Non-herpetic Acute Limbic Encephalitis: Cerebrospinal Fluid Cytokines and Magnetic Resonance Imaging Findings

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Abstract

Objective Non-herpetic acute limbic encephalitis (non-herpetic ALE) is regarded as a new subgroup of limbic encephalitis. In the present study, clinical findings and cerebrospinal fluid (CSF) cytokines in patients with non-herpetic ALE were investigated.

Patients and Methods For adult inpatients in our hospital and related hospitals from 1996 to 2001, non-herpetic ALE was examined according to the criteria described in this study. Six patients were diagnosed as having non-herpetic ALE, and their clinical data and magnetic resonance imaging (MRI) were analyzed. In the CSF samples of the 6 patients with non-herpetic ALE and 6 patients with herpes simplex encephalitis (HSE), the concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and interferon (IFN)-γ were determined using sandwich-type enzyme-linked immunosorbent assay (ELISA) kits.

Results The six patients with non-herpetic ALE showed all the acute encephalitis features, such as fever, altered consciousness, seizures, memory impairment, and mild CSF pleocytosis. MRI demonstrated selective abnormal signals in the limbic system, including the bilateral hippocampi and amygdalae. The levels of CSF IL-6 and IFN-γ in patients with non-herpetic ALE were significantly lower than those in patients with HSE (p<0.05 and p<0.01, respectively). The levels of both TNF-α and IL-1β were below the detection limits in both groups.

Conclusion Six patients were newly diagnosed as having non-herpetic ALE in this study. These patients revealed both acute limbic encephalitis and MRI abnormalities in the bilateral hippocampi and amygdalae. The levels of IL-6 and IFN-γ in the CSF of patients with non-herpetic ALE were significantly lower than those of patients with HSE, possibly reflecting an immunological process in this type of ALE rather than direct viral infection.

Key words: acute limbic encephalitis, herpes simplex encephalitis, paraneoplastic limbic encephalitis, polymerase chain reaction, serologic testing

Introduction

Since 1990, a survey of herpes simplex virus (HSV) central nervous system (CNS) infections has been conducted with the primary focus on adult inpatients in the Kyushu and Okinawa regions of Japan. In the course of the survey, non-herpetic acute limbic encephalitis (non-herpetic ALE) was identified as a new subgroup of limbic encephalitis along the spectrum that includes herpes simplex encephalitis (HSE) and paraneoplastic limbic encephalitis (1–3). In 1994, we described four patients with non-herpetic ALE; these patients differed from those with HSE in terms of the lack of evidence of HSV infection based on polymerase chain reaction (PCR) studies and enzyme-linked immunosorbent assay (ELISA or EIA) antibody testing, and demonstrated magnetic resonance imaging (MRI) findings localized to parts of the limbic system, such as the bilateral hippocampi and amygdalae. In addition, non-herpetic ALE has a favorable prognosis, unlike HSE and paraneoplastic limbic encephalitis. Non-herpetic ALE has been increasing in Japan in recent years (4).

In acute viral encephalitis and meningitis, changes in the levels of various cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and interferon (IFN)-γ,
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have been reported (5–9). These cytokines are known to reflect the pathophysiology of CNS infections. In the present study, six patients with non-herpetic ALE are presented along with their clinical data and MRI findings, and cerebrospinal fluid (CSF) cytokines are analyzed.

Patients and Methods

We examined adult inpatients with non-herpetic ALE from 1996 to 2001 at Kurume University Hospital and its affiliated hospitals. The clinical data were analyzed for each patient. The diagnosis of non-herpetic ALE (1–3) was determined according to the following criteria: 1) the presence of acute limbic encephalitis; 2) MRI visualization of abnormalities in the bilateral hippocampi and amygdalae; 3) evidence of pleocytosis, increase in protein content, and normal glucose levels in the CSF; 4) negative PCR for HSV in the CSF and negative ELISA (or EIA) antibodies for HSV-1 and -2 in the serum and CSF; and 5) absence of malignancy.

