were no sera from 33 patients with 2 Basedow's disease, 4 post-infectious acute disseminated encephalomyelitis (ADEM), 2 viral encephalitis, 2 Creutzfeldt–Jakob disease, other autoimmune disorders or collagen diseases with neurological symptoms, including 4 multiple sclerosis, 4 myasthenia gravis, 2 paraneoplastic neurological syndrome associated with Hu-antigen, 2 rheumatoid arthritis, 3 systemic lupus erythematosus, 3 Sjögren syndrome, 3 Behçet disease, 2 mixed connective tissue disease that showed any immunological reaction to the recombinant NAE (Fig. 2). This confirmed our recent finding that anti-NAE autoantibodies were highly specific to HE.

3.2. Neurological manifestations

The neurological manifestations of patients are summarized in Table 1 and Fig. 3. There is no significant difference in the responsiveness to steroid between NAE(+) (excellent, 9; good, 5; fair 3) and NAE(−) patients (excellent, 3; good, 4; fair 1) but a bit better response in NAE(+) (Table 1 and Fig. 3). Consciousness disturbance appeared most frequently (80%, 20 of 25; 82%, 14 of 17 in NAE(+), 75%, 6 of 8 in NAE(−)). Seizures were also common (68%, 17 of 25; 64%, 11 of 17 in NAE(+), 75%, 6 of 8 in NAE(−)). Cognitive impairments/psychiatric symptoms such as memory disturbance, abnormal behaviors or hallucination occurred in 76% (19 of 25; 76%, 13 of 17 in NAE(+), 75%, 6 of 8 in NAE(−)). Involuntary movements including myoclonus/tremor and chorea were also present (52%, 13 of 25) with no difference between NAE(+) (52%; 9 of 17) and NAE(−) (50%; 4 of 8). Ataxia was much less frequent (12%, 3 of 25 in total; 5%, 1 of 17 in NAE(+); 25%, 2 of 8 in NAE(−)).

3.3. Laboratory and MRI findings

The laboratory and MRI findings of patients were summarized in Table 1 and Fig. 4. EEG abnormalities such as slow background activities and/or episodic spikes/slow waves showed very high prevalence (90%, 20 of 22) in patients examined, with

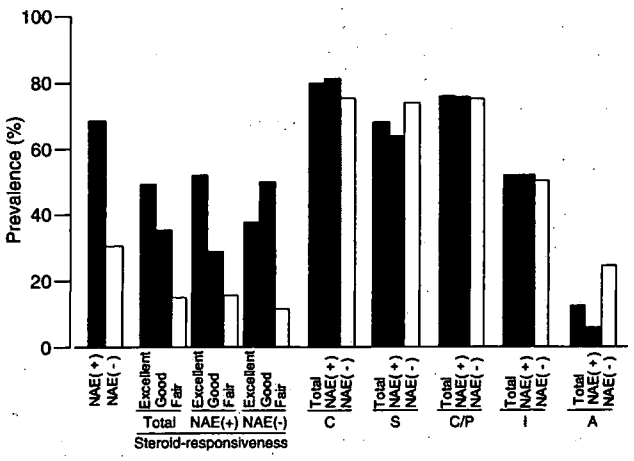

Fig. 3. Neurological manifestations compared between patients with and without anti-NAE autoantibodies. NAE(+), presence of anti-NAE autoantibodies; NAE(−), absence of anti-NAE autoantibodies. C, consciousness disturbance; S, seizures; C/P, cognitive impairment/psychiatric symptoms; I, involuntary movements: A, ataxia.

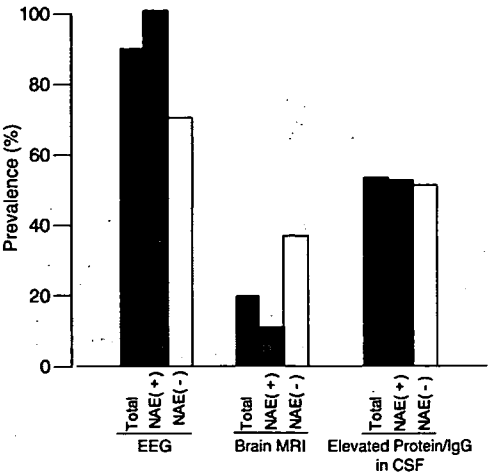

Fig. 4. Laboratory and MRI findings in patients.

a difference between NAE(+) (100%, 15 of 15) and NAE(−) (71%, 5 of 7) ($p<0.05$). By contrast, abnormalities on brain MRI were much less frequent (20%, 5 of 25), with no difference between NAE(+) (11%, 2 of 17) and NAE(−) (37%, 3 of 8). The elevated protein/immunoglobulin G in CSF was present (54%, 12 of 23), with no difference between NAE(+) (53%, 8 of 15) and NAE(−) (50%, 4 of 8).

4. Discussion

After Brain et al. reported the first case of encephalopathy associated with HT, there has been a debate on the nosology and nature on HE, despite the accumulation of over 100 reported cases (Behan et al., 1988; Chaudhuri and Behan, 2003; Chong et al., 2003). It is because of the wide spectrum clinical features in patients with HE, the high prevalence of anti-thyroid antibodies in the normal population (e.g. 5–10% in male, 10–25% in female in Japan), and the lack of specific diagnostic marker. HE patients presented with a variety of clinical features such as acute encephalopathy, psychosis/cognitive impairment, ataxia, recurrent acute disseminated encephalomyelitis (ADEM), involuntary movements (chorea, myoclonus or tremor) and Creutzfeldt–Jakob disease-like clinical features (Behan et al., 1988; Chaudhuri and Behan, 2003; Chong et al. 2003; Ferracci et al., 2004; Fatourechi, 2005).

In this study, the patients who presented with encephalopathy and fit the criteria for HE based on the presence of anti-thyroid antibodies and the responsiveness to immunotherapy such as steroids, immunosuppressants and/or IVIg/plasmapheresis, demonstrated a high prevalence of anti-NAE autoantibodies in their sera (68%; 17/25; $p<0.001$, compared to patients with HT without encephalopathy [10%, 2/20]). This strongly supported our previous finding of a high prevalence (83%, 5 out of 6) of anti-NAE autoantibodies in patients with HE (Fujii et al., 2005). There were no sera from patients with other disorders including autoimmune conditions or collagen diseases that showed any immunological reaction to recombinant NAE, suggesting a high specificity of anti-NAE autoantibodies to encephalopathy with HT. One third of patients examined here did not have anti-NAE

autoantibodies in their sera. NAE(−) patients can be associated with different autoantibodies because our preliminary study demonstrated other possible autoantibodies detected in NAE(−) patients (data not shown, in progress).

In the neurological features of the patients examined here, consciousness disturbance (80%), seizures (68%), cognitive impairment/psychiatric symptoms (76%) and involuntary movements (52%) were common in HE, while ataxia (12%) was much less frequent. As the clinical form, acute encephalopathy (AE) was the most common (76%). Chaudhuri and Behan investigated 18 cases of HE clinically and immunologically, and indicated that headaches (90%), seizures (67%), focal neurological deficit (67%), stupor/coma (67%), psychosis (50%) were common and ataxia (16%) and hemiparesis (16%) were rare (Chaudhuri and Behan, 2003). Although Chaudhuri and Behan emphasized myelopathy as a common clinical feature in HE with a similarity to ADEM, myelopathy was not observed in patients examined in our study. In addition, the anti-NAE autoantibodies were not detected in 4 patients with post-infectious ADEM in our study, suggesting that the clinical form of ADEM appeared relatively less frequent than Chaudhuri and Behan supposed.

In this study, relapsing was less frequent (16%) than that in Chaudhuri and Behan's study (67%). Chaudhuri and Behan carefully followed-up their patients with HE over a period of 16 years, and clarified the outcome of HE patients (Chaudhuri and Behan, 2003). The low frequency of relapse in our study seemed to depend on the short periods of the clinical courses examined (most patients were within one year). Thus, this short-term observation could have caused an underestimation of the relapse rate of HE in our study.

On laboratory/MRI findings in our study, EEG abnormalities were common (90%), compared to the low prevalence of abnormalities on brain MRI (20%). Elevation in CSF protein/IgG in our study was also a common feature (54%). Although there was no major difference in patients between NAE(+) and NAE(−) in the clinical features and laboratory/MRI findings in the present study, EEG abnormalities appeared at higher frequency and steroids tended to be more effective in NAE(+) patients.

