection, such as influenza or rotavirus [8,9]. It is important for pediatricians to acknowledge that MERS can be observed in patients with KD, which is an acute febrile systemic vasculitis, not directly related to a pathogen.

What is the possible mechanism underlying MERS with KD? The exact pathogenesis of MERS is uncertain, however, MERS seems to comprise cerebral edema due to electrolyte/water imbalance, including hyponatremia, as an underlying pathophysiology [8,13]. Activation of the immune system seems to be a central feature of KD, and the concentrations of many proinflammatory cytokines and chemokines, including tumour necrosis factor α, interleukins 1, 6, and 8, and vascular endothelial growth factor (VEGF), are elevated during the acute phase [1,2]. Elevated VEGF could result in vascular leakage, hypoalbuminemia, and noncardiac edema [14]. Actually, cerebral edema has been histopathologically observed in patients with KD [15], which could possibly progress to MERS.

Two of the six patients with KD complicated by MERS (Table 1, patient 1 and one patient previously reported [10]) had a cardiac aneurysm as a sequela. The duration of a fever has been confirmed to be a predictor of a coronary artery aneurysm in KD [1]. Other independent risk factors have been reported, including an elderly onset and the presence of hyponatremia. Children 6 years and older account only for around 5% of patients with KD [16], however, they often have delays in diagnosis, and an increased incidence of cardiovascular abnormalities (20% vs. 15% under 6 years) [16,17]. The hyponatremia observed in 45% in patients with KD has also been reported to be an independent risk factor for cardiovascular sequelae [18]. Actually, the two patients having a cardiac aneurysm fulfilled the triple risks, prolonged fever (21 and 13 days), elderly onset (8 and 14 years), and hyponatremia (119 and 128 mEq/l). Elderly onset and hyponatremia are also characteristic of MERS, therefore, it is reasonable that patients with KD complicated by MERS likely have risk factors for cardiac abnormalities.

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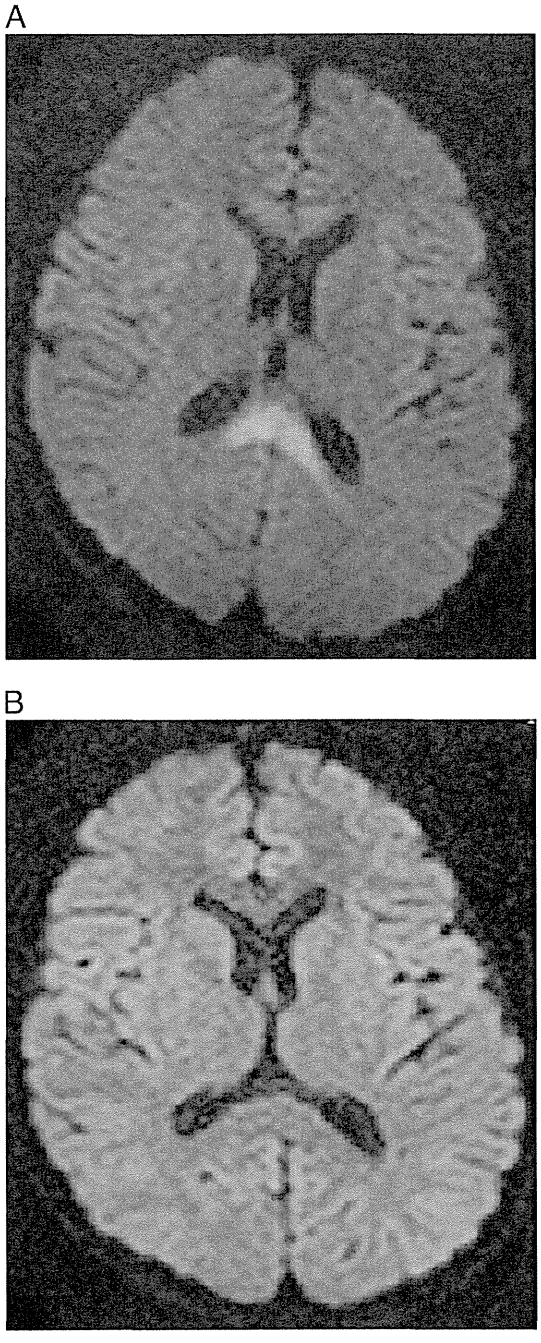

Fig. 1. Diffusion-weighted image of patient 1 on day 7 (A) shows a high signal lesion in the splenium of the corpus callosum, which disappears on day 15 (B).