CSF nested PCR assays were performed at the acute stage of illness as described previously (10), including those for HSV and other herpesvirus groups: varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus 6 (HHV-6). The following primer sequences were chosen for the DNA polymerase gene region that is common to the herpesvirus groups: sense primer, 5΄-CGACTTTGCCAGCCTGTACC-3΄; and anti-sense primer, 5΄-AGTCCGTTGTCCTCCTAGTG-3΄. If the PCR was positive, the individual herpesviruses HSV-1, HSV-2, VZV, CMV, EBV, and HHV-6 were investigated by individual restriction profiles using BanHI and SmalI. For the serological tests, EIA IgG and IgM antibodies for HSV or complement fixation (CF) titers for HSV, including other herpesvirus group members and other neurotropic RNA viruses, were measured in the sera and CSF samples taken during the acute through the convalescent stages. For the HSV EIA testing (11), HSV type 1 antigen (HF strain) was used; sera and CSF were diluted to 1:200 and 1:20, respectively, and the final absorbance value was converted to a ratio of test serum absorbance to positive reference serum absorbance (serum EIA IgG positive 0.4, CSF EIA IgG positive 0.04, and serum EIA IgM positive 1.2, CSF EIA IgM positive 0.12).

Determination of cytokine concentrations: CSF samples were taken 5 to 20 days after onset (mean: 9.5 days) of disease from 6 patients with non-herpetic ALE, and from 6 patients with HSE; the samples were stored at –80°C. The concentrations of TNF-α, IL-1β, IL-6, and IFN-γ in the CSF were determined with sandwich-type ELISA kits (R&D Systems, Minneapolis, MN). The detection limits were 4.4 pg/ml for TNF-α, 3.9 pg/ml for IL-1β, 3.1 pg/ml for IL-6, and 8 pg/ml for IFN-γ, respectively. Data were presented as means±SD. The statistical significance was evaluated using Student’s t test. P values of less than 0.05 were considered significant.

All MRI studies were performed using a 1.5T superconducting magnet system. Spin echo (SE) T1- and T2-weighted images and fluid-attenuated inversion recovery (FLAIR) images were obtained. In all patients, an initial MR study at the acute stage of illness and a follow-up study at the convalescent stage were carried out. Computed tomography (CT) scans were taken of all patients, and 123I-IMP single photon emission CT (SPECT) was performed on three patients.

Results

Clinical data (Table 1)

Six patients were found; their mean age was 40.5 years (range 18–73 years) with a 3:3 male : female ratio. Four of these six patients had developed sporadically acute encephalitis during the past 6 years in Kurume City and its surrounding areas, encompassing a population of approximately one million people. Another patient (Patient 4) was treated at Yamaguchi City, and the remaining patient (Patient 5) developed the disease in Tokyo, and was transferred to our hospital to be near his hometown during convalescence.

All patients showed similar acute encephalitic symptoms such as fever, altered consciousness, seizure, and memory impairment. Meningeal signs were either mild or not observed. In most patients, slight-to-moderate increases in the erythrocyte sedimentation rate and C-reactive protein were seen, and tumor markers such as carcinoembryonic antigen (CEA) were negative. Patient 1 showed increased aspartate aminotransferase (AST) and alanineaminotransferase (ALT). Patient 5 presented with a transiently increased CK of 8,991 IU/l. Patient 3 was complicated by aspiration pneumonia; both Patients 1 and 3 required respirators at the acute stage. For Patients 1, 3, and 6 a continuous midazolam drip was administered to control status epilepticus. All patients presented with mild CSF pleocytosis, an increase in protein content, and normal glucose concentrations. In a few patients, IgG indices were normal. In all patients, serum anti-Hu and -Yo antibodies were negative. The electroencephalogram (EEG) in Patient 2 revealed periodic lateralized epileptiform discharges (PLEDs), while the EEG in Patient 3 exhibited periodic synchronous discharges (PSD).