Chaudhuri and Behan recommend immunosuppressants (e.g. azathioprine) as a potentially effective treatment besides steroids from the perspective of T-cell sensation to the antigen in HE (Chaudhuri and Behan, 2003). Although steroids have been widely administered to patients with HE in our study and others, steroid-responsiveness shows a temporally limited quality and other immunosuppressant agents are necessary to sustain long-term clinical response (Chaudhuri and Behan, 2003). Indeed, in our patient (Case 24) who showed an excellent steroid-responsiveness on the initial attack but poor response on the following attacks, this was successfully prevented from relapsing after the administration of an immunosuppressant (azathioprine) was started.

Chong et al. assumed that the combination of encephalopathy, presence of anti-thyroid antibodies and responsiveness to steroid administration seemed unlikely to be due to chance, and, however, there was no evidence of a pathogenic role for anti-thyroid antibodies in encephalopathy associated with HT (Chong et al., 2003). On the contrary, Ferracci et al. speculated that autoimmunity to neural antigens cross-reacting with thyroid antigens was the pathogenic basis of encephalopathy with HT (Ferracci et al., 2004). Additionally, the neuropathological finding of an autopsied case and brain perfusion studies in patients with HE suggested brain vasculitis, and supported the disease entity of HE (Nolte et al., 2000; Zettinig et al., 2003; Piga et al., 2004).

Sawka et al. searched for cases of encephalopathy associated with HT in Mayo Clinic from 1950 to 1996 years, and assumed that HE could be a rare autoimmune condition associated with a common autoimmune HT, in part with unknown origin (Sawka et al., 2002). In the present study, however, a large number of cases of encephalopathy associated with HT were still present, and two thirds of these patients carried anti-NAE autoantibodies even after neurological specialists had carefully excluded other possible conditions causing encephalopathy. Such discrepancy may be driven from differences between the profiles of patients treated by neurologists and compared to those treated by endocrinologists; i.e. neurologists see patients with neuropsychiatric symptoms of various causes while endocrinologists more frequently see patients with HT and less frequently encephalopathy.

Fatourechi et al. stated that a distinct clinical entity of encephalopathy associated with HT was present but the use of the term "Hashimoto's encephalopathy" was unfavorable until the pathogenesis of this condition was better defined (Fatourechi, 2005). Although the pathogenic role for anti-NAE autoantibodies in HE remained obscure, the present study demonstrated that anti-NAE autoantibodies were more specific to HE than anti-thyroid antibodies. This strongly suggests that "Hashimoto's encephalopathy" is a distinct clinical entity associated with HT although the underlying immunological condition should be better defined. Both the anti-NAE autoantibodies and anti-thyroid antibodies can be generated in the common immunological background related to HT, such as T-cell mediated antibody production (Weetman and McGregor, 1994; Stassi and De-Maria, 2002).

In conclusion, anti-NAE autoantibodies, in addition to anti-thyroid antibodies, are emphasized to as a useful serological diagnostic marker of HE, and should be included in the diagnostic criteria of this condition. Physicians must more attentively consider the possibility of HE, and test serum for anti-NAE autoantibodies as well as carefully excluding other conditions causing encephalopathy in patients with HT.

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Letter to the Editor

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Encephalitis of Unknown Etiology with Anti-GluR ε2 Autoantibody, Showing Divergent Neuroradiologic and Clinical Findings

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Dear Sir,

A patient with severe temporal lobe atrophy, memory disturbance, and personality deterioration caused by encephalitis of unknown etiology was admitted for evaluation. Cerebrospinal fluid (CSF) studies disclosed no virus, but autoantibodies were detected against the N-methyl-D-aspartate-type glutamate receptor epsilon 2 (GluR ε2). GluR ε2 channels have been implicated in synaptic plasticity and localization associated with neural development and learning [1]. Recently autoantibodies against GluR ε2 were found in some patients with Rasmussen's encephalitis [2] and nonherpetic limbic encephalitis [3], suggesting an autoimmune pathogenesis for some encephalitis. Surprisingly in our case, neuropsychiatric symptoms did not worsen when progressively severe neuroradiologic alterations in the temporal lobes appeared after hospitalization.

Case Report

A 36-year-old man was admitted to our hospital for evaluation concerning the etiology of severe memory impairment. Neither he nor family members had a prior history of epilepsy, dementia, autoimmune diseases, or neuropsychiatric disorders. He had no previous history of alcohol and/or drug abuse. He had been diagnosed with diabetes 2 years previously, but was lost to follow-up before any treatment. He had had a headache which lasted for several days 5 months before admission to our hospital. A short time later he developed severe memory impairment and pathologically increased appetite; he repeatedly stole food, even eating pet foods.

Table 1 presents laboratory, neuropsychologic, electroencephalographic, and neuroradiologic findings over time. Biochemical examinations were normal except for a serum glucose concentration of 320 mg/dl and a glycosylated hemoglobin (HbA1c) value of 15.7%. Antibodies in the serum for HIV and syphilis were negative. The Wechsler Adult Intelligence Scale-Revised (WAIS-R) showed a verbal intelligence quotient (VIQ) of 85, a performance IQ (PIQ) of 85, and a full scale IQ (FIQ) of 84. The Wechsler Memory Scale-Revised (WMS-R) showed very poor general memory, visual memory, verbal memory, and delayed-recall memory (scores of <50, 64, <50, and <50, respectively), while the score on the attention-concentration scale was within the normal range (a score of 106). Electroencephalography (EEG) showed normal background activity and no epileptic discharges. Routine CSF study showed no abnormalities except for moderate elevation of protein (60 mg/dl; normal range 10–40). CSF cell count was 3/mm^3 (normal range 1–6).

MRI of the brain demonstrated severe diffuse cerebral atrophy, with accentuation in the mesial temporal lobes including the hippocampi (fig. 1A), which was suggestive of progressive dementia. However, repeat MRI (fig. 1B) on the 13th hospital day disclosed a new area of high signal intensity centered at the right superior temporal gyrus, suggesting progressive encephalitis. Despite this striking signal alteration, CSF protein and cell counts were within the normal range on three occasions, days 14, 49, and 88. Body temperature remained within the normal range throughout the course of illness. Polymerase chain reaction (PCR) did not detect herpes simplex virus (HSV)-1 or 2, human herpes virus-6 or 7, cytomegalovirus, or Epstein-Barr virus in the CSF on days 49 or 88. Systemic radiologic examination did not disclose a malignant neoplasm while anti-Hu antibodies were not detected in the CSF at a dilution of 1:2,000 by Western blotting, probably excluding paraneoplastic limbic encephalitis. Blood sugar remained well below 200 mg/dl.

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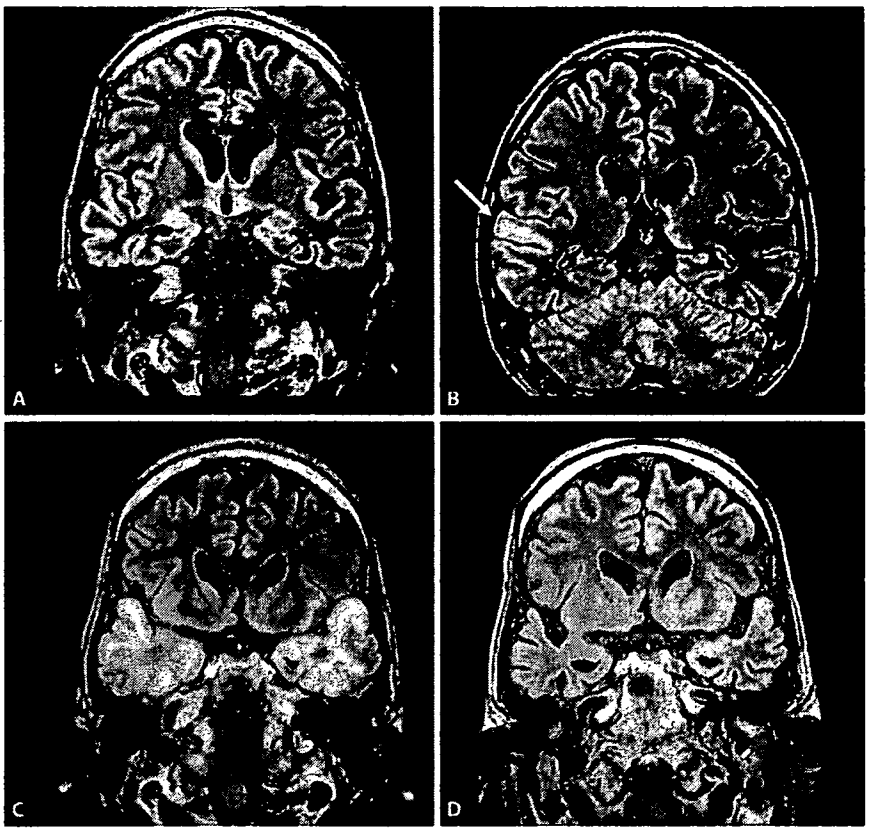

Fig. 1. Coronal FLAIR MRI sequences. **A** Day 4: diffuse cerebral atrophy is seen, especially in the mesial temporal lobes including the hippocampi. **B** Day 13: a new area of high signal intensity is centered in the right superior temporal gyrus. **C** Day 46: severe signal alteration with edema affects extensive areas of the temporal lobes. **D** Day 172: abnormal signal disappeared and brain atrophy remained the same as on day 4 (**A**).