It seems that cardiac abnormalities are more common in patients with KD having neurological manifestations, for example, two of the six patients with MERS, 2/2 and 2/5 with transient hemiplegia and facial nerve palsy, respectively [4,7]. Those with transient consciousness disturbance during the acute phase of KD have also been reported to have coronary aneurysms in 19% (6/32) [7]. It is possible that the severity of KD (severe vasculitis) may result in neurological manifestations. Further clinical, radiological and immunological studies are necessary to clarify the frequency, mechanism, and prognosis of KD complicated by MERS.

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Late Delirious Behavior With 2009 H1N1 Influenza: Mild Autoimmune-Mediated Encephalitis?

abstract

Delirious behavior associated with influenza usually has an onset within a few days after fever and lasts <24 hours. As we encountered several patients with 2009 H1N1 influenza who presented with late-onset and long-standing delirious behavior, we retrospectively evaluated the clinical, radiologic, and laboratory features to elucidate the possible pathophysiology. This information was collected on 5 previously healthy patients (2 boys and 3 girls, aged 10–15 years) with 2009 H1N1 influenza who presented with late onset (>3 days after fever) and long-standing (>48 hours) delirious behavior. Each exhibited mild to moderate drowsiness between the episodes of delirious behavior. Electroencephalography was normal except for 1 patient with high voltage and slow activity bilaterally in the occipital regions. Brain MRI was normal. The outcome was excellent with no neurologic sequel in 4 of the 5 patients. In all 5 patients, autoantibodies against *N*-methyl-D-aspartate type glutamate receptor were elevated or positive in cerebrospinal fluid or serum; the autoantibody levels normalized in the 3 patients who had follow-up studies. This study indicates that 2009 H1N1 influenza has a tendency to cause late-onset and long-standing delirious behavior, at least in Japanese children. Mild autoimmune-mediated encephalitis should be considered as an underlying cause. *Pediatrics* 2012;129:e1068–e1071

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KEY WORDS

2009 H1N1 influenza, delirium, anti-NMDA-type GluR antibodies

ABBREVIATIONS

CSF—cerebrospinal fluid
GluR—glutamate receptor
MERS—clinically mild encephalitis/encephalopathy with a reversible splenial lesion
NMDA—*N*-methyl-D-aspartate
NR2B—NMDA-type GluRε2
PCR—polymerase chain reaction

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Infection or fever is known to be a common cause of delirium in children. It has been reported that >10% of the patients with influenza during the 2005–2006 season in Japan (299/2846) developed delirious behavior.[1] It usually develops within a few days after onset of fever (91.6% within 2 days, 97.3% within 3 days),[1] and lasts for <24 hours.[2]

Delirious behavior has been reported as the most common neurologic symptom in patients with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) (54%, 29/54).[3,4] MRI revealed a reversible splenial lesion with homogenously reduced diffusion in 5 of 11 patients with influenza-associated delirium during the 2007–2008 season.[5] These 11 patients had onset of delirium within 3 days after fever onset and had a duration of <12 hours. This suggested that a reversible splenial lesion may be an associated condition in patients with influenza-associated delirium.

Neurologic complications have recently been reported in children with 2009 H1N1 influenza; these include acute necrotizing encephalopathy, acute encephalopathy with biphasic seizures and late reduced diffusion, and MERS.[6,7] Because we have also encountered several patients with 2009 H1N1 influenza who developed late-onset and long-standing delirious behavior, we evaluated the clinical, radiologic, and laboratory features in an attempt to elucidate the possible causes of the delirium.

PATIENT PRESENTATION

Information on patients with 2009 H1N1 influenza who developed late-onset (>3 days after fever) and long-standing (>48 hours) delirious behavior was collected retrospectively after approval by the institutional review board of the Kameda Medical Center. The diagnosis of 2009 H1N1 influenza was established by polymerase chain reaction (PCR) with a nasopharyngeal swab or, if PCR was not performed, rapid antigen-detection assay for influenza A in the setting of 2009 H1N1 influenza epidemic. In Japan, almost all the cases of influenza A were caused by 2009 H1N1 influenza virus during the 2009–2010 season (21 710 of 21 745, 99.8%). Delirious behavior is divided into the following components: visual hallucinations; sensory misperceptions other than visual ones (such as auditory hallucinations); emotional changes (such as laughter and fear); unresponsiveness; incoherent speech; purposeless movements; and impulsive behavior[2,5]; only patients with some of these components and diagnosis of 2009 H1N1 influenza were enrolled in this study. We reviewed the clinical charts of the patients to accrue information about symptoms, medication, treatments, outcomes, and the results of cerebrospinal fluid (CSF) analysis, MRI and EEG.