Regarding PCR and serology assays of the 6 patients, HSV-1 and -2 genomes were analyzed by nested PCR; these tests included those for the other herpesvirus groups (VZV, CMV, EBV, HHV-6) as well, but these groups were not detected in the initial CSF samples. CSF EIA IgG and IgM for HSV were not observed in any of the patients. Serum EIA IgG and IgM antibodies for HSV, CF titers for HSV, and antibodies to other herpesviruses and neurotropic viruses such as Japanese encephalitis (JE) virus were all negative, with a few exceptions. Namely, a serum EIA IgG of 4.2 for HSV was observed in Patients 2, 3, and 6; an EBV VCA IgG of 1:80 was observed in Patient 1; an HHV-6 of 1:160 was observed in Patient 5; and an EBV VCA IgG of 1:80 was observed in Patient 6. Since these antibodies were unchanged during the acute and convalescent stages, these findings...
indicated a previous infection.

All patients were given acyclovir (30 mg/kg per day) intravenously for 10–14 days during the acute stage of illness, although the efficacy of the acyclovir treatment remained uncertain. For Patients 4 and 6, prednisolone (60 mg per day) was also given for 14 days, but its efficacy was unclear as well. Patients 2 and 3 had moderate sequelae such as convulsive seizures or an amnestic syndrome, including recent memory impairment and retrograde amnesia, and they were hospitalized and required wheelchairs at 6 months after onset. The remaining 4 patients had mild sequelae such as seizures or memory impairment, and were able to return to their home or jobs within 6 to 12 months. In a follow-up study carried out one year after onset of illness, none of the patients had clinical data suggestive of any malignancy.

**CSF cytokines (Fig. 1)**

Levels of CSF IL-6 are presented as means±SD. The level for non-herpetic ALE was 14.95±15.56 pg/ml, and that for HSE was 147.83±142.08 pg/ml. The level of CSF IFN-γ in non-herpetic ALE patients was <8 pg/ml, while those in HSE patients averaged 53.38±42.46 pg/ml. The levels of CSF IL-6 and IFN-γ in non-herpetic ALE patients were significantly lower than those in patients with HSE (p<0.05 and p<0.01, respectively). The levels of TNF-α and IL-1β were below the detection limits in both groups.

**MRI findings (Table 2, Figs. 2, 3)**

MRI demonstrated consistently selective abnormal signals mainly in the bilateral hippocampi and amygdalae; Patients 2 and 6 revealed mild asymmetry. In four patients, T2-weighted and FLAIR images showed high signal intensities with mild swelling in the areas mentioned above at the acute stage; thereafter, MRI abnormalities decreased or disappeared followed by limbic atrophy during the convalescent stage. In most patients, the CT scans exhibited no definitive abnormalities. In Patients 2, 3 and 5, SPECT revealed wider hypoperfusion lesions than the corresponding MRI lesions in the medial temporal lobe.

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**Table 1. Clinical Characteristics of 6 Patients with Non-herpetic ALE**

