

to memorize new words and concepts at school, and intractable seizures (visual seizures, simple and complex partial seizures on extremities and face, and secondary generalized seizures).

2.2. Laboratory data (Table 1)

On admission, the blood analysis was unremarkable other than a mild decrease in the platelet count and a mild elevation in liver enzymes. Lactate and pyruvate in serum (on day 1) and CSF (on day 2) were normal. CSF showed transient pleocytosis and a mild elevation of protein content. Extensive tests for viral infection yielded negative results other than mumps virus-IgM, which was weakly positive on day 3 but negative on day 10, and parotitis did not appear clinically. Serum anti-glutamate receptor (GluR) $\epsilon 2$ IgM and anti-GluR $\epsilon 2$ IgG autoantibodies were positive on day 2. Serum anti-GluR $\delta 2$ IgM and IgG (on day 2), CSF anti-GluR $\epsilon 2$ and GluR $\delta 2$ autoantibodies were negative.

2.3. Neuroimaging (Fig. 2)

MRI was normal on day 3. On day 14, multiple high-intensity lesions appeared in the bilateral cerebral cortex with frontal and parietal predominance on fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 2A and B). This distribution was consistent with the epileptic foci on EEG at this time. These lesions were not Gadolinium-enhanced, and no abnormality was noted on T1, T2 or diffusion-weighted images. White matter, basal

ganglia, brainstem, and cerebellum were spared. These high-intensity lesions were almost gone by day 34 (Fig. 2C). Generalized cerebral cortical atrophy, predominantly in the bilateral frontal lobes and hippocampi, appeared on day 61 (Fig. 2D and F). On day 117, the frontal lobe atrophy was vastly improved but the hippocampal atrophy persisted (Fig. 2E and G). On day 10, single photon emission-computed tomography (SPECT) showed hyperperfusion in the left frontal and parietal lobes (Fig. 2H), which was consistent with the high-signal lesions observed on FLAIR imaging (Fig. 2B). There was a simultaneous reduced blood flow with widespread distribution including the hippocampus (not shown). Blood flow recovered throughout the brain on day 80, and hyperperfusion was apparent in parietal and occipital lobes (not shown) and bilateral hippocampus (Fig. 2I).

3. Discussion

We reported herein on a young male patient presenting with seizures who showed a prodromal period with fever and eruption. The clinical symptoms and course met the criteria of AERRPS [2,3]. Based on these symptoms and the mild pleocytosis in CSF, a diagnosis of encephalitis was made for this patient. Together with the parenchymal cellular infiltration [5], such findings support the validity of the term of 'encephalitis' also in AERRPS, although no infective agents have been identified thus far in this entity [1–3].

Table 1
Laboratory data

WBC	3840/ μ l	
PLT	117×10^3 / μ l	
AST	51 IU/L	
ALT	54 IU/L	
Serum lactate	16.1 mg/dl	
Serum pyruvate	0.88 mg/dl	
CSF lactate	16.1 mg/dl (day 2)	
CSF pyruvate	0.89 mg/dl (day 2)	
CSF cell count	47/3 (day 2) and 19/3 (day 15)	
CSF Protein	32 mg/dl	
Viral culture (pharynx, blood, stool, and CSF) for rhinovirus, coxsackievirus, parainfluenza virus, influenza virus, RS virus, echovirus, enterovirus 71, poliovirus, and rotavirus		All negative
Blood titer for:		
Mycoplasma	(day 1)	All negative
Herpes simplex virus (HSV), <i>Varicella zoster virus</i> (VZV)	(day 3)	
Cytomegalovirus, adenovirus, Japanese encephalitis virus, <i>Rubella virus</i> , measles virus	(day 11)	
PCR for HSV and VZV in CSF	(day 6)	Negative
Serum antinuclear antibody, C-ANCA, P-ANCA, lupus anticoagulant		Negative
Serum mumps virus IgM	(day 3)	Weakly positive
	(day 11)	Negative
Mumps virus IgG	(day 70)	Negative
Serum IgG-GluR $\epsilon 2$, IgM-GluR $\epsilon 2$	(day 2)	Positive
IgG-GluR $\delta 2$, IgM-GluR $\delta 2$	(day 2)	Negative
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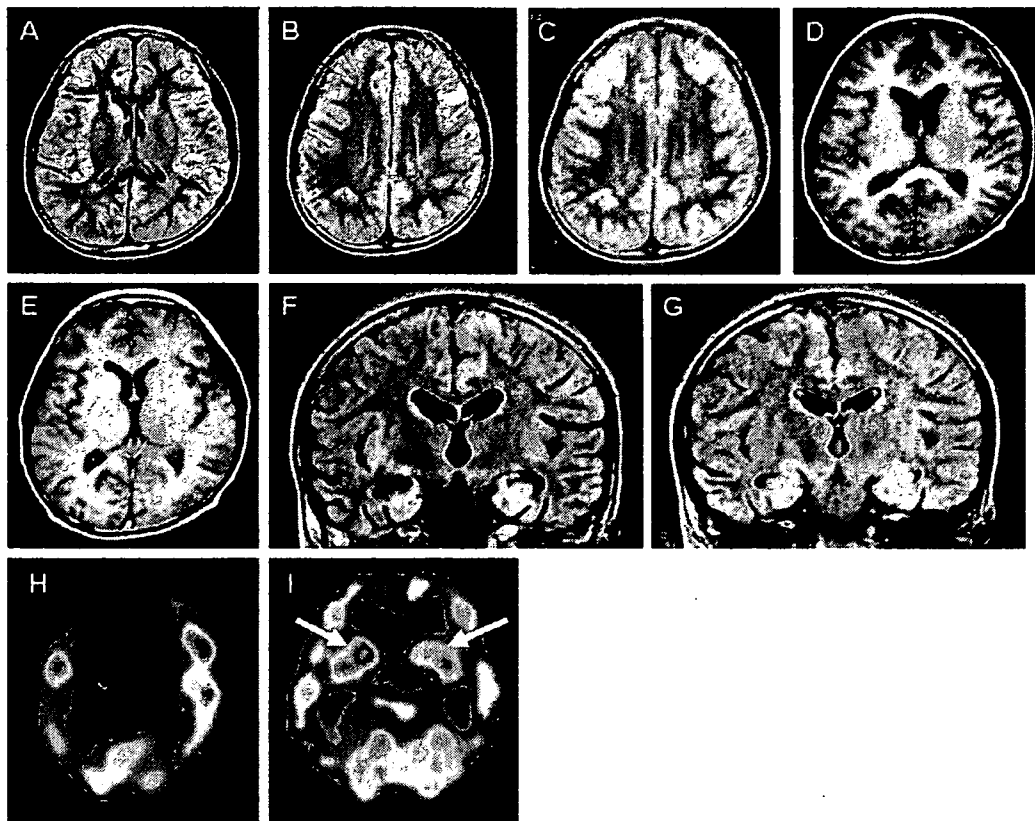


Fig. 2. Neuroimaging of the patient. Magnetic resonance imaging (MRI) [A–C, F, and G: fluid-attenuation inversion recovery (FLAIR) images; (D) and (E), T1-weighted images] and single photon emission-computed tomography (SPECT) (H and I) of the patient. On day 14 of illness (A and B), multiple cerebral cortical lesions were distributed in the cerebral cortex, predominantly in the left parietal and bilateral frontal lobes. White matter, basal ganglia, thalamus, cerebellum (not shown), and brainstem were spared. On day 34 (C), cortical lesions (B) almost disappeared on FLAIR imaging. On day 61 (D and F), diffuse cerebral cortical atrophy with predominance in the frontal lobes (D) and hippocampus (F) was noted. On day 117 (E and G), the cortical atrophy had almost disappeared (E) but the hippocampal atrophy remained (G). On day 10, hyperperfusion was apparent in the left frontal, parietal, and right frontal lobes (H), consistent with high-signal lesions (B). On day 80, hyperperfusion appeared in the bilateral hippocampus (I, arrows).

Encephalitis with multifocal cortical cerebral lesions on MRI, without involvement of other brain regions, is extremely rare. Such findings have been reported in presumed autoimmune conditions, including neuro-Behçet disease and Rasmussen's encephalitis [6,7]. In addition, autoantibodies against GluR ϵ 2 were seen in the present patient, as is reported in Rasmussen's encephalitis [8], acute limbic encephalitis [8], and occasionally in AERRPS [3]. The GluR ϵ 2 autoantibodies in the present patient might be involved in the pathogenesis of the multifocal cortical lesions and refractory seizures, as suggested by similar findings of GluR autoantibodies in an animal model of Rasmussen's encephalitis [9]. The lack of motor sequelae and the mild degree of brain atrophy observed in the current case are common to many cases with AERRPS, in contrast to the considerable intractability of the epilepsy [1,2]. This suggests the presence of a nondestructive, but excitatory action, caused by autoantibodies binding to cortical neurons in this entity. In the present patient, however, GluR ϵ 2 autoantibodies were absent from the CSF of the patient.

