

Case report

Refractory epilepsy accompanying acute encephalitis with multifocal cortical lesions: Possible autoimmune etiology

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Abstract

We report on a 14-year-old male suffering from acute encephalitis, whose clinical course met the criteria for acute encephalopathy with refractory, repetitive partial seizures (AERRPS). He presented with extremely refractory partial and secondary generalized seizures, and required high-dose barbiturate infusion therapy for 57 days under mechanical ventilation. Seven weeks after onset, the seizures were ameliorated by treatment with sodium bromide, carbamazepine, clobazam, and high-dose phenobarbital. Magnetic resonance imaging on day 14 of admission showed multifocal cortical lesions scattered in the bilateral hemispheres; these disappeared on day 34. Diffuse and mild atrophy of the cerebral cortex, and moderate atrophy of the hippocampus, appeared by day 61. Serum anti-glutamate receptor $\alpha 2$ autoantibodies were detected on day 2. The patient was discharged after 113 days of admission with intractable epilepsy, memory disability, and regression of intelligence. We discuss the etiological significance of the multifocal lesions, which are unusual findings on neuroimaging of AERRPS.

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1. Introduction

Awaya et al. [1] reported on children with a “peculiar type of post-encephalitic epilepsy”, presenting with extremely refractory partial seizures during a prolonged acute phase and sequelae of intractable epilepsy. Approximately 40 similar cases have been reported in Japan. Sakuma et al. [2] proposed the terminology “acute encephalitis with refractory, repetitive partial seizures (AERRPS)” for this entity, with the criteria being: (1) prolonged acute phase of more than 2 weeks; (2) partial seizures of the same symptoms persisting from the

acute phase to convalescence; (3) seizures frequently evolving into convulsive status especially during the acute phase; (4) marked intractability of seizures; and, (5) exclusion of related disorders such as known viral encephalitis or metabolic disorders. Additional features including responsiveness to certain antiepileptic agents, and the presence of serum anti-glutamate receptor antibodies were reported in some cases [1,3]. AERRPS is now an accepted clinical entity in Japan, based on these characteristics; however, this disease entity has not achieved worldwide consensus, despite recent reports of cases whose clinical features meet the criteria of AERRPS [4,5]. Here, we describe a patient whose clinical course was compatible with a diagnosis of AERRPS, in which multifocal cortical lesions were detected on magnetic resonance imaging (MRI). This finding is quite

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unusual in viral encephalitis, and suggests an autoimmune basis for the pathogenesis. Such a finding has also not been described in patients with AERRPS, and we discuss the associated nosological concerns.

2. Case report

2.1. Clinical course (Fig. 1)

A 14-year-old boy presented with fever and headache persisting for 3 days. Following a 5-day remission, the symptoms reappeared in association with vomiting and eruption, as well as generalized tonic convulsion. On admission, the patient was stuporous. Body temperature was 37.9 °C. Scarlet fever-like eruption was noted on the trunk, but otherwise there were no remarkable findings. Cranial computed tomography (CT) was normal. Routine assays of blood and cerebrospinal fluid (CSF) were within normal range, and electroencephalography (EEG) showed sporadic diffuse slow waves.

On the day of admission, he developed bilateral facial twitching and eyelid fluttering, which were controlled with a bolus infusion of diazepam and continuous intravenous administration of midazolam. He remained stuporous during the interictal period. On day 2, frequent twitching in the face, hand, and foot recurred, often evolving into generalized convulsions. Treatment with a suppository of phenobarbital (PB), as well as intravenous phenytoin, pyridoxine, and lidocaine were not

effective. The seizures lasted for 0.5–2 min and appeared every few minutes, sometimes culminating in secondary generalized tonic-clonic convulsions, or an epileptic status. High-dose PB with a concentration of 150 µg/ml, or continuous infusion of thiamylal at 7 mg/kg/h under mechanical ventilation, did not suppress the seizures completely. High-dose immunoglobulin and steroid pulse therapy of 30 mg/kg/day methylprednisolone for 3 days also showed no beneficial effect. Ictal EEG showed focal rhythmic 5 or 10 Hz spikes in the bilateral frontal, central or occipital areas, with occasional generalization.

On day 27, the thiamylal was replaced by thiopental sodium (TP), which controlled the seizures when administered at a dosage of 2–6 mg/kg/h. At this time, the EEG showed a burst-suppression pattern. Under infusion of these barbiturates during the acute phase, we tried several oral antiepileptic drugs: sodium valproate, zonisamide, clobazam (CLB), sodium bromide (NaBr), and carbamazepine (CBZ). Only CLB produced any improvement in this acute phase.

The seizures ceased after 3 weeks of therapy with TP, which was gradually replaced by oral PB. Brief partial seizures recurred and persisted 0–5 times per day. Thereafter, the patient gradually recovered and was able to perform normal daily activities without aid. On day 113, he was discharged under treatment with PB, CLB, NaBr, and CBZ, which were effective to some degree at this stage of the illness. He had sequelae of intellectual regression with an intelligence quotient of 66, disability