Table 1. Laboratory, clinical, and neuroradiologic course

	Hospital day																		
	0	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150	//	300
CSF																		
Cell count	3		1			0				2								
Protein	60		37			34				40								
Anti-Hu			negative															
Anti-GluR										positive								
Viral DNA PCR						negative				negative								
WAIS-R (FIQ)	84								91							116		90
WMS-R																		
General	<50								59		58					61		<50
Attention	106								101		113					113		101
EEG BGA	8-11z alpha				9 11z alpha					9-11z alpha								9-11z alpha
MRI	↑ general atrophy		↑ right temporal high intensity		↑ bil. temporal high intensity			↑ bil. temporal high intensity							↑ high intensity: disappeared	↑ general atrophy only		

BGA = Background activity; bil. = bilateral.

On day 46, MRI showed that the severe signal alteration with edema had extended to wide areas of the temporal lobes (fig. 1C). Diffusion-weighted image (DWI) also demonstrated new areas of high intensity at the temporal lobes. Moreover, ^{99m}Tc single-photon emission computed tomography (SPECT) showed significant hyperperfusion in mesial and lateral portions of both temporal lobes, suggesting encephalitis of unknown etiology localized to the temporal lobes. Surprisingly, however, the neuropsychiatric status did not deteriorate, and disturbances of consciousness or epileptic seizures did not occur. On reexamination, WAIS-R and WMS-R showed no significant change (VIQ 85, PIQ 100, FIQ 84, and a score of 101 on the attention-concentration scale). MRI findings had not improved by day 74 despite 10 days of acyclovir therapy. CSF immunoassay for 14-3-3 protein was negative, suggesting that broad, persistent neural injury was not actively progressing. Repeated EEG showed no abnormalities of background activity or epileptic discharges. The patient did not manifest any epileptic seizures, including epilepsia partialis continua and nonconvulsive status epilepticus. Although we did not examine CSF for myelin basic protein or oligoclonal bands, acute disseminated encephalomyelitis was unlikely since MRI signal alterations were diffuse rather than scattered, and repeated EEGs were within the normal ranges.

CSF obtained on day 88 was then examined for autoantibodies against GluR ε2, as these have been reported in some patients with nonherpetic limbic encephalitis [3]. Serum and CSF were tested for anti-GluR ε2 at dilutions of 1:20 and 1:15, respectively. Only CSF IgG, not IgM, autoantibodies were demonstrated. On day 172, the extent of signal alteration clearly had decreased, and the abnormal signal subsequently disappeared (fig. 1D). Overall brain atrophy remained the same as on admission. SPECT showed the disappearance of hyperperfusion in the temporal lobes; the mesial temporal areas now showed hypoperfusion. A third WAIS-R and WMS-R examination showed no notable change. Symptoms and neuroradiologic findings have remained stable after discharge from the hospital.

Discussion

We suspected that the patient initially might have had encephalitis of unknown etiology with severe residual memory impairment and marked atrophy of the mesial temporal cortex. We have had no similar clinical experience in which the first insult causing severe memory impairment was not evident as a history of disturbance of consciousness or epileptic seizure. Five months after the presumed first insult, findings indicated an encephalitis of uncertain etiology showing a marked discrepancy between worsening MRI findings and stable clinical status. Although MRI and SPECT showed severe signal alteration with hyperperfusion in the temporal lobes, neuropsychiatric symptoms did not deteriorate. We know of no reported case of encephalitis with such a divergent clinicoradiologic course. A previously reported case of nonherpetic limbic encephalitis in which neuroradiologic findings disappeared after 6 months showed no relapse [4]. Since some relapsing cases of herpetic encephalitis did not have HSV detectable in CSF by PCR [5], we could not exclude the possibility that his first insult represented herpetic encephalitis, but few clinical symptoms characteristic of herpetic encephalitis were present.

Although the patient's illness may have been caused by an undetected infectious agent, we would propose a different explanation: autoimmune encephalitis. A cell-mediated immune response may have caused tissue damage during an infectious episode 5 months before admission, resulting in production of autoantibodies against GluR ε2. Alternatively, antibodies developing in response to the infectious agent may later have acted as autoantibodies against GluR ε2 because of molecular homology.

Apparent clinical stability in the presence of dramatically worsening neuroradiologic findings during hospitalization may have reflected an initial insult before admission so severe that the WAIS-R and WMS-R could not detect a further decline in temporal lobe function during the admission. Although we could not determine whether autoantibodies against GluR ε2 were the cause or the result of the encephalitis of unknown etiology, we believe that the autoantibodies had a profound influence on the neuroradiologic course.

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PostScript

LETTERS

Hashimoto's encephalopathy presenting with progressive cerebellar ataxia

Hashimoto's encephalopathy is an autoimmune encephalopathy that came to be regarded as a new clinical entity distinct from myxo-oedema encephalopathy, associated with Hashimoto's thyroiditis.[1 2]

Hashimoto's encephalopathy has a wide clinical spectrum with various neuropsychiatric features. The detection of antithyroid antibodies in patient sera is helpful but not sufficient for the diagnosis of Hashimoto's encephalopathy because of the high prevalence of antibodies in the normal population.

Recently, we reported serum autoantibodies against the amino (NH_2) terminal region of α enolase (NAE) as a useful diagnostic marker of Hashimoto's encephalopathy.[3]

We describe here a patient with Hashimoto's encephalopathy, who presented with progressive cerebellar ataxia with mild abnormality on electroencephalography (EEG) and showed marked improvement after steroid administration. The patient was diagnosed as having Hashimoto's encephalopathy owing to the presence of the anti-NAE antibodies as well as antithyroid antibodies in the serum.

A 41-year-old woman, who had a normal dietary history, became aware of a slight unsteadiness while walking and mild dysarthria in December 2003. She had no familial history of neurological disorders or episodes of seizures. The symptoms gradually worsened, and she was admitted to the University of Fukui hospital in September 2004 because she could not stand or walk without support.

Neurological examinations showed severe gait ataxia, slurred speech and dysmetria on finger-to-nose and heel-to-knee manoeuvres. Cognitive functions and intellectual performance were normal. Ocular movement was full and smooth and without nystagmus. Deep tendon reflexes were normal and without any pathological reflex. No apparent paresis abnormal sensations including deep sensations, extrapyramidal signs or autonomic dysfunctions were found.

Magnetic resonance imaging of the brain did not detect any atrophy of the cerebellum or any abnormal signal. EEG showed diffuse slow-wave activities (7–8 Hz) without any epileptic discharge. Analysis of the cerebrospinal fluid did not show any pleocytosis or increases in protein (15 mg/dl) and immunoglobulin (Ig)G (1.2 mg/dl) levels. Peripheral blood cell counts, electrolytes, liver and kidney functions, and levels of lactate, ammonia, vitamins B_1, B_{12} and E were all normal. Serological markers specific for collagen diseases such as antinuclear, anti-DNA, anti-Sm, anti-RNP, anti-SSA, anti-SSB, anti-glutamic acid decarboxylase (GAD) antibodies, c-antineutrophil cytoplasmic antibodies and myeloperoxidase-antineutrophil cytoplasmic antibodies were either negative or in the normal range. Titters of antibodies against Herpes simplex, Varicella-zoster, Epstein-Barrvirus, cytomegalovirus and echo viruses were not raised in the serum or in the cerebrospinal fluid. Anti-Hu, anti-Yo and anti-Ri antibodies were also negative. Tumour markers such as carcinoembryonic antigen, cancer antigen (CA)19-9 and CA125 were normal. Investigation for malignancy did not detect any sign of malignant disease. Gene analyses did not detect any mutation for hereditary spinocerebellar ataxia (SCA1, SCA6, Machado–Joseph disease and dentate-rubro-pallido-luysian atrophy) or mitochondrial diseases (MELAS and MERRF).