We therefore speculate that other GluR autoantibodies are present and involved in the pathogenesis in this case.

Interestingly, SPECT studies on this patient showed a hyperperfusion in the areas with high-signal lesions on FLAIR imaging during the acute phase, and later in the bilateral hippocampus during the chronic phase. This delayed hyperperfusion of the hippocampus may have resulted from secondary epileptogenesis induced by the refractory seizures, or from direct binding of unidentified GluR autoantibodies to hippocampal neurons [10]. These mechanisms might also be related to the hippocampal atrophy and the intellectual sequelae of the patient.

Definitive diagnosis of the present patient with AERRPS still warrants caution, despite the intriguing hypothesis of an immunological pathomechanism in this case, as the decision was based on clinical characteristics alone. Multifocal lesions are rare and GluR ϵ 2 autoantibodies are not necessarily present in AERRPS patients. The heterogeneity of this entity warrants further exploration for a better understanding of its

pathogenesis. However, there are merits in using the term of AERRPS, considering the similar long-term outcome and response to particular antiepileptic agents in other patients diagnosed with this condition [1–3]. Biological markers other than GluR ϵ 2 autoantibodies would be valuable in the diagnosis of AERRPS, particularly for the purpose of avoiding ambiguity in the clinical criteria.

In conclusion, we experienced a patient with multiple cortical lesions on MRI in the acute phase, and serum anti-GluR ϵ 2 antibodies, and whose clinical course met AERRPS. These findings are common to some types of autoimmune encephalitis, and therefore suggest an autoimmune-mediated pathogenesis in this patient.

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The Mildest Form of Acute Necrotizing Encephalopathy Associated with Influenza A

Abstract

We experienced the mildest form of acute necrotizing encephalopathy associated with influenza A. A previously healthy 13-year-old girl had mildly decreased consciousness and delirious behavior lasting for a week. Diffusion-weighted imaging showed mildly high signal intensities in the bilateral thalami, deep white matter in the centrum semiovale, and frontal lobes. Conventional T₁- or T₂-weighted images revealed no abnormalities.

Key words

Acute necrotizing encephalopathy · influenza · diffusion-weighted imaging

Introduction

Acute necrotizing encephalopathy (ANE) is a well-defined type of acute encephalopathy first described by Mizuguchi et al. [10,12]. The most important diagnostic criterion of ANE is the presence of multiple, symmetrical brain lesions in the bilateral thalami and other specific brain regions (periventricular white matter, internal capsule, putamen, upper brain stem tegmentum, and cerebellar medulla), demonstrated by CT or conventional T₁- or T₂-weighted imaging. The onset of ANE is triggered by acute febrile diseases, mostly viral, among which influenza is the most common [10]. There are several reports on ANE associated with influenza [4]. ANE is often observed among infants and children, but

occasional adult cases have also been reported [5,6]. Although ANE is common in Japan and Taiwan [10], several reports on ANE have been made from some European and American countries [8,9].

ANE is often associated with severe neurological symptoms with multiple organ dysfunction. However, we experienced a patient with the mildest form of ANE associated with influenza in which conventional MRI failed to demonstrate abnormal findings.

Case Report

The patient was a previously healthy 13-year-old girl. Her past and family histories were unremarkable. Her psychomotor development was normal. She had a febrile illness in January 2004. Her consciousness became gradually reduced two days later. She was excessively drowsy and tended to fall asleep. She also had delirious behavior 6 days after the onset of febrile illness. She intermittently spoke meaningless phrases such as "I am scared" or "I must make a practice of the athletic meeting". She was admitted to our hospital one week after the onset of febrile illness, because reduced consciousness and delirious behavior were still observed.

On admission, her body temperature was 36.1 °C. Although her consciousness was slightly decreased, the neurological examination revealed no abnormalities. Laboratory examinations revealed normal blood cell counts, and liver and renal functions.

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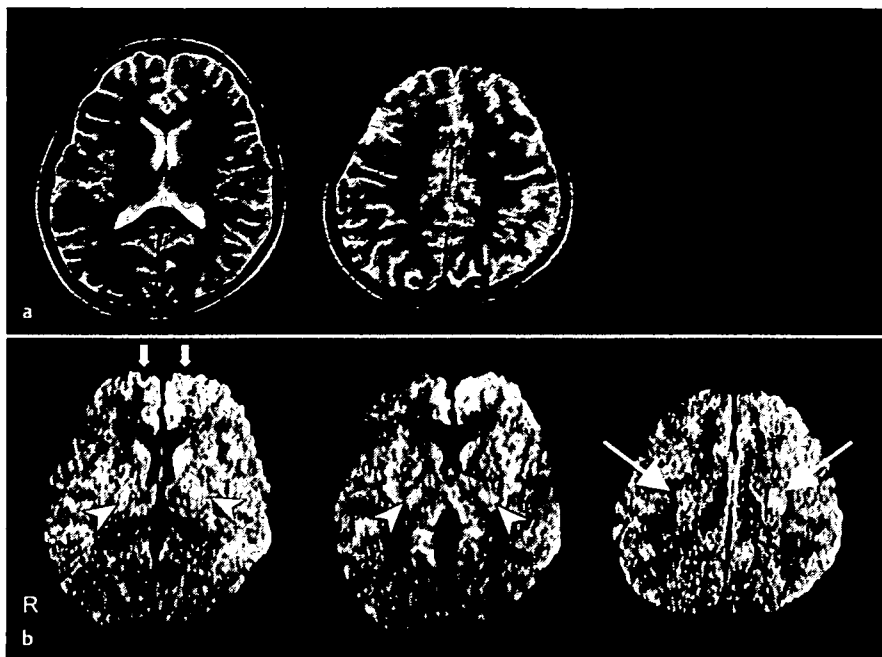


Fig. 1 MRI findings of the patient. **A** T_2 -weighted images (TR 3650 ms, TE 91 ms, FOV 230 mm², matrix size 256 × 256). No abnormalities were observed. **B** Diffusion-weighted images (TR 8000 ms, TE 131 ms, b = 1000 s/mm², FOV 230 mm², matrix size 128 × 128). Subtle hyperintensities were observed symmetrically in the bilateral thalami (arrowheads), white matter in the centrum semiovale (long arrows) and frontal lobes (short arrows).

Serum levels of electrolytes, blood glucose, and ammonia was also within the normal range. Cerebrospinal fluid analysis showed 1 cell/ μ L and protein of 21 mg/dL. Influenza A antigen was positive in a throat swab.

After admission, she became intermittently disoriented and seemed not to understand where she was or what day of the week it was. The mild disorientation was improved gradually in a week. She also spoke some incoherent phrases such as "I called my grandfather" on the day of admission. Such delirious behavior was observed on the next day of admission but was not recognized thereafter. She was discharged from our hospital one week after admission. No neurological sequelae were observed at present but she could not remember what had happened during the admission.

Computed tomography of the head and an electroencephalogram on the next day of admission were unremarkable. However, head MRI 3 days after admission demonstrated mildly high signal intensities in the bilateral thalami and the deep white matter in the centrum semiovale only on diffusion-weighted images (Fig. 1). The bilateral frontal cortex also showed mildly increased intensities (Fig. 1). Conventional T_1 - or T_2 -weighted images revealed no abnormalities (Fig. 1).

Discussion

The radiological features of our patient were symmetrical lesions involving the bilateral thalami and deep white matter that could be recognized only on diffusion-weighted images. T_1 - and T_2 -weighted images failed to demonstrate these lesions. At present, there have been no reports on such MRI findings in patients with encephalopathy. We consider that our patient had the mildest variation of ANE, because the symmetrical distribution of brain

lesions, affecting the bilateral thalami and deep white matter of the cerebrum, is characteristic of ANE.

The MRI findings of our patient suggest that diffusion-weighted images may be more sensitive to the lesions of ANE than conventional T_1 - or T_2 -weighted images. It is likely that mild lesions of ANE may alter the water diffusion without changing T_1 or T_2 relaxation times such as stroke in the superacute phase. There have been several reports on diffusion-weighted image of patients with ANE. Albayram et al. reported diffusion-weighted imaging findings of a patient with ANE [1]. They revealed an increased apparent diffusion coefficient in the centers of thalamic lesions and a reduced apparent diffusion coefficient in the periphery of lesions. Harada et al. compared the diffusion-weighted images between a patient with ANE and one with acute disseminated encephalomyelitis [3]. They demonstrated slightly lowered water diffusion in the lesions in ANE. However, these patients had clear lesions on T_2 -weighted images. The usefulness of diffusion-weighted images in the ANE in comparison with conventional T_1 - and T_2 -weighted images should be further investigated.