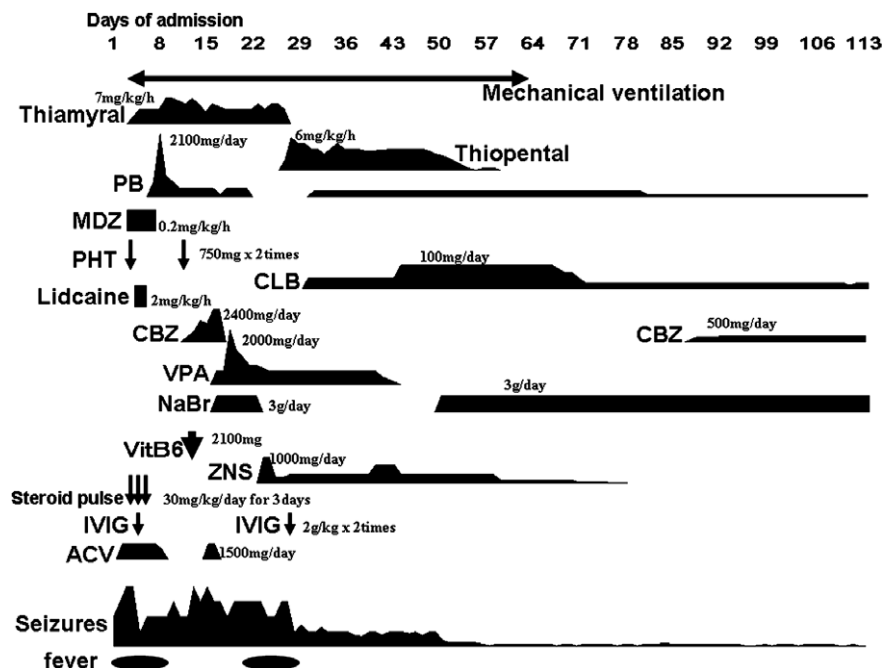


Fig. 1. Clinical course of the patient. Dosage of each drug refers to the maximum dose of continuous (thiamylal, thiopental, MDZ, and lidocaine) or one-shot (PHT, Vit.B6, steroid, IVIG, and ACV) intravenous injection or oral intake (PB, CLB, CBZ, VPA, NaBr, and ZNS). PB, phenobarbital; MDZ, midazolam; PHT, phenytoin; CLB, clobazam; ZNS, zonisamide; CBZ, carbamazepine; VPA, sodium valproate; NaBr, sodium bromide; IVIG, intravenous immunoglobulin; ACV, acyclovir.

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) ϵ 2 IgM and anti-GluR ϵ 2 IgG autoantibodies were positive on day 2. Serum anti-GluR δ 2 IgM and IgG (on day 2), CSF anti-GluR ϵ 2 and GluR δ 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 \times 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</i> virus (VZV)	(day 3)	
Cytomegalovirus, adenovirus, Japanese encephalitis virus, <i>Rubella</i> virus, 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 ϵ 2, IgM-GluR ϵ 2	(day 2)	Positive
IgG-GluR δ 2, IgM-GluR δ 2	(day 2)	Negative

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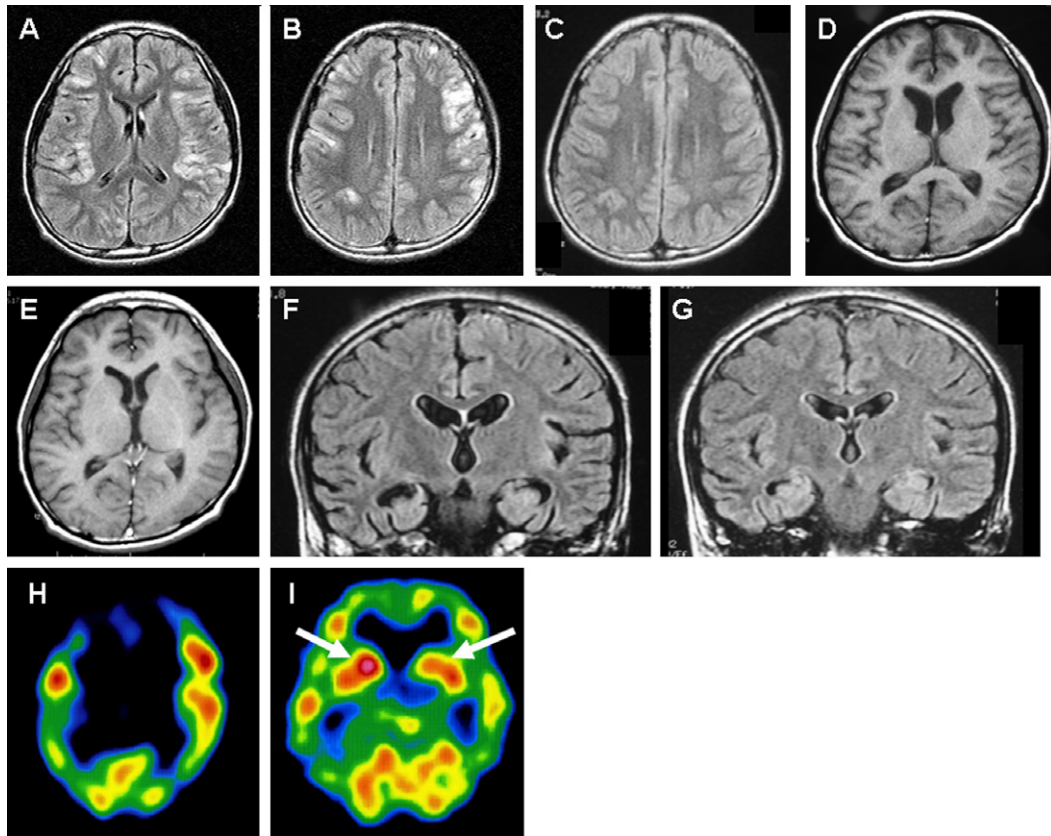


Fig. 2. Neuroimaging of the patient. Magnetic resonance imaging (MRI) [A–C, F, and G: fluid-attenuation inversion recovery (FLAIR) images; (D) and (E), T1-weighted images] and single photon emission-computed tomography (SPECT) (H and I) of the patient. On day 14 of illness (A and B), multiple cerebral 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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