Investigation for thyroid showed euthyroidism (thyroid-stimulating hormone (TSH), 1.7 μU/ml; normal, 0.4–4.0 μU/ml, free T_3, 3.4 pg/ml; normal, 2.4–4.3 pg/ml, free T_4, 0.9 ng/dl; normal, 0.9–1.8 ng/dl) and raised levels of antithyroid peroxidase (50.0 U/ml; normal, 0–0.3 U/ml) and antithyroglobulin antibodies (4.9 U/ml; normal, 0–0.3 U/ml). Anti-NAE antibodies in the serum—a diagnostic marker of Hashimoto's encephalopathy—were strongly positive before steroid treatment, then changed to a weak signal on an immunoblot, after treatment, determined using its recombinant protein expressed in human cultured cells, as described previously (fig 1).[3] The ethics committee of the University of Fukui approved this research. Written permission was obtained from the patient.

After intravenous administration of high-dose methylprednisolone (1 g/day) for 3 days, followed by oral administration of prednisolone (30 mg/day), the ataxia improved markedly, and the patient was able to walk unaided 3 weeks after the start of the treatment. The ataxia almost disappeared after continuous treatment for 3 months. Severity of ataxia was evaluated by the size of the estimated area when the patient stood on a stabilimeter. Estimated areas became markedly smaller on the stabilimeter after steroid treatment: pre-treatment area, $13.9 \times 8.4 = 116.76$ cm^2, post-treatment area, $4.8 \times 3.4 = 16.32$ cm^2. Slow-wave activities on EEG partially improved after the treatment.

Pure cerebellar ataxia can be caused by various reagents (alcohol or drugs), or may accompany vitamin deficiencies, viral infections, collagen diseases, autoimmune conditions (anti-GAD antibodies), spinocerebellar degenerations, neoplasm or mitochondrial diseases with or without cerebellar atrophy. Although anti-GAD antibodies were detected in the sera from patients with ataxia and type 1 diabetes,[4] the antibodies were not detected in our patient. Other possible causes of ataxia were excluded by the clinical history, and laboratory and radiological findings in the present case. Although hypothyroidism is another well-known cause of ataxia, she had normal thyroid functions.

Patients with Hashimoto's encephalopathy present with a variety of neuropsychiatric symptoms or signs such as hypertonia, tremors, myoclonus, choreoathetosis, seizures, dementia, psychiatric symptoms and strokes.[1 2] Ataxia is also reported in some patients with Hashimoto's encephalopathy.[2 5] Compared with these reported cases of Hashimoto's encephalopathy with ataxia, the clinical findings in our patient are unique: (1) absence of neurological findings other than ataxia except for mild EEG abnormality and (2) the insidious onset and slow progression of ataxia. Other reported cases of ataxia showed acute or subacute progressions accompanied by other neurological symptoms or signs.[2 5] Selim and Drachman[5] reported six patients with cerebellar ataxia associated with

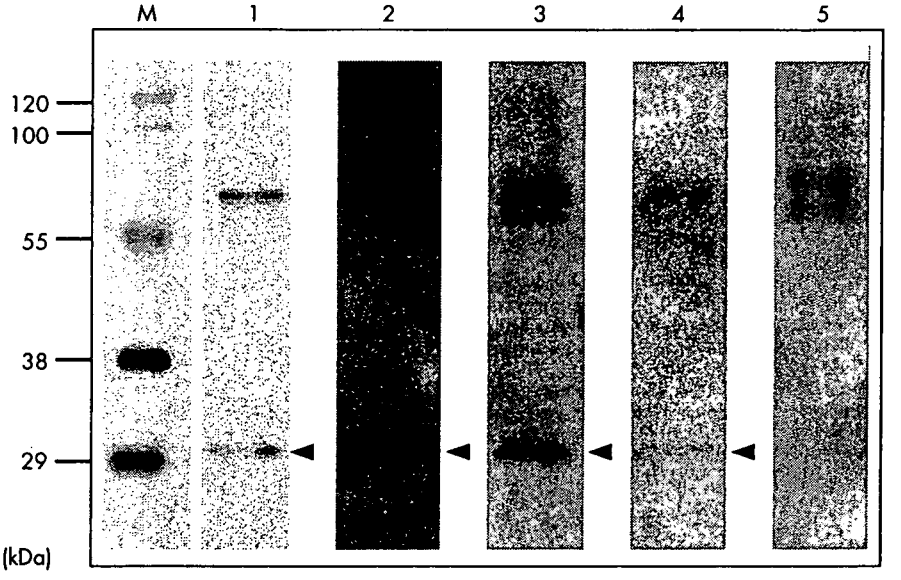

Figure 1 Immunoblot of a recombinant amino (NH_2) terminal region of α enolase (NAE) with sera from an ataxic patient with Hashimoto's encephalopathy. M, molecular weight marker; lane 1, recombinant NAE protein; lane 2, serum from a positive control (patient with Hashimoto's encephalopathy, lanes 3, serum from the present case before steroid treatment; lane 4, serum from the present case after steroid treatment; lane 5, serum from a normal control. Arrowheads indicate the position of NAE. Sera were diluted 300-fold. A strong signal against the NAE was detected in serum from the present case, and became weaker after steroid administration.

Hashimoto's thyroiditis, in most of whom cerebellar atrophy was shown on magnetic resonance imaging. One of their reported cases was treated by intravenous immunoglobulin IgG, and ataxia partially improved.[3] Although responsiveness to intravenous immunoglobulin suggested autoimmune mechanisms in the pathogenesis of ataxia in this patient, it remains uncertain whether or not ataxia and cerebellar atrophy were aetiologically associated with Hashimoto's thyroiditis. By contrast, our patient with progressive ataxia had a positive serological diagnostic marker, anti-NAE antibodies and showed an excellent response to steroid treatment, leading to a diagnosis of Hashimoto's encephalopathy.

In conclusion, this report suggests that a diagnosis of Hashimoto's encephalopathy is warranted in patients with progressive pure ataxia and anti-NAE antibodies are a useful serological marker of diagnosis. Moreover, Hashimoto's encephalopathy should be included in a differential diagnosis of a treatable ataxia.

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Letter to the Editor

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A Chronic Progressive Case of Enteroviral Limbic Encephalitis Associated with Autoantibody to Glutamate Receptor ε2

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Dear Sir,

Enteroviruses – coxsackieviruses and echoviruses – are frequent causes of aseptic meningitis, particularly in children. These viruses occasionally cause mild diffuse encephalitis but are rarely life threatening [1]. Herein, we describe a patient with chronic progressive limbic encephalitis caused by enterovirus, who was positive for autoantibodies against glutamate receptor (GluR) IgG-ε2 in the cerebrospinal fluid (CSF), and in whom lesions were found in the bilateral hippocampus, medial temporal lobe and hypothalamus.

A 22-year-old right-handed male was referred to us in August 1995 because of fever, a 3-week history of sudden onset memory loss, repetitive questioning and subacute progressive mental confusion. He had no pyramidal or extrapyramidal disturbances or cerebellar ataxia. Fluid-attenuated inversion-recovery (FLAIR) MRI of the brain showed hyperintense lesions in the bilateral hippocampal structures (fig. 1A). No enhancement was seen after intravenous gadolinium. Routine laboratory tests, including complete blood count and blood chemistry, were normal. Serum antinuclear, anti-DNA, anti-Sm, anti-SSA/SSB, anti-RNP, anti-Scl-70 and anti-Hu antibodies were negative. Analysis of CSF showed 5 cells/mm^3 (mononuclear), protein concentration 54 mg/dl and glucose 63 mg/dl. PCR for herpes simplex virus (HSV) DNA was negative. He was treated with acyclovir (30 mg/kg/day for 14 days) and betamethasone (16 mg/day for 7 days) based on the diagnosis of limbic encephalitis. His symptoms and MRI abnormalities gradually disappeared by the second hospital month, and he was discharged without any sequelae.

In November 1995, the patient again experienced a week of fever, headache and disorientation. At second admission, the patient was disoriented with memory impairment, including anterograde and retrograde amnesia. His Mini-Mental State Examination score was 17/30. FLAIR MRI again revealed hyperintense lesions in the bilateral hippocampal structures (fig. 1B). CSF examination showed 6 cells/mm^3 (mononuclear), protein concentration 42 mg/dl and glucose 56 mg/dl. He improved again by treatment with acyclovir and betamethasone.