Five previously healthy Japanese patients (2 boys and 3 girls, aged from 10–15 years) met the criteria for enrollment in this study, the onset of their disease being during the period from September 2009 to February 2010. A diagnosis of 2009 H1N1 influenza was confirmed by PCR in 2 patients examined (patients 2 and 4); the other 3 were given the diagnosis based on a positive antigen-detection assay result for influenza A in the setting of the 2009 H1N1 influenza epidemic. The clinical records of the 5 patients are summarized in Tables 1 and 2. All were treated with zanamivir hydrate after the diagnosis of influenza A, and the fever was alleviated before the onset of delirious behavior. Zanamivir hydrate was discontinued in 3 patients (patients 1, 2, and 5) before the full period of 5 days because of the onset of delirium. Onset of fluctuating delirium was observed between days 3 and 6 after the fever, with a duration of 6 to 15 days in patients 1 to 4, all of whom showed mild to moderate drowsiness between the episodes of delirious behavior. Patient 5 had episodes of delirium with mild drowsiness between days 5 and 10; occasional subsequent episodes of delirium occurred during the follow-up period of 12 months. No patient developed seizures. The results of neurologic examination were unremarkable except for the delirium or drowsiness. Cerebrospinal fluid (CSF) analysis was normal in the 4 examined patients. EEG was normal except for in patient 1 in whom there was high voltage and slow activity bilaterally in the occipital regions. MRI of the brain was normal in all patients. Methylprednisolone (30 mg/kg per day for 3 days) or dexamethasone (0.4 mg/kg per day for 5 days) was administered to 3 patients (patients 1, 2, and 4) on

TABLE 1 Clinical Data for Influenza H1N1 Patients With Late-Onset and Longstanding Delirious Behavior

Pt	Age/Gender	Tx	End of Fever	Duration of Delirium	Delirious Behavior Components	Consciousness Between Delirium	Tx for Delirium
1	10/F	ZNV (2–5 d)	5 d	5–12 d	Em (anger, weeping), Inc, Un	Mild drowsiness	DEX (d 6–10)
2	12/M	ZNV (1–3 d)	3 d	3–9 d	Imp, Vis, Mis, Inc	Drowsiness	mPLS (d 4–6)
3	11/M	ZNV (2–6 d)	4 d	6–14 d	Em (laughter, weeping, fear), Imp, Mis	Drowsiness	None
4	15/F	ZNV (2–6 d)	4 d	6–20 d	Vis, Mis, Inc, Un	Mild drowsiness	mPSL (d 17–19)
5	12/F	ZNV (2–4 d)	3 d	5–10 d	Em (anger, weeping), Imp, Inc, Un	Mild drowsiness	None
				11 d 12 mo	Em (anger), Inc	Alert	Resperidone

DEX, dexamethasone; d, day; Em, emotional changes; F, female; Imp, impulsive behavior; Inc, incoherent speech; M, male; Mis, misperception; mPSL, methylprednisolone; Pt, patient; Tx, therapy; Un, unresponsiveness; Vis, visual hallucination; ZNV, Zanamivir.

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TABLE 2 Laboratory Data for Influenza H1N1 Patients With Late-Onset and Longstanding Delirious Behavior

Pt	CSF study	MRI results	EEG results	NMDA GluR testing results	Outcome
1	Normal (6 d)	Normal (7 d, 10 d)	Normal (6 d, 13 d), HVS bilateral O (8 d)	Elevated GluRε2 (0.82, serum; 6 d) Normal GluRε2 (0.44, serum; 12 mo)	CR
2	NE	Normal (3 d, 4 d, 7 d)	Normal (6 d, 8 d)	Elevated GluRε2 (0.79, serum; 6 d) Normal GluRε2 (0.31, serum; 12 mo)	CR
3	Normal (11 d)	Normal (11 d, 14 d, 40 d)	Normal (11 d, 14 d, 40 d)	Positive NMDA-GluR (NR1+NR2)(CSF; 11 d)	CR
4	Normal (10 d, 17 d)	Normal (9 d, 20 d)	Normal (10 d, 17 d)	Elevated GluRε2 (0.33, CSF; 10 d) Normal GluRε2 (0.20, CSF; 55 d)	CR
5	Normal (4 mo)	Normal (7 d) Normal (4 mo)	Normal (7 d) Normal (4 mo)	Elevated GluRε2 (0.34, CSF; 4 mo)	Intermittent delirium

CR, complete recovery; GluRε2, anti-NMDA-type GluRε2 antobody; HVS, high voltage slow; NE, not examined; NMDA GluR, anti-NMDA-type glutamate receptor antibody; NMDA-GluR (NR1+NR2), anti-NMDA-type GluR subunit heterocomplex (NR1+NR2) antobody; O, occipital.
Normal values of GluRε2 (ELISA) in serum, 0.43±0.13, GluRε2 in CSF, 0.16±0.05.