There have been several neuropathological studies on ANE. In patients with severe ANE, the lesions show edema, petechial hemorrhage, and necrosis, suggesting local breakdown of the blood-brain barrier [10–12]. These pathological changes were more severe in the depth of the lesions. Edema was a chief pathological finding in the periphery of the lesions, whereas progressive rarefaction was observed in the center. On the other hand, brain lesions are reversible in patients with mild ANE [16]. Clinical and pathological data suggest that an alteration of permeability of the vessel wall without disruption will occur in patients with mild ANE [10,11,14]. This suggests that cytotoxic edema will be a main pathological component in patients with mild ANE and will explain the reason why lesions in our patient were detected only in diffusion-weighted images, because diffusion-weighted

images are more sensitive to cytotoxic edema than conventional T₁- or T₂-weighted images.

It is interesting that the bilateral frontal cortex showed high intensities on diffusion-weighted images in our patient. Delirious behavior in our patient may be attributable to frontal lobe lesions. There have been no reports on frontal lobe involvement in patients with ANE, although frontal lobes are affected in patients with other types of acute encephalopathy [13,15]. Neuroimaging findings of our patient may suggest that frontal lobe lesions in ANE may have been missed because they cannot be recognized without diffusion-weighted images.

Acute disseminated encephalomyelitis (ADEM) should be included in the differential diagnosis of children with bilateral thalamic lesions. Although MRI in ADEM demonstrates bilateral lesions, their distribution is usually asymmetric [2]. In contrast, brain lesions in our patients were symmetrical. Brain lesions in patients with ADEM are clearly demonstrated by conventional T₂-weighted images, whereas they were not recognized in conventional T₁- or T₂-weighted images in our patient. Pleocytosis is common among patients with ADEM, whereas our patients showed normal cell counts in the cerebrospinal fluid. Therefore, we consider that the diagnosis of ANE will be more compatible with our patient than that of ADEM.

The clinical features of ANE have been intensively studied in Japan, Taiwan, and South Korea [7,10]. Most patients with ANE have coma often precipitated by a seizure within 24 hours from the onset. The series of patients in Japan and Taiwan showed that coma was observed in 98% of patients and convulsions in 94% [10]. A Korean study revealed impairment of consciousness and seizures in 13 of 14 patients. On the other hand, delirious behavior has not been reported during the acute stage of ANE. These facts indicate that the clinical manifestation of our patient was exceptional for ANE. However, patients with ANE like ours may be missed or underestimated, because CT and conventional T₁- or T₂-weighted images failed to demonstrate brain lesions. Some patients similar to ours may be found in those with mildly decreased consciousness and/or delirious behavior if diffusion-weighted images would be routinely performed. It should be stressed that careful interpretation of MRI will be mandatory. The MRI findings of our patient were certainly subtle.

Disclaimer

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Original article

Acute encephalitis with refractory, repetitive partial seizures: Case reports of this unusual post-encephalitic epilepsy

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Abstract

We report on three acute encephalitis patients with refractory, repetitive partial seizures (AERRPS). All three suffered acute febrile episodes associated with status epilepticus, which necessitated high-dose barbiturate therapy under artificial ventilation for several weeks. Electroencephalography (EEG) revealed a predominance of diffuse epileptiform discharges initially, subsequently developing into periodic bursts of these discharges. Reduction of the barbiturate dosage resulted in clinical and subclinical partial seizures appearing repetitively in clusters. Prolonged fever persisted for 2–3 months, even several weeks after normalization of cell counts in the cerebrospinal fluid. The EEG showed an improvement after resolution of this fever, and seizures became less frequent, although still intractable. Oral administration of high-dose barbiturate and benzodiazepines were partially effective during the acute phase, and a barbiturate dependency, lasting for years, was noted in one patient. Steroid administration was effective in stopping the febrile episodes in one patient, with concurrent improvement in seizure control. Magnetic resonance imaging showed enhancement of bitemporal cortical areas in one patient, and high signal intensity on T2 weighted image in the bilateral claustrum in another patient. Diffuse cortical atrophy appeared within two months after the onset of encephalitis in all patients. The evolution of the seizures and EEG findings suggested a high degree of cortical excitability in AERRPS. In this report, we propose a tentative therapeutic regimen for seizure control in this condition. We also hypothesize that a prolonged inflammatory process exists in the cerebral cortex with AERRPS, and may be pivotal in the epileptogenesis.

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Keywords: Post-encephalitic epilepsy; High-dose barbiturate; Glutamate receptor; Autoantibody; Steroid

1. Introduction

Epilepsy can appear as a sequel to encephalitis, usually with a latent period of months to years after termination of the acute phase [1,2]. However, on rare occasions, prolonged, refractory, status epilepticus accompanies the acute encephalitis from the beginning,

and intractable partial seizures persist after recovery from the acute illness. Fukuyama et al. [3] reported such an entity as a “peculiar type of post-encephalitic epilepsy” in 1986, and approximately 40 similar Japanese cases were subsequently reported. Sakuma et al. [4] proposed the term of acute encephalitis with refractory, repetitive partial seizures (AERRPS) to describe this epileptic syndrome, with a diagnostic criteria of (1) acute phase lasting two or more weeks, (2) persistent partial seizures of a similar nature occurring from the acute phase through to the recovery phase, (3) frequent

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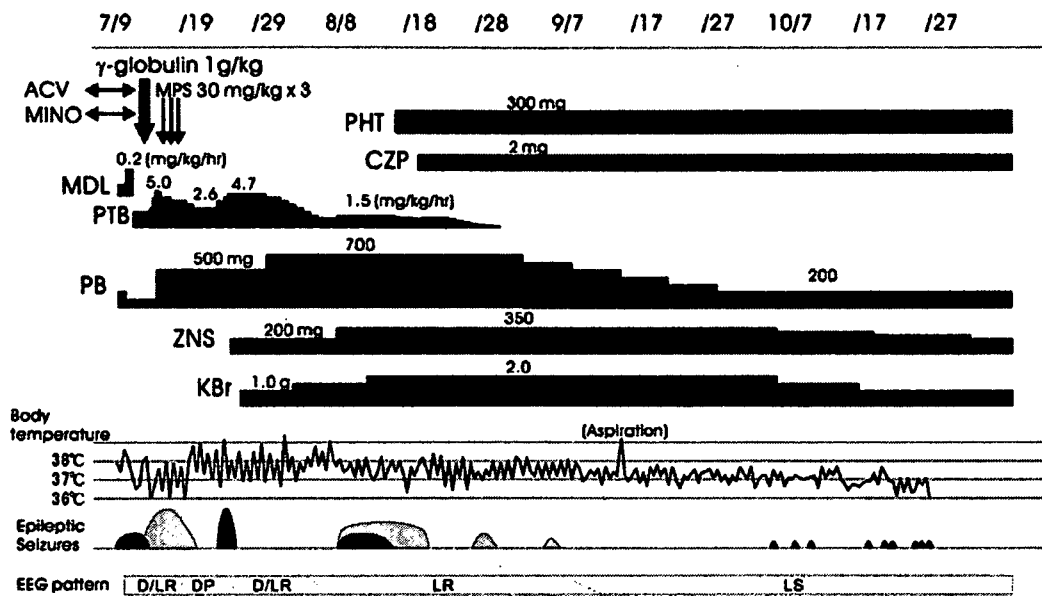


Fig. 1. Clinical course of patient 1. ACV, acyclovir; CZP, clonazepam; KBr, potassium bromide; MDL, midazolam; MINO, minomycin; MPS, methylprednisolone; PB, phenobarbital; PHT, phenytoin; PTB, pentobarbital; ZNS, zonisamide. For epileptiform discharges on electroencephalography, D, diffuse; DP, diffuse periodic; LR, localized rhythmic; LS, localized sporadic. Grey and black areas represent the frequency of clinical and subclinical seizures, respectively.