In January 1998, this patient first experienced a generalized seizure. In October 1998, the seizures increased in frequency, and he was admitted to our hospital. He had an amnestic syndrome and his attention was easily distracted by irrelevant environmental incidents. He also exhibited sleep apnea syndrome, and MRI showed expansion and swelling of a left temporal lobe lesion (fig. 1C). He was intubated and treated with acyclovir, betamethasone and an anticonvulsant. In February 1999, although the left temporal lobe lesion had reduced, an expanded lesion was observed in the right temporal lobe with gadolinium enhancement in the hypothalamus (fig. 1D, E). Based on the suspected diagnosis of secondary autoimmune encephalitis, mizoribine (a purine, antimetabolic, immunosuppressive agent) was added. After that, no relapse of the symptoms of encephalitis or change in MRI findings was observed. In March 2001, MRI demonstrated severe atrophy of the bilateral hippocampal gyrus and uncus (fig. 1F). He was alert and followed simple commands. However, he had severe impairment of memory retention, and he could not be extubated because of sleep apnea syndrome.

Through the course of illness, the patient was examined extensively for the causes of chronic progressive limbic en-

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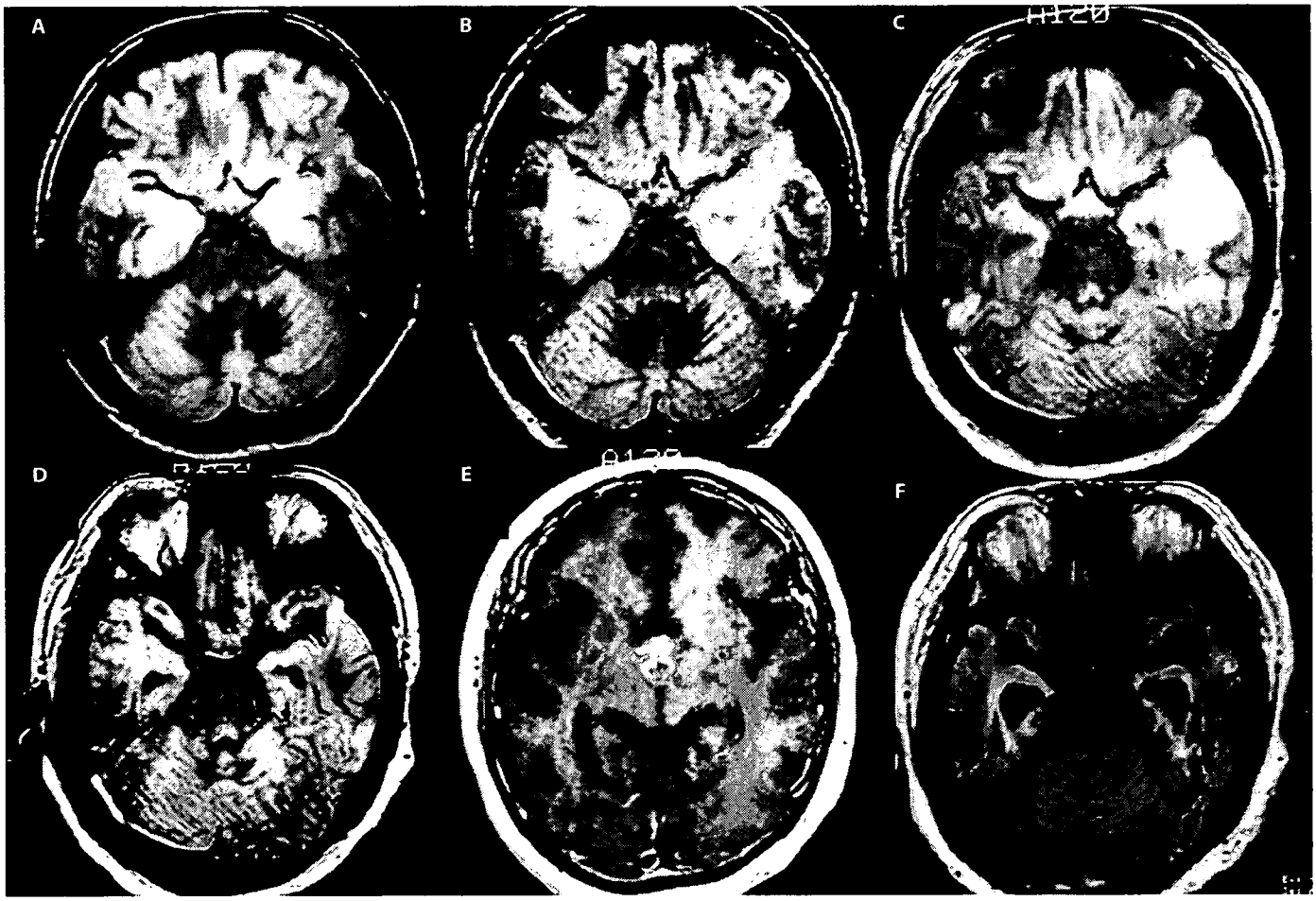

Fig. 1. Serial axial FLAIR MRI (**A–D, F**) and gadolinium-enhanced T_1-weighted image (**E**). Hyperintense lesions were seen in the bilateral hippocampus in August 1995 (**A**) and November 1995 (**B**). Expansion of the hyperintensity was seen in the left temporal lobe in January 1998 (**C**). In February 1999, hyperintensity was detected in the right temporal lobe and gadolinium enhancement in the hypothalamus (**D, E**). Severe atrophy of the bilateral hippocampus was observed in March 2001 (**F**).

cephalitis. He did not have any immunosuppressive disorders, such as HIV or agammaglobulinemia, and exhibited no abnormalities in either humoral or cell immunity. PCR studies of CSF were negative for HSV-1, HSV-2, cytomegaly, varicella-zoster and human herpes virus 6. Measles, rubella and mumps were also serologically excluded. However, RT-PCR [2] revealed enterovirus RNA in 2 CSF samples obtained in August and November 1995. Although enterovirus RNA was not detected after 1998, 3 CSF samples exhibited positivity for autoantibodies against GluR IgG-ε2 from 1998 to 1999 [3].

The nonpolio serotypes most often associated with central nervous system (CNS) infection include echoviruses 7, 9, 11 and 30; coxsackievirus B5 and enterovirus 71 [1]. Although infection with enterovirus 71 has a high mortality rate, most patients with enteroviral CNS infection exhibit a mild, generalized disease that resolves without sequelae. Severe and chronic cases of focal encephalitis have been reported [4–6], even in immunocompromised hosts [7, 8]. Hokezu et al. [9] reported an immunocompetent patient with recurrent limbic encephalitis in which RT-PCR was able to detect echovirus 7 RNA in CSF samples. The present case was remarkable because chronic progressive limbic encephalitis and severe sequelae occurred in this patient without immunodeficiency and autoantibodies against GluR IgG-ε2 being detected in the CSF of this patient. Limbic encephalitis is caused by HSV, nonherpetic viruses, paraneoplastic condition or autoimmune disorders. Recently, the presence of autoantibodies against GluR-ε2 in the CSF has been suggested to be involved in the parainfectious autoimmune pathogenesis of limbic encephalitis. Autoantibodies against GluR-ε2 may be associated with some symptoms of limbic encephalitis and sequelae (epilepsy and mental deterioration) of widespread encephalitis in childhood [10]. Moreover, they were speculated to be associated with atrophy of the hippocampus and impairment of memory. In

this case, we presumed that autoantibodies against GluR IgG-ε2 might have influenced the chronic progressive course. Enteroviral infection should be included in the differential diagnosis of limbic encephalitis. Furthermore, viral infections, such as enterovirus, can trigger the production of autoantibodies against GluR IgG-ε2 in patients with limbic encephalitis.

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Expression of vascular endothelial growth factor by plasma cells in the sclerotic bone lesion of a patient with POEMS syndrome

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Key words POEMS syndrome · VEGF · plasmacytoma · bone scintigraphy

Sirs: Bone lesions are frequently present in patients with POEMS syndrome [1, 2]. Since solitary bone lesions are often plasmacytomas, they must be aggressively treated with surgery or radiotherapy. We report a case of POEMS syndrome with a solitary bone lesion. In this patient, plasma cells in the osteosclerotic lesion were the source of vascular endothelial growth factor (VEGF).