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (yr)/sex</th>
<th>Onset date</th>
<th>Clinical symptoms</th>
<th>Cerebrospinal fluid pressure (mmH₂O)</th>
<th>Cerebrospinal fluid cells (×10³/mm³)</th>
<th>Cerebrospinal fluid protein (mg/dl)</th>
<th>Cerebrospinal fluid IL-6 (pg/ml)</th>
<th>PCR &amp; EIA for HSV</th>
<th>EEG</th>
<th>Sequelae</th>
</tr>
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<tr>
<td>1</td>
<td>34/M</td>
<td>1’96</td>
<td>(+) (+) JCS10</td>
<td>n.d.</td>
<td>10 (4 : 1)*</td>
<td>72</td>
<td>(–)</td>
<td>(+)</td>
<td>moderate slowing</td>
<td>(+)</td>
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<tr>
<td>2</td>
<td>60/F</td>
<td>10’98</td>
<td>(+) (+) JCS2</td>
<td>180</td>
<td>5 (5 : 0)</td>
<td>28.5</td>
<td>(–)</td>
<td>(+)</td>
<td>PLEDs</td>
<td>(+)</td>
</tr>
<tr>
<td>3</td>
<td>73/F</td>
<td>6’99</td>
<td>(+) (+) JCS20</td>
<td>200</td>
<td>32 (15 : 1)</td>
<td>11.9</td>
<td>(–)</td>
<td>(+)</td>
<td>(+)</td>
<td>(++)</td>
</tr>
<tr>
<td>4</td>
<td>35/M</td>
<td>11’99</td>
<td>(+) (+) JCS20</td>
<td>210</td>
<td>8 (7 : 1)</td>
<td>3.6</td>
<td>(–)</td>
<td>(+)</td>
<td>(+)</td>
<td>(++)</td>
</tr>
<tr>
<td>5</td>
<td>23/M</td>
<td>3’01</td>
<td>(+) (+) JCS10</td>
<td>n.d.</td>
<td>5 (4 : 1)</td>
<td>28</td>
<td>(–)</td>
<td>(+)</td>
<td>mild slowing</td>
<td>(+)</td>
</tr>
<tr>
<td>6</td>
<td>18/F</td>
<td>9’01</td>
<td>(+) (+) JCS10</td>
<td>180</td>
<td>320 (7 : 1)</td>
<td>86</td>
<td>(–)</td>
<td>(+)</td>
<td>spikes</td>
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Here, we present two representative patients with non-herpetic ALE; one was the oldest subject in this study, and the other presented with status epilepticus preceding fever and encephalitic symptoms.

Patient 3: A 73-year-old woman was admitted to a nearby hospital with suspected dehydration in the middle of June 1999. On admission, she showed altered consciousness with a fever of 37°C. She became somnolent, had convulsive seizures, developed a fever of 39°C, and was transferred to our University Hospital. She revealed a score of 10 to 20 points on the Japan Coma Scale (JCS), with myoclonus in her right limbs, nuchal stiffness, and decreased deep tendon reflexes. Serum tumor markers such as CEA and anti-Hu and -Yo antibodies were negative. The serum CF titer for HSV was <1 : 4, and the patient had an EIA IgG of 4.2 and an IgM of <0.1 for HSV. The patient’s serum was negative at the acute and convalescent stages for other herpesvirus groups and neurotropic viruses, including JE virus and influenza A and B. CSF EIA IgG and IgM for HSV were negative. HSV genomes were assayed by nested PCR, as were other herpesviruses (VZV, CMV, EBV, and HHV-6), but none of these were detected in the initial CSF sample. The CSF contained 32 cells/mm³, protein 29 mg/dl, glucose 94 mg/dl, TNF-α <4.4 pg/ml, IL-1β <3.9 pg/ml, IL-6 11.9 pg/ml, and IFN-γ <8 pg/ml. The MRI exhibited abnormal signal intensity in the bilateral hippocampi and amygdalae, as well as in the bilateral cingulate gyri and insulas (Fig. 2A, B, C).

### Table 2. Distribution of MRI Abnormalities

<table>
<thead>
<tr>
<th>Patient No</th>
<th>MRI: days after onset</th>
<th>Hippocampus</th>
<th>Amygdala</th>
<th>Cingulate gyrus</th>
<th>Insula</th>
<th>Temporal lobe*</th>
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<tbody>
<tr>
<td>1</td>
<td>5 Rt</td>
<td>(+)</td>
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<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
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<tr>
<td></td>
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<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>2</td>
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<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td></td>
<td>Lt</td>
<td>(±)</td>
<td>(±)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>3</td>
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<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(−)</td>
</tr>
<tr>
<td></td>
<td>Lt</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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<td>(−)</td>
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<tr>
<td>4</td>
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<td>(−)</td>
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<tr>
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<td>(+)</td>
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<td>(−)</td>
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</tr>
<tr>
<td>5</td>
<td>5 Rt</td>
<td>(+)</td>
<td>(+)</td>
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</tr>
<tr>
<td></td>
<td>Lt</td>
<td>(+)</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>6</td>
<td>10 Rt</td>
<td>(±)</td>
<td>(±)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td></td>
<td>Lt</td>
<td>(+)</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
</tbody>
</table>

Rt: right, Lt: left, *lateral portion of temporal cortex.