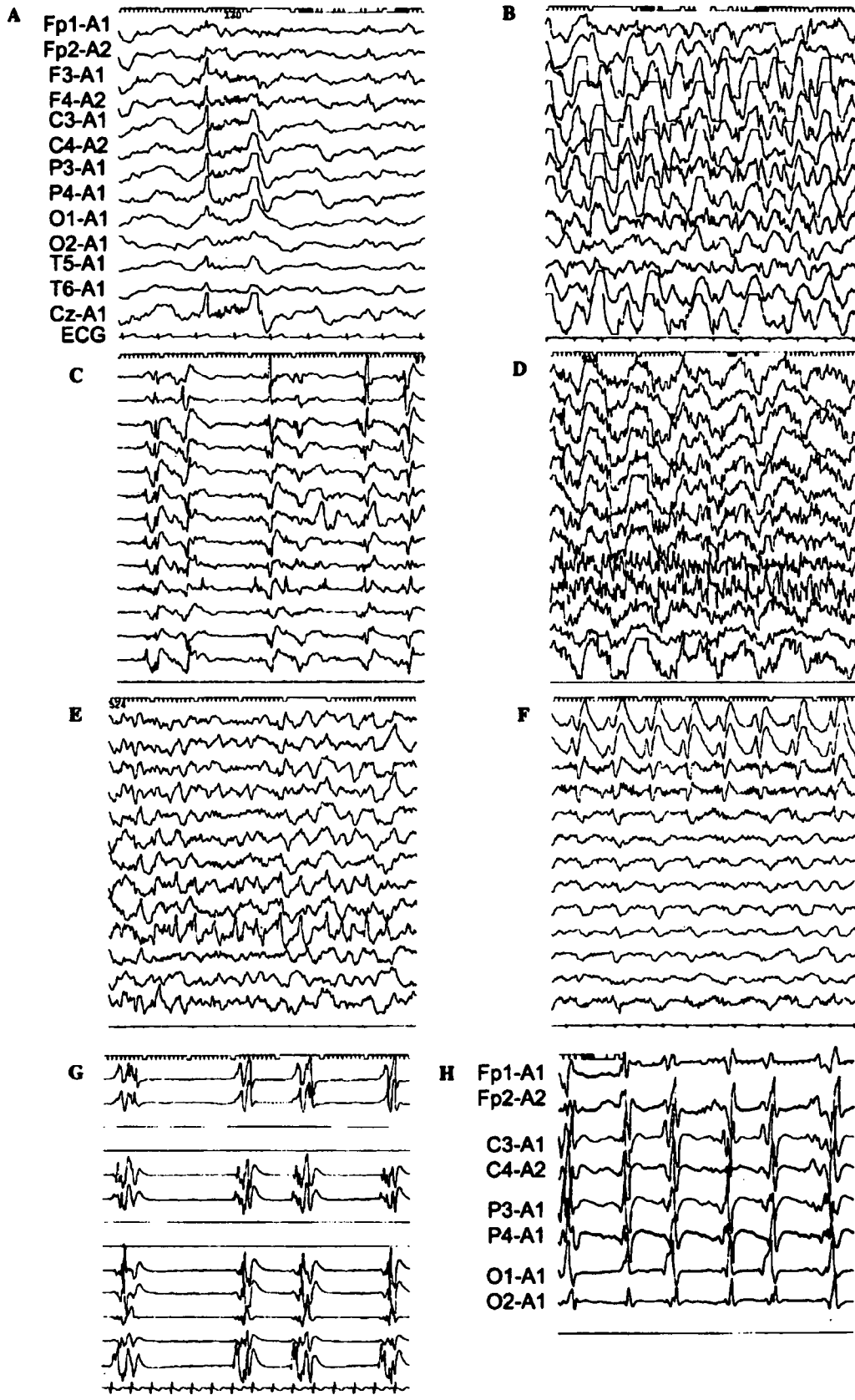
seizures often evolving into recurrent status epilepticus, (4) marked intractability of seizures, and (5) exclusion of specific etiology such as viral encephalitis and metabolic disorders. Reports of this type of post- or para-encephalitic epilepsy were rare in the English scientific literature until recently [5–8], possibly due to doubts regarding its categorization as a specific condition within the post-encephalitic epilepsies. However, as demonstrated in the cases presented here, patients with this catastrophic epileptic syndrome share a common clinical course, seizure types, electroencephalography (EEG) findings, and responses to certain antiepileptic agents. Here, we report the clinical course of three patients with AERRPS to facilitate the diagnosis and appropriate management of this condition.

2. Case report

Patient 1 (Fig. 1). The patient is a 10-year-old boy who had suffered from bronchopneumonia with high fever. Headache and fluctuation of consciousness appeared on the sixth day of illness, when tonic-clonic convulsion emerged. On admission he was comatose, and neck stiffness was noted, but sleep EEG (Fig. 2A) and magnetic resonance (MR) imaging were normal. On day 2–3 of admission, recurrent tonic seizures could not be controlled by continuous midazolam (MDL) infusion. Pentobarbital anesthesia was started under artificial ventilation, and was increased up to 5 mg/kg/h due to recurrent and persistent emergence

of tonic seizures or rhythmic paroxysmal discharges at occipital areas with occasional generalization (Fig. 2B). A tentative diagnosis of AERRPS was made, and high-dose γ -globulin and steroid pulse therapy were administered. Although high-dose barbiturate therapy yielded a burst-suppression pattern on EEG, spike components were prominent at frontal and occipital areas. Subsequently, a distinct pattern of diffuse, high-voltage periodic bursts of epileptiform discharges appeared by day 8 (Fig. 2C). Trial tapering of pentobarbital, in association with phenobarbital administration to a serum level of 50 μ g/ml or more, resulted in the reemergence of clusters of partial seizures. Several days after increasing the pentobarbital infusion rate, along with starting zonisamide and potassium bromide, the pattern of periodic discharge was replaced by usual burst-suppression pattern. Pentobarbital infusion was tapered again, with a simultaneous increase in phenobarbital dosage to a serum level of 90 μ g/ml. However, frequent localized, rhythmic paroxysms (Fig. 2D) recurred with concomitant ocular deviation, nystagmus, facial flushing, and/or motion arrest. A couple days after successive additions of phenytoin and

Fig. 2. Electroencephalographic findings in AERRPS (A–F, patient 1; G, patient 2; H, patient 3). (A) day 1, (B) day 3, (C) day 9, (D) day 14, (E) day 20, (F) day 31, (G) day 7, (H) day 20 of admission. (C, G and H) shows the diffuse periodic (DP) pattern, and (D–F) corresponds to the localized, repetitive (LR) pattern in Figs. 1, 4 and 5. In (C) focal spikes are noted at right occipital region during the suppression phase. In (G) F3, F4, P3 and P4 electrodes were not used.