A 42-year-old man developed distal dominant polyneuropathy two months after myocardial infarction. Following the onset of neurological symptoms, he exhibited edema, bristly skin, and swelling of the liver in the abdominal CT. Platelet counts were 822,000/mm^3, and immunoelectrophoresis demonstrated M-protein of IgA λ. Serum IL-6 and VEGF were measured using standardized ELISA (SRL, Inc., Tokyo, Japan). Although the IL-6 level was normal (2.1 pg/ml. Normal value; <4.0 pg/ml), the serum VEGF level was significantly elevated (18,500 pg/ml). He was diagnosed with POEMS syndrome. However, bone marrow aspiration from the ileum exhibited a normal appearance, and CT of the chest and the abdomen revealed no abnormal lesions, suggesting solitary or extramedullary plasmacytoma. Following steroid pulse therapy, treatment with prednisolone reduced the serum VEGF to 860 pg/ml with marked improvement of muscle weakness and skin lesions. Although the neuropathy remained clinically stable, he again exhibited edema and bristly skin 9 months after the pulse therapy, and the serum VEGF was increased to 5,120 pg/ml. Bone scintigraphy demonstrated a spot

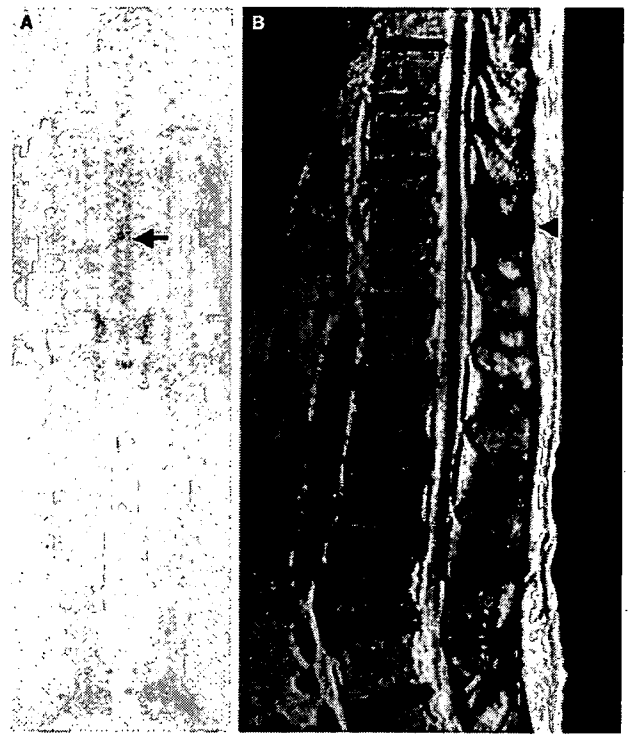

Fig. 1 (A) Bone scintigraphy showing a hot spot in Th12 (arrow). (B) T2 weighted MR image revealing a sclerotic lesion in the acantha of this vertebrae (arrowhead)

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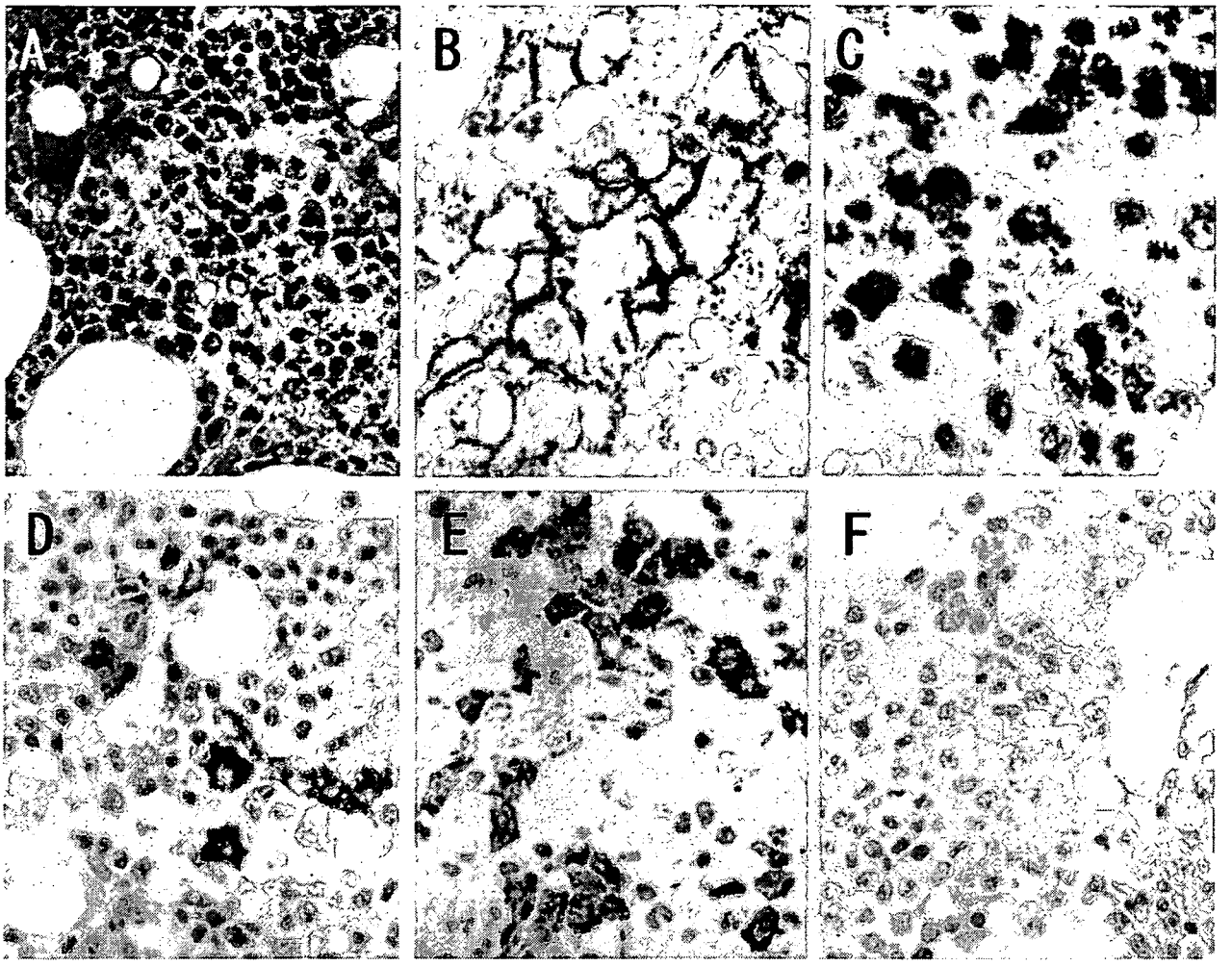

Fig. 2 (A) Hematoxylin and eosin staining exhibiting a slight increase in plasma cells in the osteosclerosic lesion. (B) Immunohistochemical stain of CD38. (C) Immunohistochemistry revealing immunoreactivity for VEGF in the cytoplasm of plasma cells. (D-F) Immunohistochemical stain of IgA (D), λ light chain (E), and κ light chain (F)

of abnormal accumulation in Th11 of the spine (Fig. 1). Bone radiography and MRI revealed a sclerotic lesion in the spinous process of the vertebra (Fig. 1). As solitary plasmacytoma was suspected, resection of the Th11 acantha was performed. After the operation, the serum VEGF levels gradually reduced to 620 pg/ml, and he has not shown the relapse of symptoms or re-elevation of the serum VEGF levels. The histological diagnosis of the resected Th11 acantha was plasmacytoma. Focal accumulation of CD38-positive plasma cells was found in the osteosclerotic lesion (Fig. 2A, B). Immunohistochemical staining for VEGF (anti-VEGF-Ab-2; Calbiochem, Darmstadt, Germany) demonstrated positive staining in the cytoplasm of most plasma cells (Fig. 2C). These cells were strongly positive for IgA and λ light chain (Fig. 2D-F).

POEMS syndrome is a rare multisystemic disease that is associated with plasma cell dyscrasia and is characterized by elevated serum VEGF levels [3, 4]. Since the symptoms of POEMS syndrome correlate well with changes in VEGF levels, VEGF is probably involved in the pathogenesis of POEMS syndrome [5, 6]. In this condition, plasma cells, platelets, tumor cells, endothelial cells, or non-myelinating Schwann cells have been proposed as a source of VEGF [7–9]. However, it remains unclear which cell type is responsible for the increased VEGF production. The present case suggests that plasma cells in the osteosclerotic lesions could be one major source of VEGF.

Many treatment strategies, including irradiation, corticosteroids, and alkylator-based therapy, have been used for POEMS syndrome [1, 2]. Recent report indicated the therapeutic potential in treating POEMS syndrome of using autologous peripheral blood stem cell transplantation with high-dose chemotherapy [10]. Corticosteroid and a combination of melphalan and corticosteroid are effective in approximately 22% to 56% of patients [1]. The present patient responded to steroid therapy. However, he did not show continued improvement. Previously, radiation or excision of bone lesions have been the most effective treatment for POEMS syndrome [1, 2]. Therefore, intensive examination for bone lesions should contribute to improved outcome in the treatment of POEMS syndrome.