**Figure 2.** MRIs of Patient 3 with non-herpetic acute limbic encephalitis. A: Seven days after onset, an axial T1-weighted MRI image reveals bilateral low signal lesions in the hippocampi and amygdalae (arrows; arrows are shown only on the left side). B: Two weeks after onset, a FLAIR MRI image shows high signal intensities in the same areas bilaterally (arrows). C: A FLAIR MRI image shows abnormal signals in the bilateral insulas (arrow).
At the acute stage, mild swelling in the limbic system was observed; at the recovery stage, these changes disappeared. The EEG showed PLEDs in the right cerebral hemisphere. Prompt acyclovir treatment was initiated intravenously at a dose of 1.5 g per day. The patient then developed aspiration pneumonia and was transferred to our ward. After recovering from the impairment of consciousness, the patient developed recent memory impairment and retrograde amnesia. Three months later, she started walking for rehabilitation, and she was transferred to another hospital.

Patient 6: An 18-year-old girl was admitted to our University Hospital with generalized tonic seizures on September 5, 1999. Her seizures improved within a few days. However, she then complained of headaches with tonic seizures, and developed status epilepticus. She developed a fever of 39°C and was transferred to our ward. She showed a score of 10 to 20 points on JCS, without nuchal stiffness, and decreased deep tendon reflexes. The serum CF titer for HSV was <1 : 4; her EIA IgG was 4.2 and IgM was <0.1 for HSV; the other tests for other herpesviruses, except for an EBV VCA IgG of 1 : 80, were all negative. CSF EIA IgG and IgM for HSV were negative. HSV genomes were assayed by nested PCR, as were the other herpesvirus groups, and none were detected in the initial CSF sample. Serum anti-Hu and -Yo antibodies were negative. The CSF contained 320 cells/mm³, protein 86 mg/dl, glucose 56 mg/dl, TNF-α <4.4 pg/ml, IL-1β <3.9 pg/ml, IL-6 39.3 pg/ml, and IFN-γ <8 pg/ml. The MRI revealed a left-sided predominant abnormal intensity in the hippocampi and amygdalae. The EEG showed moderate slowing in the right cerebral hemisphere. Acyclovir treatment was initiated intravenously at 1.0 g per day. Prednisolone was administered periorally at 60 mg per day. She was given phenobarbital, midazolam, phenytoin and carbamazepin for the status epilepticus. During recovery, the patient developed recent memory impairment. Three months later she was discharged, and she returned to her high school.

Discussion

Our six patients with non-herpetic ALE were differentiated from those with HSE by the lack of evidence of HSV-1 or -2 infection in extensive serologic and PCR studies. As far as we were able to ascertain, no viral genomes or antibodies for other herpesviruses (i.e., VZV, CMV, EBV, or HHV-6) were detected. Prompt acyclovir therapy may have inhibited PCR and EIA antibody production in response to HSE; however, our previous study suggested that this antiviral drug has no influence on the development of the HSV antibody (12). In HSE, MRI lesions often progress unilaterally across the whole temporal lobe, and symmetrical limbic system lesions have been reported as being extremely rare (13–15), while in non-herpetic ALE, bilateral abnormalities in the hippocampus and amygdala are more common, as shown in this study. In the present cases, paraneoplastic limbic encephalitis was excluded as a possible diagnosis because of the acute onset and the lack of malignancy. Thus, our six patients were identified as having non-herpetic ALE, which was not related to either herpesviruses or malignancies. These patients should be regarded as belonging to a distinct subgroup of patients with limbic encephalitis/encephalopathy; tentative relationships among non-herpetic ALE, HSE, paraneoplastic limbic encephalitis, and related diseases are shown in Fig. 4.