the basis of a diagnosis of influenza encephalopathy or limbic encephalitis associated with 2009 H1N1 influenza and was followed by clinical recovery within a few days. The outcome was excellent with no neurologic sequelae in 4 of the 5 patients (as discussed, patient 5 had intermittent delirium). Testing for autoantibodies against *N*-methyl-D-aspartate (NMDA)-type glutamate receptor (GluR) subunit heterocomplex (NR1+NR2; patient 3) or NMDA-type GluRε2 (NR2B; patients 1, 2, 4, and 5) in CSF or serum were positive or elevated in the 5 patients; these values normalized on follow-up studies in 3 patients so examined (1, 2, and 4). We could not compare the antibody levels in serum and CSF because no patient had analysis of both at the same time. Abdominal sonography or CT revealed no abnormality, and specifically excluded an ovarian teratoma.

DISCUSSION

The most important finding in this study is that these 5 patients with 2009 H1N1 influenza and delirious behavior were clinically (late-onset between days 3 and 6 and long-standing for >6 days) and radiologically (no splenial lesion) distinct from previously reported patients with delirious behavior secondary to influenza.[1,2,5] Delirious behavior in influenza usually appears on the day of or the day after the onset of fever, and lasts for <24 hours; it is considered to be a limbic symptom, derived from the temporal lobes.[1,2,8] MRI has revealed a concurrent splenial lesion, of uncertain pathophysiological significance, in approximately half the previously reported patients.[5] Delirious behavior may be observed during the early febrile period of influenza encephalopathy, sometimes before seizures or any disturbance of consciousness.[2] We found reports of only 4 children with influenza (not 2009 H1N1) who exhibited similar clinical manifestations to those observed in our 5 patients.[8,9] All were Japanese children aged from 3 to 12 years, and all were affected during a different calendar year. It is, therefore, reasonable to postulate that 2009 H1N1 influenza is more likely than other influenzas to cause late-onset and long-standing delirious behavior, at least in Japanese children.

The identification of anti-NMDA-type GluR antibodies in these 5 patients may provide a clue as to the pathogenesis of this type of delirious behavior. Anti-NMDA-receptor encephalitis is associated with an anti-NMDA-type GluR subunit heterocomplex (NR1+NR2) antibody and is characterized by neuropsychiatric syndromes, memory problems, seizures, dyskinesias, and movement disorders, with some cases requiring prolonged intensive care support.[10] Anti-NMDA-receptor encephalitis is predominantly observed in young women, because ~60% of the patients have tumors, most commonly ovarian teratomas.[10] Despite the severity, patients often recover after tumor removal and immunotherapy, suggesting an immune-mediated pathogenesis. Anti-NMDA-type GluRε2 antibody, which is homologous to NR2B, has been detected in the CSF of patients with acute limbic encephalitis, both with and without ovarian teratomas,[11] and in Rasmussen syndrome.[12] Of the patients in this small series, all 5 had these antibodies, which longitudinally normalized in 3 patients examined in this manner. Steroid therapy was effective in the 3 patients treated. In addition, positive anti-NMDA-type GluRε2 antibody and effective mPSL administration were previously reported for a 12-year-old Japanese girl with late-onset and long-standing delirious behavior associated with seasonal influenza.[8] These findings suggest that the 5 patients with 2009 H1N1 influenza suffered from a mild autoimmune-mediated encephalitis with anti-NMDA-type GluR antibodies. It would be of interest to compare the levels of anti-NR2B antibodies in our patients with those of patients with MERS, who often present with an acute onset and short duration of delirious behavior; however, no studies with this data have been reported at present, and we do not have this information.

All of the patients evaluated in this study were treated with zanamivir hydrate after being diagnosed with influenza A. This has been a common therapy

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in Japan since 2007, when it was recommended that oseltamivir phosphate not be used in patients with influenza aged between 10 and 19 years. Although many Japanese teenagers with seasonal influenza were treated with zanamivir in the past few years, only 1 patient treated with zanamivir hydrate for seasonal influenza has been reported to exhibit late-onset and long-standing delirious behavior similar to that of our 5 patients.[8] Therefore, it seems unlikely that zanamivir is the cause of this type of delirium. To elucidate the precise pathophysiology of this type of delirious behavior associated with 2009 H1N1 influenza, further clinical (for patients with seasonal influenza), laboratory (especially regarding anti-NMDA-type GluR antibodies in patients with MERS), and pathologic studies will be necessary.

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