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INTERNAL MEDICINE

CASE REPORT

Paraneoplastic Limbic Encephalitis Caused by Ovarian Teratoma with Autoantibodies to Glutamate Receptor

Sadahisa Okamoto[1], Teruyuki Hirano[1], Yukitoshi Takahashi[2], Taro Yamashita[1], Eiichiro Uyama[1] and Makoto Uchino[1]

Abstract

We report a rare case of paraneoplastic limbic encephalitis with autoantibodies to glutamate receptor (GluR) in the cerebrospinal fluid (CSF). The 35-year-old woman with consciousness disturbance was diagnosed initially as non-herpetic encephalitis. Her signs and symptoms improved with acyclovir and steroid pulse therapy. However, after the treatment, an ovarian tumor was discovered, and we detected autoantibodies to GluR in the CSF. A possible association between the ovarian teratoma and GluR is suggested.

Key words: paraneoplastic limbic encephalitis, ovarian teratoma, glutamate receptor

(DOI: 10.2169/internalmedicine.46.6466)

Introduction

Paraneoplastic limbic encephalitis (PLE) is a relatively rare, remote, non-metastatic neurological complication of carcinoma. PLE occurs subacutely in association with specific neuronal antibodies (1). In a Japanese survey, non-herpetic acute limbic encephalitis (non-herpetic ALE) was identified as a new subgroup of limbic encephalitis with the spectrum that includes herpes simplex encephalitis (HSE) and PLE (2, 3). Antibodies to glutamate receptor (GluR) in the central nervous system (CNS) are reported to be an important autoimmune factor in Rasmussen's encephalitis, epilepsia partialis continua, non-herpetic acute encephalitis, acute encephalitis and paraneoplastic cerebellar ataxia (4-7). Here, we describe a case of PLE associated with an ovarian teratoma and detect autoantibodies to GluR and an elevation of interleukin-6 (IL-6) in the CSF. This case illustrates a potential association between an ovarian teratoma and autoantibodies.

Case Report

A 35-year-old woman with confusion and impaired consciousness was transferred from a local general hospital to the neurology department of Kumamoto University Hospital. She had no symptoms until September 2004, she complained of headache, fever and short-term memory loss. Her symptoms gradually worsened. In the first hospital, the patient was diagnosed with viral encephalitis. Acyclovir (1.5 g per day) was administered intravenously for 11 days and 500 mg of methylprednisolone per day was added for 3 days. However, her condition did not improve, and she developed delusional thinking and auditory hallucinations.

When she was transferred from the first hospital, her temperature was 35.8℃. She showed psychiatric depression and an agitated confusional state with severe impaired attention, orientation and persistence of the depressive state. Physical examination revealed no abnormalities. Palpation of the abdomen revealed no mass. Neurological examination and systemic examination were entirely normal.

The results of laboratory tests including blood counts, biochemical tests, and C-reactive protein were within normal range. There were no evident endocrine or metabolic abnormalities. Tests for antinuclear antibodies were negative. Her CSF pressure was 75 mmH_2O. The fluid was clear and contained 15 cells/μl, 66 mg/dl of glucose, 34.7 mg/ml of protein, 2.96 mg/ml of IgG, 14.9 pg/ml of IL-6 (normal <9.7), 3.1 pg/ml of IL-4 (<11.6), 2.6 pg/ml of IL-2 (<4.6), 2.8 pg/ml of tumor necrosis factor-α (<6.2), 4.1 pg/ml of IL-10 (<6.1) and 7.1 pg/ml of interferon-γ (<46.6). Microscopic examinations of CSF for tumor cells and microorganism were

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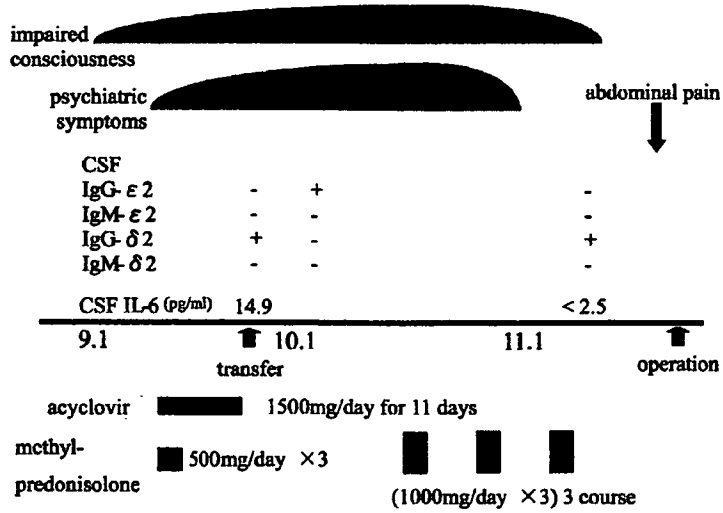

Figure 1. Clinical course. IgG-ε2, IgM-ε2, IgG-δ2, IgM-δ2: IgG and IgM autoantibodies to GluR ε2 or δ2.

negative, and cultures yielded no growth. There was no remarkable elevation of anti-viral antibody titers including mumps, rubella, echo, and varicella-zoster virus in paired serum samples. Polymerase chain reaction (PCR)-based tests for herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpesvirus-6, 7 (HHV-6, 7) in the CSF were negative. Magnetic resonance imaging (MRI) of the brain was normal.

Clinical course (Fig. 1)

The consciousness impairment progressed. The patient was restless, constantly in motion and talked incessantly and incoherently. We inferred that the limbic system was the locus for her psychiatric symptoms. A diagnosis of non-herpetic acute limbic encephalitis was made on the basis of negative findings of herpetic group (HSV, CMV, EBV) on PCR and slightly elevated IL-6 in the CSF. PLE was thought to be unlikely in the absence of a positive cytologic examination and with a normal range of tumor markers such as neuron specific enolase and soluble IL-2 receptor. In addition, a previous gynecological examination performed five months before this administration showed no significant abnormalities and the uterus and the adnexal structures were normal in size and echotexture. Methylprednisolone (1,000 mg per day) was administered intravenously for a 3 days course three times. Risperidone (2 mg per day) and olanzapine (10 mg per day) were also used to manage her confusion. After three courses of methylprednisolone, symptoms regressed and the CSF IL-6 level returned to normal range. A follow-up MRI also showed normal findings.

The patient's condition was improving, but, at three weeks after treatment, a tumor was discovered in her lower abdomen. A pelvic MRI revealed a solid tumor filling the pelvic cavity. Tumor markers associated with ovarian tumor showed 55 U/ml of CA125 and 170 U/ml of CA19-9. She had a sudden onset of high fever and abdominal pain in the lower abdomen a few days later. The resistance of the abdominal wall increased and moderate tenderness was elicited. The diagnosis was panperitonitis due to rupture of the ovarian tumor. She had an emergency right salpingo-oophorectomy. There was no apparent metastasis to the pelvic wall. The tumor was solid and included hair and cartilage. The pathologic diagnosis was an immature teratoma of grade 2 with an immature neuroepithelial component (Fig. 2). After surgical resection, she received chemotherapy. The patient is currently well at 2 years after surgical treat-

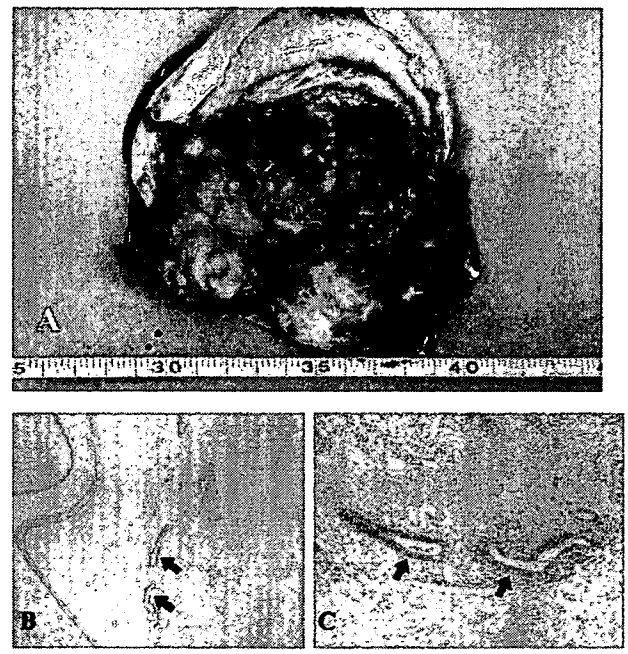

Figure 2. Pathological findings of ovarian tumor: (A) The tumor was solid and included hair and cartilage on macroscopic examination. (B), (C) Neuroepithelial cells (arrows) are shown (B,C: HE stain, B×40, C×100).