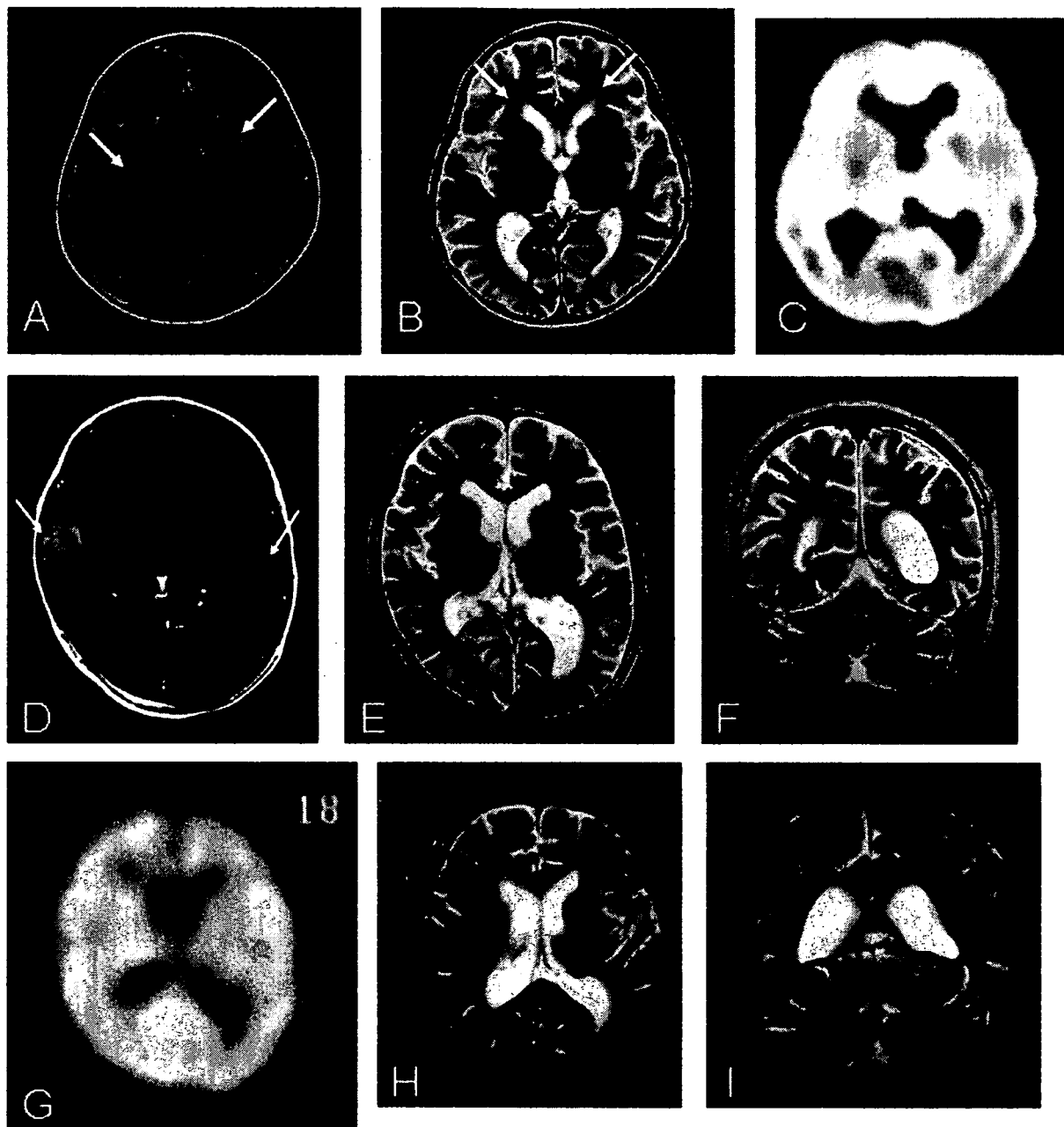


Fig. 3. Neuroradiological findings of patients with AERRPS (A–C, patient 1; D–G, patient 2; H and I, patient 3). (A) Fluid-attenuation inversion recovery (FLAIR) image showed high signal intensity in bilateral claustrum (arrows). (B) Diffuse cortical atrophy appeared during the recovery phase, in association with a high-intensity lesion at the periventricular white matter (arrows) on T2-weighted MR image (T2WI). (C) SPECT study revealed a slight decrease of blood flow at the bilateral frontal cortex. (D) Enhancement of bilateral temporal cortex is observed. (E and F) Diffuse, mild cortical atrophy can be seen in the cerebrum (E) and cerebellum (F) on T2WI. (G) Widespread decreased perfusion with left-sided predominance is seen in the cerebral cortex and basal ganglia. (H and I) T2WI. Diffuse, mild atrophy of cerebral and cerebellar cortex is seen.

clonazepam treatment regimen, a marked decrease in epileptiform discharges were noted. Pentobarbiturate could be completely tapered off after 51 days of continuous infusion. Although clinical seizures did not recur, frontal or occipital rhythmic paroxysms occasionally appeared on EEG (Fig. 2E and F). After resolution of persistent fever at 60 days after admission, these subclinical rhythmic paroxysms disappeared and the

EEG showed only sporadic focal spikes thereafter. The phenobarbital was gradually tapered from 700 to 300 mg (serum level from 70 to 30 $\mu\text{g/ml}$). Partial seizures, identical to those of the acute phase, recurred at this lower dose, but at a frequency of less than once per day. During the above clinical course, bilateral high signal-intensity lesions on T2-weighted and fluid-attenuation recovery (FLAIR) magnetic resonance

(MR) images appeared in the claustrum on day 11 (Fig. 3A), and persisted thereafter. After 3 months of illness, diffuse atrophy of the cerebral and cerebellar cortex appeared (Fig. 3B). Single photon emission computed tomography (SPECT) analysis revealed a slight decrease in blood flow at the bifrontal areas (Fig. 3C). After 3 months of illness, the patient showed mild truncal hypotonia and flaccid tetraparesis. Pyramidal tract sign was negative on both toes, but ankle clonus was positive bilaterally. Nasal tube feeding was ceased at 4 months of illness, and his motor skill has recovered to almost normal during the following several months.

Patient 2 (Fig. 4). A seven-year-old girl became unconscious and suffered from a cluster of generalized clonic convulsions after 3 days of febrile episodes. On admission, the brain computed tomography (CT) showed no abnormalities. Midazolam did not suppress the recurrent seizures, and thiopental infusion was started. Due to the emergence of eyelid twitching and smacking on day 6 of admission, the thiopental infusion rate was raised to 5 mg/kg/h. Diffuse, periodic bursts of epileptiform discharges appeared on EEG on day 7 (Fig. 2G), and thiopental could not be tapered due to emergence of frequent subclinical seizures with frontal or occipital foci. After administration of high-dose phenobarbital and CaBr₂, propagation of focal epileptic discharges markedly decreased, and thiopental was tapered off by day 24. Localized rhythmic epileptiform discharges persisted, and generalization increased after tapering the dose of phenobarbital. High-grade fever persisted until three months of illness. The complication of pneumonia occurred during the acute phase, but this could not totally account for the prolonged fever. Resolution of this fever coincided with amelioration of EEG (Fig. 4A). Although an enhanced brain CT showed no abnormalities on day 16 of admission, MR imaging at 32 days revealed enhancement at the bilateral parieto-temporal cortex and adjacent subcortical white matter (Fig. 3D). This enhancement disappeared at 48 days. Mild atrophy of the cerebral and cerebellar cortex was present since the acute phase (Fig. 3E and F). SPECT studies at three months of admission revealed a widespread hypoperfusion of the cerebral cortex (Fig. 3G), which persisted thereafter. After trials with various combinations of antiepileptics, the complex partial seizures were controlled to less than 2–3 times per day by treatment with phenobarbital and zonisamide (Fig. 4B). Clusters of seizures occasionally appeared thereafter, particularly when the blood level of phenobarbital was lowered, but were terminated by increasing the phenobarbital dosage transiently, or by pentobarbital infusion for a couple of days without artificial ventilation. Motor and intellectual sequel of moderate severity persists to date. No pyramidal tract sign has been noted on examination, but ankle clonus is positive bilaterally.

Patient 3 (Fig. 5). The patient is a nine-year-old girl, who had just recovered from three days of febrile episodes, and exhibited delirious behavior and unconsciousness. The CSF cell count and brain CT were normal on admission. Due to repetitive generalized seizures with smacking and vomiting, the patient was treated with high-dose thiamylal infusion under artificial ventilation. Ictal episodes with eyelid twitching emerged when the thiamylal was tapered on day 20 of admission. EEG showed a pattern of diffuse, periodic burst discharges (Fig. 2H), changing to frequent rhythmic epileptiform discharges with frontal predominance thereafter. Ictal episodes of clonic motion of the left hand or jaw, ocular gaze, tongue tremor and salivation appeared in clusters. Due to the prolonged fever and progressive anemia and neutropenia, granulocyte-colony stimulating factor (G-CSF) and methylpredonisolone pulse therapy were administered. The fever subsequently resolved and hemoglobin and leukocyte counts returned to normal with a simultaneous disappearance of partial seizures and a decrease of localized, rhythmic EEG activity. As the serum IgG gradually decreased to 196 mg/dl, phenobarbital was replaced by valproate sodium. Epileptic seizures reappeared but remained at a frequency of 2–3 times per week. Brain CT and MR imaging showed mild cortical atrophy of the cerebrum and cerebellum after one month of illness (Fig. 3H and I). During the recovery period, the patient could walk by herself and talk in sentences. She showed an ability to solve school tasks of 7 years of age on discharge at 6 months of illness.

3. Characteristics of epileptic seizures and evolution of EEG findings

At initial presentation, our AERRPS patients manifested with repetitive generalized convulsion. Diffuse slow waves were only briefly recognized on EEG at the initial clinical presentation (Fig. 2A and B), less than 2–3 days after admission. Barbiturate coma with burst-suppression pattern, which necessitated the administration of pressor agents, could only suppress the seizures. Subsequently, a distinct pattern of diffuse, periodic bursts of spikes appeared (Fig. 2C, G and H). This activity was characterized by the high amplitude (150–200 μ V) of spikes and the attenuated activity between spike bursts, which is not usually observed during barbiturate coma. Epileptic foci were also identified as additional localized spikes during the suppression phase (Fig. 2C). When the dose of barbiturate infusion was decreased, localized rhythmic discharges with occasional generalization appeared repetitively (Fig. 2D), which remained subclinical or accompanied by minor seizures including arrest of motion, ocular deviation, staring, twitch of eyelids,