Approximately 30 patients with non-herpetic ALE have been reported in Japan (16–18); their congressional abstracts, including a few original papers, have described these as cases of non-herpetic ALE with MRI abnormalities in the bilateral hippocampi and amygdalae. In addition, negative
IL-6 is a cytokine that plays a variety of important roles in the inflammatory response (24, 25); IL-6 thus plays an important role in the host response to infection. IL-6 is known to induce hepatic protein synthesis during the acute phase response, including the synthesis of C-reactive protein and fibrinogen. Previous studies have shown that CSF IL-6 is often elevated in patients with inflammatory disorders of the CNS (6, 8, 25). An elevated level of IL-6 in the CSF would therefore be likely to indicate the existence of inflammation of the CNS. The levels of IL-6 in the CSF of patients with non-herpetic ALE were significantly lower than those in patients with HSE. This finding suggests that inflammation in the CNS of non-herpetic ALE patients is milder than that of HSE patients.

IFN-γ is known to be an inhibitor of viral replication (26, 27). CSF IFN-γ is often elevated in viral meningitis and HSE, but not in postinfectious encephalitis, including measles or rubella encephalitis, bacterial meningitis, or ADEM (5–7, 28–30). Elevated IFN-γ in the CSF may indicate viral infection in the CNS (5). Our data revealed that CSF levels of IFN-γ were not elevated in non-herpetic ALE patients. We speculate that non-herpetic ALE may be caused by a postinfectious immune response or by a transient autoimmune response, rather than by direct viral infection.

Since the initial description by Corsellis et al in 1968 (31), paraneoplastic limbic encephalitis (paraneoplastic LE) associated with malignancy has been reported by other authors (32, 33). Paraneoplastic LE differs from non-herpetic ALE in terms of its subacute or chronic course. Pathogenetic antineural antibodies, such as the anti-Hu antibody, which is observed mainly in small-cell carcinomas of the lung and anti-Ma2 antibody-related testicular carcinoma, are well known. Gultekin et al (33) analyzed 50 patients with clinically diagnosed paraneoplastic LE, in which neurologic symptoms preceded the diagnosis of malignancy in 60% of the patients; anti-neural antibody tests were also positive in 60% of patients. In contrast, a patient with HSE and with anti-Hu antibody has been reported (34). In this patient, pathologically characteristic findings of both HSE and paraneoplastic LE, as well as the detection of HSV genome by PCR in the temporal lobe, were observed. It is of note that HSE and paraneoplastic LE overlapped in this case.

On the other hand, Bien et al (35) reported four patients with non-paraneoplastic LE that resembled paraneoplastic LE; all patients presented with intractable temporal lobe seizures and memory impairment. Biopsied specimens from these patients were histologically examined and no viruses or malignancies were observed. The CSF findings of their patients tended to be mild, as observed in the present patients with non-herpetic ALE, but the clinical course of those patients was subacute or chronic, similar to paraneoplastic LE. Hennessy et al (36) described two adult patients with chronic temporal epilepsy and pathologic features consistent with Rasmussen’s encephalitis. Moreover, a case of chronic recurrent meningoencephalitis simulating limbic encephalitis has been reported (37), and limbic encephalitis patients with systemic lupus erythematosus, as well as those with potassium channel antibodies, have also been described (38, 39).

In conclusion, the present study is suggestive of a postinfectious pathogenesis of non-herpetic ALE, as based on changes in cytokine levels in the CSF. However, no autopsy cases from this subgroup have been examined, and no control study of acyclovir or corticosteroid therapy has been conducted. Further investigations will therefore still be necessary to clarify the pathogenesis of this type of ALE.

Acknowledgments: This study was supported by a Grant-in-Aid for Scientific Research (C) (12670631) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We wish to thank Associate Prof. K. Sakai, the Department of Neurology, Kanazawa Medical College, for measuring the anti-Hu and -Yo antibodies. In addition, Dr. Y. Nakazawa, Emeritus Prof. of the Department of Psychiatry, Kurume University School of Medicine, Dr. A. Miyagawa, the Department of Psychiatry, Kurume University School of Medicine, and Dr. M. Okada, the Second Department of Internal Medicine, Nihon Medical College, are to be thanked for providing detailed information on Patients 1, 2 and 5.

References