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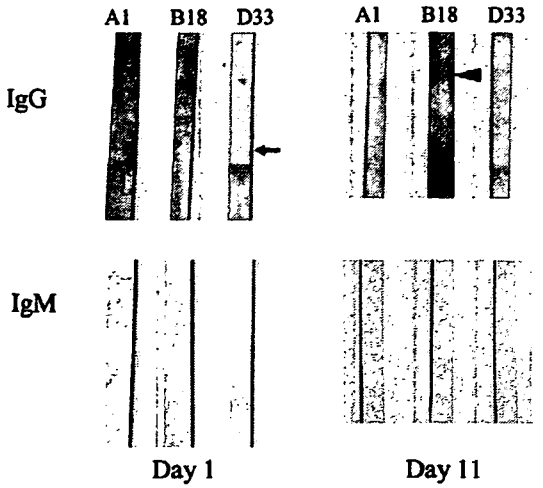

Figure 3. Detection of autoantibodies to whole molecule GluR ε2 and δ2 subunit in the cerebrospinal fluid samples from this patient. Data for IgG and IgM autoantibodies are shown. A1 = control strip. ; B18 = strip of nitrocellulose membrane containing whole GluR ε2 proteins reacted with CSF of this patient.; D33 = strip of nitrocellulose membrane containing whole GluR δ2 proteins reacted with CSF of this patient. arrowhead = whole molecule of GluR ε2 (about 180 kd), arrow = whole molecule of GluR δ2 (about 100 kd), stained with patient's autoantibodies followed by alkaline phosphate-labeled second antibodies. GluR IgG-ε2 and IgG-δ2 autoantibodies were detected in the CSF samples at the first and 11th day of admission, respectively.

ment with no evidence of recurrence of the tumor. Psychotropic drugs were gradually tapered in 4 weeks and discontinued. She has neither physical nor mental disabilities.

After surgery, to clarify the potential association between encephalitis and ovarian tumor, anti-Hu, Yo, Ri, Ma, Ta, Tr and Amphyphysin antibodies in the patient's CSF that had been stored before treatment were tested. All antibodies were negative. However autoantibodies to the glutamate receptor (GluR) subunits epsilon (ε)-2 and delta (δ)-2 were detected in the serum and CSF (Fig. 3). A sample of ovarian tumor extract was tested with immunoblotting analysis. However expression of GluR ε2 or GluR δ2 was not confirmed by immunoblot analysis using antibodies against GluR ε2 or GluR δ2.

Discussion

The present patient suffered from limbic encephalitis associated with an immature ovarian teratoma. She had autoantibodies to GluRs and elevated IL-6 level in the CSF. These findings suggest that the neurological symptoms were attributed to the paraneoplastic autoimmune mechanisms.

Recently, six cases of ovarian teratoma (mature: 2 cases, immature: 4 cases) in association with PLE have been reported. The clinical characteristics of literature cases including the present case are summarized in Table 1 (8-13). There were cases of mild CSF pleocytosis without infectious etiology and no antineural antibodies except in one case (8). Neurological symptoms of all six cases including ours improved or completely resolved after treatment.

Neurological symptoms in most patients did not improve after the first course of steroid pulse therapy, but those pa-

Table 1. Literature Cases of Paraneoplastic Encephalitis with Ovarian Teratoma

Patients	*Fadare et al.* [8]	*Nokura et al.* [9]	*Okamura et al.* [10]	*Taylor et al.* [11]	*Aydiner et al.* [12]	*Munakata et al.* [13]	*Present case*
Age (year)	33	19	15	24	39	25	35
Neurological form	limbic encephalitis	limbic and brainstem encephalitis	limbic encephalitis	encephalo -myelitis	limbic encephalitis	limbic encephalitis	limbic encephalitis
Clinical symptoms							
Impaired consciousness	-	+	+	+	+	+	-
Dysmnesia	+	+	+	+	+	+	+
Psychiatric symptom	-	+	+	+	+	-	+
Seizures	-	+	-	-	+	+	-
Cerebrospinal fluid							
Cells (μ l)	normal	34	normal	23	65	normal	15
Protein (mg/dl)	normal	19	normal	normal	64	normal	35
MRI abnormalities	N.D.	normal	normal	medulla	normal	bilateral hippocampi	normal
Treatment	operation	operation	operation	operation, IVIg steroid	operation	operation steroid	steroid operation
Pathologic diagnosis	mature	immature	immature	mature	immature	immature	immature
Sequelae	-	amnesia	-	-	affective disorder, amnesia	amnesia seizure	-

N.D.: not described, IVIg: intravenous immunoglobulin therapy

tients improved after resection of the ovarian tumor. In this patient, we continued three courses of pulse therapy because of the elevation of IL-6 in the CSF. Thereafter, symptoms in this patient improved significantly. Therefore we speculate that autoimmune mechanisms contributed to the encephalitis in this patient.

It is impossible to exclude the possibility that the tumor was a coincidental association and that the neurological syndrome was causally related to mechanisms other than paraneoplatic mechanisms. However, we were unable to demonstrate any infectious etiology and serological data suggesting a systemic vasculitis. Neurological symptoms and increasing tumor size presented simultaneously. Taken together, her clinical presentation, CSF profile, neuroimaging, detection of autoantibodies and elevated cytokine level argues strongly in favor of a paraneoplastic etiology.

In this patient, autoantibodies against GluRε2 and GluR δ2 were detected, although the tumor expressed no detectable GluR ε2 or GluR δ2. These data suggest that autoantibodies to GluRs may be produced after neuronal injuries. Tumor immunity may induce activation of autoreactive cytotoxic T cells and produce cytotoxic cytokines etc, which may result result in neuronal damage. The data also suggest that an autoimmune mechanism against ovarian tumor may cross react with GluRs. Although the role of autoantibodies to GluRs is not clear, autoantibodies against GluR ε2 (NMDA 2B) are reported to cause neuronal apotosis in hippocampal neurons (14). Therefore, autoantibodies to GluRs, even which are produced after some neuronal injuries may affect the symptoms of paraneoplastic limbic encephalitis. Additional cases are needed to elucidate the relationship between PLE and autoantibodies to GluR.

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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 legions 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 ε2 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.

Keywords: Refractory seizures; Repetitive seizures; Status epilepticus; High-dose barbiturate; Multifocal cortical legions; MRI

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

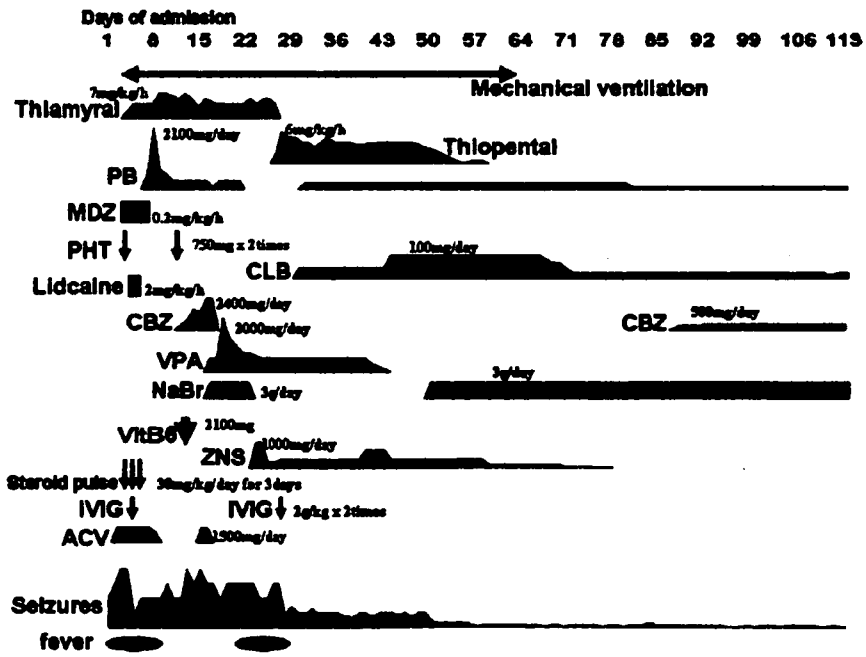

Fig. 1. Clinical course of the patient. Dosage of each drug refers to the maximum dose of continuous (thiamylal, thiopental, MDZ, and lidocaine) or one-shot (PHT, Vit.B6, steroid, IVIG, and ACV) intravenous injection or oral intake (PB, CLB, CBZ, VPA, NaBr, and ZNS). PB, phenobarbital; MDZ, midazolam;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