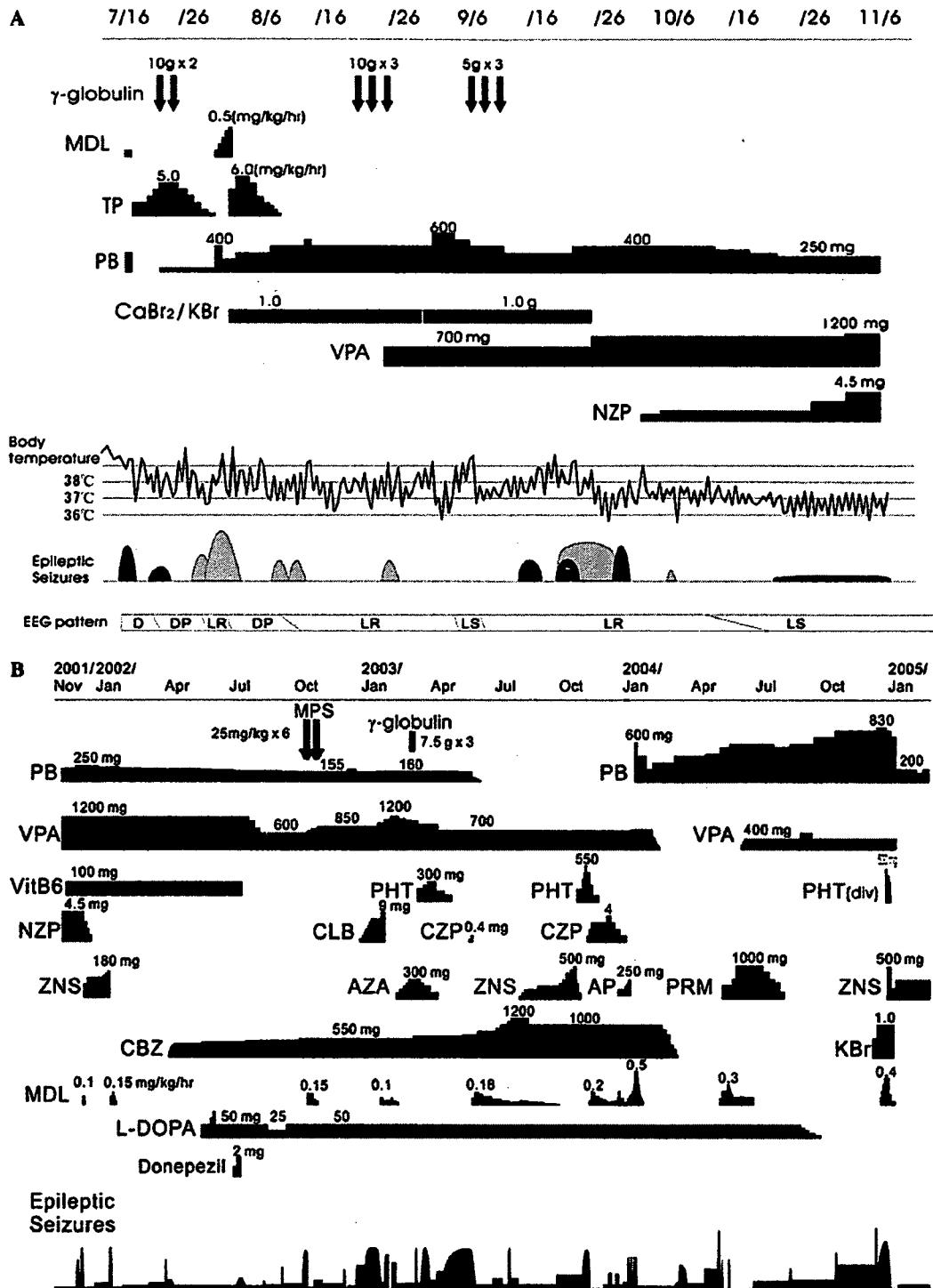


Fig. 4. Clinical course of patient 2. (A) acute phase and (B) chronic phase. (B) After reduction of the phenobarbital dosage, the complex partial seizures became refractory to various combinations of antiepileptics, and also became repetitively aggravated in clusters. Methylprednisolone pulses and γ -globulin administrations during the chronic phase had no apparent effect on the post-encephalitis epilepsy. Elevation of the serum phenobarbital level to 103 μ g/ml drastically decreased the seizures at three and half years of admission, enabling the patient to be discharged. During chronic phase, a partial beneficial effect of L-DOPA on her behavior was noted initially, but later the effect became ambiguous. AP, acetylpheneturide; AZA, acetazolamide; CaBr₂, calcium dibromide; CLB, clobazam; NZP, nitrazepam; PRM, primidone; VitB6, vitamin B6; VPA, valproate sodium.

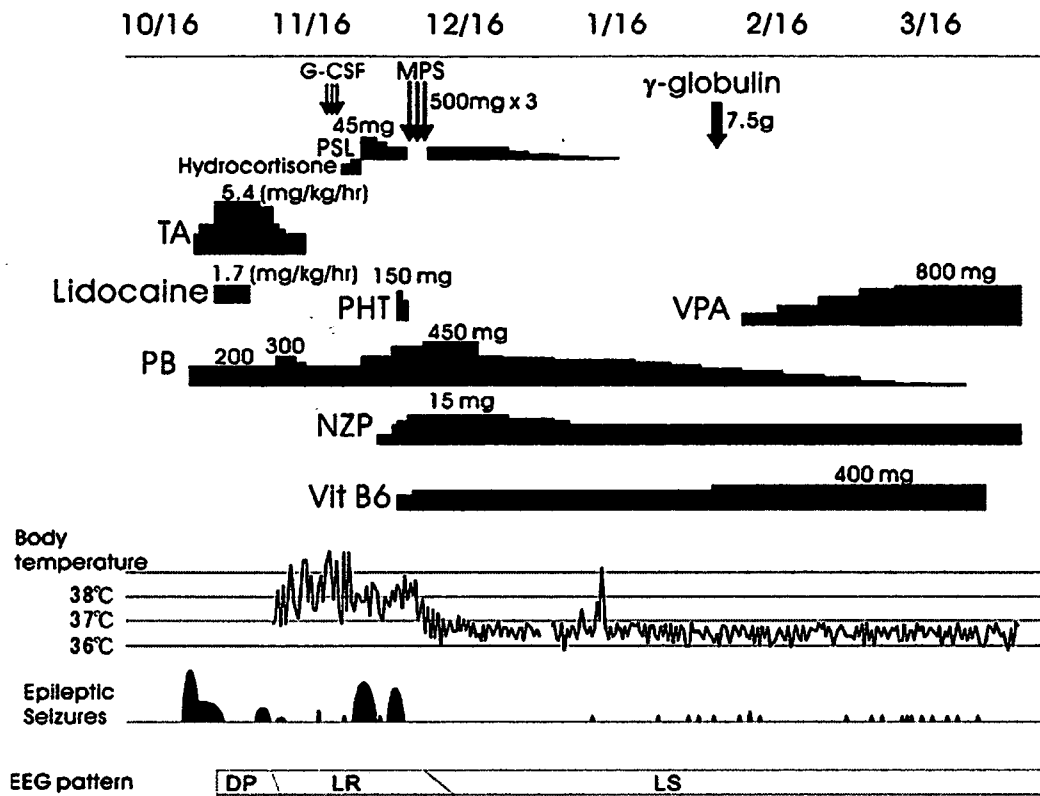


Fig. 5. Clinical course of patient 3. PSL, prednisolone; TA, thiamylal.

smacking, salivation, flushing of face, elevation of heart rate, and clonic motion of jaw and unilateral hand/leg. These seizure types persisted even after the decrease of localized rhythmic discharges, and remained intractable. This decrease of rhythmic discharges showed a close temporal relationship to the resolution of prolonged fever (Figs. 1, 4A and 5) in all three patients. EEG during wakefulness showed 4–6 Hz slow posterior activity with an amplitude of lower than 100 μ V.

4. Characteristics of laboratory findings (Table 1)

All three patients showed a mildly increased CSF cell count, but without elevation of the protein level or IgG index. CSF IL-8 in patient 1 was 759.4 pg/ml (normal, 6.0–25.4) on admission and 518.7 pg/ml two days later. Despite these data that suggested the presence of encephalitis, no causative infective agents could be identified. Lactate and pyruvate levels in the CSF, organic acid metabolites in urine, and serum antinucleus antibody levels were also normal. Serum autoantibody against GluR ϵ 2 was negative on admission and day 25 in patient 1, and on day 8 in patient 2, but became positive at 2–18 months of illness in patient 2. Normocytic anemia with a hemoglobin level of 7.8–9.4 g/dl appeared at 2–5 weeks of illness, accompanied by mild elevation

of ferritin to 250–500 ng/ml (normal 26–211); this normalized during the following 1–2 months, in correlation with resolution of the prolonged fever.

5. Discussion

The clinical features of the patients presented here meet the criteria of AERRPS [4]. Similarities in seizure types and intractability, and in the efficacy of certain anticonvulsants, support the importance of establishing AERRPS as an independent clinical condition or disease entity. In addition, there were commonalities in evolution of the epileptiform discharges, as well as some correlation between the changes in EEG findings and the termination of prolonged fever. These latter similarities have not been emphasized in previous reports on AERRPS. These findings provided a basis on which to further investigate this condition as a primary disorder of unknown pathogenesis.

Periodic EEG patterns accompany acute brain lesions of various etiologies [9,10], in most cases with poor prognosis. In these cases, reduction of barbiturate infusion was quite difficult, particularly during the period showing periodic bursts on EEG. Such an EEG pattern is not considered as ictal change [11], but can be considered as a manifestation of increased neuronal

Table 1
Characteristics of clinical course and laboratory findings of patients with AERRPS

	Patient 1	Patient 2	Patient 3
Age at onset	10 years	7 years	9 years
Sex	M	F	F
Febrile period	2 months	3 months	1.5 months
Follow-up length	1 year	5 years	10 years
Outcome			
Motor	Normal (clumsy)	Unable to keep standing	Normal (clumsy)
Intellect	IQ 60 at 11 years of age	No purposeful use of hands, no meaningful words	IQ 50 at 19 years of age
Duration of continuous barbiturate infusion	51 days	25 days	23 days
Effective agents for seizure control	PB (~90.6 µg/ml), KBr, CZP (chronic phase: ZNS, PHT)	PB (~145 µg/ml) (chronic phase: transient or partial effect with CBZ and ZNS)	PB (~83.3 µg/ml), steroids (chronic phase: VPA)
Peak CSF cell count (/µl)	19 (M 53 P 5)	40/3 (M 22 P 18)	11/3 (M only)
CSF glucose/protein (mg/dl)	73.0/38.5	85/25	93/6
CSF lactate/pyruvate (mg/dl)	14.3/0.91	10.4/0.52	10.0/0.80
CSF NSE (pg/ml, normal < 10)	26.1	NE	NE
Screening for infective agents (CSF PCR or changes in serum titer, all negative results)	Influenza, mycoplasma Japanese encephalitis virus, HSV, EBV, throat virus culture, CSF bacterial culture	Influenza, mycoplasma, Japanese encephalitis virus, HSV, EBV, CMV, VZV, measles, rubella, echovirus 3, 4, 6, 9, coxsackie virus B2, 4, adenovirus 7, CSF bacterial culture	HSV, EBV, CMV, measles, rubella, throat virus culture, CSF bacterial culture
Peak AST (IU/L)	72	248	102
ESR (on admission) (/h)	11	NE	NE
WBC (on admission) (/µl)	3700	7700	7500
Peak CRP (mg/dl)	4.6	15.4	4.0
Trough Hb (g/dl)	9.4	8.1	8.1
Peak ferritin (ng/ml)	256.1	753.1	392.5
Serum GluR ε2 antibody	Negative	Negative → positive	NE
MRI findings	Cortical atrophy ^a Clastrum lesion	Cortical atrophy ^a Enhanced lesion at temporo-parietal cortex	Cortical atrophy ^a

CBZ, carbamazepine; CMV, cytomegalovirus; CZP, clonazepam; EBV, Epstein-Barr virus; IQ, intelligence quotient; HSV, herpes simplex virus; NE, not examined; PB, phenobarbital; PHT, phenytoin; VPA, valproate sodium; VZV, varicella-zoster virus; ZNS, zonisamide.

^a Mild, diffuse atrophy of cerebral and cerebellar cortex.

Table 2
Tentative therapeutic regimen for seizure control in AERRPS

	Recommended	Optional/second line of choice
Acute phase	High-dose barbiturate infusion (under artificial ventilation if necessary)	Steroid pulse ^b (+maintenance after therapy), γ-globulin ^b , hypothermia ^b
Recovery phase ^a	Oral high-dose barbiturate (blood PB ~100 µg/ml, PTB) KBr/CaBr ₂ Benzodiazepines	Zonisamide, phenytoin
Chronic phase	Barbiturate (blood PB 20 µg/ml or higher, PTB) Zonisamide Benzodiazepines	KBr Phenytoin (Carbamazepine ^c)
At aggravation of seizures in cluster during chronic phase	Transient increase of barbiturate dosage, barbiturate infusion	

PB, phenobarbital; PTB, pentobarbital.

^a A period after disappearance of diffuse, periodic bursts of high voltage spikes on EEG, and before resolution of persistent fever in the present patients.

^b Not established.

^c Effective in occasional cases (personal communication).

excitability, and should be distinguished from the usual burst-suppression induced by barbiturate anesthesia. The appearance of such a periodic pattern during barbiturate coma may have resulted from an excitatory neuronal pool together with suppressed activity of the non-epileptogenic neuronal population [12], a so-called “spike-burst suppression” pattern [13]. Another characteristic of epilepsy in AERRPS is that an identical seizure pattern, consisting of complex partial seizures with or without secondary generalization, predominates during the acute and chronic phases in individual patients. This suggests that the essential pathology underlying the long-term refractory seizures is initiated during the acute phase of illness, in contrast to the usual post-encephalitic epilepsy with a latent period. Elevation of NSE in the CSF was mild in patient 1, which is consistent with other cases of AERRPS, and is in contrast to the marked elevation of NSE in intractable, post-encephalitic epilepsy with latent periods [14]. Mechanisms of epileptogenesis may be therefore different between these conditions.

The refractory epileptic seizures of AERRPS begin at the onset of encephalitis as status epilepticus or clusters of seizures. In these initial stages, high-dose barbiturate anesthesia is the sole means to suppress such seizures, with a reduction of its dose being difficult for weeks, as seen in the present patients. High-dose phenobarbital often remains as the most effective agent for seizure control during the chronic phase, which underscores the therapeutic strategy for this catastrophic epileptic syndrome. Sakuma et al. [4] reviewed the efficacy of anti-convulsants in 21 AERRPS cases, and found that barbiturate infusion was effective in 15 out of 17 cases, including 5 cases treated with pentobarbital sodium of higher than 5 mg/kg/h. In addition, phenytoin and clonazepam were partially effective during the acute phase of this syndrome in a few cases. During the recovery phase, phenobarbital of 10 mg/kg/d or more (3/4), potassium bromide (2/2), clonazepam (6/15) and zonisamide (3/14) became effective. Carbamazepine (0/14) and acetazolamide (0/8) were not effective in any cases in this series of patients.

Prolonged fever in the children presented here was accompanied by progression of anemia and elevation of serum ferritin, which are compatible with the presence of chronic, systemic inflammation. However, no causative etiology for this inflammation could be identified. Interestingly, resolution of the prolonged fever correlated temporally with the amelioration of epileptic discharges on EEG, suggesting that a certain level of inflammation persisted in the central nervous system even weeks to months after normalization of the CSF cell count, and could have accounted for the prolonged fever lasting 2–3 months, as well as for the epileptogenesis observed in this etiology. Such a peculiar, prolonged fever has been also described previously for patients

whose clinical features were compatible with AERRPS [15]. Having seen the difference in the severity of sequelae among the present patients, we speculate that the duration of prolonged fever, or possibly, the severity of central inflammation, may be related to the prognosis of patients with AERRPS. Similarly to the Rasmussen’s encephalitis case reported previously [16], inflammatory cell infiltrates have been identified in brains of patients with clinical course similar to AERRPS [7], and serum Glu ϵ 2 autoantibody has been detected in an AERRPS patient [17]. This latter patient was treated with a steroid pulse, massive γ -globulin and mild hypothermia therapies, and the sequelae were mild in this case. Although such an effect of anti-inflammatory therapies on AERRPS is still anecdotal, termination of inflammation may have a beneficial effect on the epilepsy in some AERRPS cases, similarly to certain immune-mediated encephalitis [18–21].

Neuroimaging in AERRPS patients usually shows non-specific, mild atrophy of the cerebrum. We identified cortical enhancement in one of the present patients, which may represent the persistence of cortical inflammation after normalization of CSF pleocytosis. The claustrum lesions in patient 1 are seen in certain cases of encephalitis [22,23], although the pathogenesis of these lesions remains unclear. We assume this finding may be secondary to the refractory status epilepticus in the present patient, since claustrum is included in the brain structures that are vulnerable to seizure-induced damage [24,25].

In conclusion, we delineated the clinical course of three AERRPS patients. We propose a tentative therapeutic regimen for AERRPS in Table 2, but further understanding of the etiology of this specific condition is needed, as is the pursuit for effective agents, including anti-inflammatory therapy, to improve the prognosis for this catastrophic epileptic syndrome.

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Case report

Acute cerebellar ataxia and consecutive cerebellitis produced by glutamate receptor $\delta 2$ autoantibody

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Abstract

Acute cerebellar ataxia is usually a self-limited benign disease, which may develop in children after certain viral infections or vaccinations. There are several reports of acute cerebellar ataxia associated with autoantibodies. Glutamate receptor $\delta 2$, a member of the glutamate receptor family, is predominantly expressed in cerebellar Purkinje cells and plays a crucial role in cerebellar functions. To date anti-GluR $\delta 2$ autoantibody was detected in a patient with chronic cerebellitis. Herein, an 18-month-old boy presented with cerebellar ataxia 9 days following a mild respiratory tract infection. Although cerebellar ataxia gradually improved, it worsened yet again following mumps and varicella virus infection. Cerebro-spinal fluid examination and magnetic resonance imaging of the brain demonstrated pleocytosis and meningeal enhancement, respectively. Furthermore, glutamate receptor $\delta 2$ autoantibody was detected in serum and cerebro-spinal fluid. Thus, we believe that the glutamate receptor $\delta 2$ autoantibody may play a role in cerebellar ataxia and consecutive cerebellitis.

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Keywords: Acute cerebellar ataxia; Cerebellitis; Glutamate receptor $\delta 2$ autoantibody

1. Introduction

Acute cerebellar ataxia (ACA) is usually a self-limited benign disease, showing temporary cerebellar signs such as gait disturbance and action tremor, which may develop in children after certain viral infections or vaccinations [1]. As a prodromal illness causing ACA, varicella is the primary cause, followed by mumps, mycoplasma and the Epstein-Barr virus [2]. Glutamate receptor $\delta 2$ (GluR $\delta 2$), a member of the glutamate receptor family, is predominantly expressed in cerebellar Pur-

kinje cells and plays a crucial role in cerebellar functions [3]. Herein, we describe a patient with ACA and consecutive cerebellitis associated with anti-GluR $\delta 2$ autoantibody.

2. Case report

An 18-month-old boy exhibited gait instability (day 0 of illness) and hand tremor 9 days following a mild respiratory tract infection. Perinatal history and developmental stages prior to this illness were normal. Gait disturbance worsened and the infant was admitted to hospital on day 7. Routine laboratory tests, cerebrospinal fluid (CSF) examination and magnetic resonance

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imaging (MRI) of the brain and spinal cord demonstrated normal findings. Gait disturbance and hand tremor gradually improved and the patient was discharged. On day 13, varicella skin lesions appeared and the patient was administered acyclovir (800 mg/day for 5 days). However, gait disturbance and hand tremor worsened on day 14, and the patient was unable to walk on day 16. The child was re-admitted to hospital on day 18. The patient's sister demonstrated apparent parotitis on the same day. CSF examination on day 18 demonstrated pleocytosis (144 mononuclear cells and 6 polynuclear cells/ μ l), protein 28 mg/dl and glucose 50 mg/dl. The mumps virus was detected in CSF by the polymerase chain reaction (PCR), while the varicella and herpes simplex virus were not. A brain MRI, on day 22, demonstrated normal findings except for meningeal enhancement (Fig. 1). The patient was referred to our hospital on that day. On examination, the child was awake and alert. The patient could sit without assistance but was unable to walk. Mild tremor of the hands and muscular hypotonia were noted. CSF examination, on day 22 of illness, demonstrated 27 mononuclear cells/ μ l, protein 41 mg/dl, glucose 41 mg/dl, lactate 12.6 mg/dl, pyruvate 0.86 mg/dl, myelin basic protein 45.5 pg/ml and negative oligoclonal band. CSF cytokines were normal except for a mild elevation of interleukin-2 (15.9 pg/ml, normal < 4.6). Autoantibody to GluR δ 2 (only IgM without IgG) was positive in serum and CSF. The patient was able to walk with support and



Fig. 1. An axial gadolinium-enhanced T1-weighted MRI, on day 21, shows meningeal enhancement (arrow).

was discharged on day 37. On day 60, the patient could walk with a wide-base gait. On the same day, IgM anti-GluR δ 2 antibody was weakly positive, however, IgG anti-GluR δ 2 antibody remained negative in serum. Anti-varicella and mumps virus IgG antibodies were measured by enzyme-linked immunosorbent assay, showing a more than fourfold rise in antibody titer between day 22 and 60, 500 and 2100 and <230 to 3800, respectively. Six months after the onset, lymphocyte stimulation tests (LST) were conducted using homogenate of D33 (cell line expressing GluR δ 2 subunits) [4]. Cell proliferation was measured by 3 H-thymidine uptake, and the ratio of the counts of the stimulated samples to the control counts was evaluated as the stimulation index (SI), with an SI > 2 regarded as positive [4,5]. SI with D33 homogenate stimulation was 3.8.

3. Discussion

ACA is diagnosed on clinical grounds with CSF pleocytosis (>5/ μ l) present in approximately one half of ACA children, ranging from 0 to 107/ μ l. The absence of neuroimaging abnormalities is not a prerequisite of ACA diagnosis [1,2]. Several authors reported acute ataxic cases with MRI abnormalities, involving the cerebellum and/or brain stem, as ACA [6]. Others reported such cases as acute cerebellitis (AC). Sawaishi et al. reviewed case reports of AC; all had cerebellar lesions, and meningeal enhancement was detected in 3 out of 18 cases and CSF pleocytosis was present in 14 out of 18 cases, ranging from 0 to 1450/ μ l [7]. However, the distinction between ACA and AC is somewhat obscure; meningeal enhancement could suggest that the re-exacerbation of ataxia observed in this patient was due to consecutive cerebellitis. Thus, the characterization of ACA and AC must be established more precisely.

GluR δ 2 is predominantly expressed in cerebellar Purkinje cells [3]. In previous studies, GluR δ 2 gene knock-out or mutated mice displayed ataxia and injection of the antibody, specific for the ligand-binding region of GluR δ 2, into the subarachnoid supracerebellar space of adult mice caused transient cerebellar dysfunction, including ataxia [3]. Anti-GluR δ 2 autoantibody has also been reported in a patient with chronic cerebellitis, showing fluctuation of cerebellar ataxia for 2 years [8]. In that case, anti-GluR δ 2 IgM and IgG antibodies were both positive during the first episode of ataxia. In our patient, anti-GluR δ 2 IgM antibody was positive not only in plasma but also CSF, and the level decreased with clinical improvement. However, lymphocytes stimulated by LST are usually T cells, thus a positive LST result with homogenate of D33, a cell line expressing GluR δ 2 subunits, could comprise T cell activation

[4,5]. We estimated that these GluR δ 2 autoantibodies and a positive LST result were produced by cross-reaction as a result of molecular mimicry following viral infection, and played an important role in consecutive cerebellitis in the present case.

To date, there have been several reports of ACA or AC associated with autoantibodies, such as anti-centrosome antibody post-varicella and anti-triosephosphate isomerase antibody after Epstein-Barr viral infection [9,10]. However, these reports did not contain detailed clinical descriptions, thus, it is difficult to say whether there are any clinical differences, including CSF and brain MRI findings, in ACA/AC with or without related autoantibodies. Follow-up of cerebellar ataxia and anti-GluR δ 2 autoantibody in our patient could further clarify this relationship. Moreover, humoral or cytological immunologic examinations in ACA/AC patients might clarify their pathogenesis.

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Case report

A case of acute cerebellitis accompanied by autoantibodies against glutamate receptor $\delta 2$

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Abstract

A 13-year-old boy presented with a six-day history of headache and gradually developed severe meningeal irritation symptoms. Brain magnetic resonance imaging revealed left cerebellar swelling and obstructive hydrocephalus. Then he showed transient ataxia, but recovered without any sequelae soon after high dose steroid therapy. IgG type of autoantibodies against glutamate receptor $\delta 2$ (GluR $\delta 2$) were detected in the serum, but not in the cerebrospinal fluid in his early clinical course. It was suggested that autoantibodies against GluR $\delta 2$ might not have injured the tissue due to the immunological action, but might be induced as a consequence of cerebellar damage. Early steroid treatment for acute cerebellitis might have been effective to prevent the progress of the disease and improve the prognosis.

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1. Introduction

Acute cerebellitis is a neurological condition consisting of nausea, headache, and loss of consciousness in addition to the acute onset of cerebellar symptoms, and sometimes accompanies fever and meningeal signs which are rarely seen in acute cerebellar ataxia (ACA) [1]. Neuroimaging studies by MRI are also useful to differentiate acute cerebellitis from ACA and other diseases.

Although the etiology of acute cerebellitis is theoretically divided into three categories, direct infection, parainfection, and postvaccination, it is difficult to distinguish these three categories clinically. Autoantibodies

against the cerebellum have been detected in disorders such as non-familial olivopontocerebellar degeneration or paraneoplastic cerebellar ataxia. Glutamate receptor $\delta 2$ (GluR $\delta 2$) is predominantly expressed in cerebellar Purkinje cells, and plays a critical role in cerebellar functions. We report a patient with acute cerebellitis who had the IgG type of anti-GluR $\delta 2$ antibodies in the serum in his early clinical course and was successfully treated with high dose corticosteroid administration.

2. Case study

A 13-year-old boy was admitted to the hospital because of severe and intermittent headache. He had a fever and mild headache six days before admission and was treated with acetaminophen. He became afebrile at the next day but complained of worsening headache.

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