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INTERNAL MEDICINE

□ CASE REPORT □

Multifocal Encephalopathy and Autoimmune-mediated Limbic Encephalitis Following Tocilizumab Therapy

Yuko Yamaguchi[1], Koji Furukawa[1], Toru Yamamoto[1], Yukitoshi Takahashi[2], Keiko Tanaka[3] and Makio Takahashi[4]

Abstract

A 63-year-old man with rheumatoid arthritis developed multifocal encephalopathy and limbic encephalitis following therapy with tocilizumab, a humanized anti-interleukin-6 receptor antibody. Anti-glutamate receptor ε2 antibodies were later found to be positive in both the serum and cerebrospinal fluid. This case highlights the possibility of the development of encephalopathy after treatment with tocilizumab, which may also induce autoimmune limbic encephalitis.

Key words: autoantibody, anti-glutamate receptor (GluR), multifocal encephalopathy, limbic encephalitis, tocilizumab, interleukin-6

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Introduction

Recently, several emerging biological agents have been increasingly used in the treatment of collagen-vascular and hematological disorders. However, several reports have shown that these agents can induce encephalopathy (1-3), the underlying mechanisms of which are currently unknown. We herein report the case of a patient presenting with multifocal encephalopathy and limbic encephalitis following treatment with tocilizumab, a humanized monoclonal antibody against interleukin (IL)-6 receptor (IL-6R). In this case, autoantibodies against the N-methyl-D-aspartate (NMDA)-type glutamate receptor (GluR) subunit were detected. The GluR antibodies, which were possibly induced by treatment with tocilizumab, may have contributed to the pathogenesis of multifocal encephalopathy and limbic encephalitis.

Case Report

A 63-year-old man with rheumatoid arthritis (RA) was initially prescribed 7 mg/day of oral prednisolone (PSL) and 8 mg/week of methotrexate (MTX) at 60 years of age. Since the disease activity of RA was uncontrollable, he was treated with TNF-α antagonists, including 0.4 mg/kg of etanercept twice a week for five months followed by 40 mg of adalimumab every other week for 13 months, in addition to PSL and MTX. However, these agents were ineffective for treating the RA.

One month after the cessation of adalimumab therapy, the regimen was changed to 8 mg/kg of tocilizumab every four weeks (Fig. 1). Three months after the initiation of tocilizumab, the patient gradually developed cognitive impairment and weakness of the right arm. Total knee joint replacement was planned, and tocilizumab was discontinued. Two months later, he further developed weakness of the right leg and disorientation and his verbal communication progressively deteriorated. The Mini-Mental State Exam score was 4/30. Dysphagia, right-side dominant muscle weakness and rigidity in the extremities were later detected.

Laboratory blood tests showed an elevated C-reactive protein level (5.84 mg/dL) and erythrocyte sedimentation rate (105 mm/hr). The levels of angiotensin-converting enzyme and thyroid hormones were within the normal ranges. Serological tests were negative for syphilis and human immunodeficiency virus. No antinuclear, anti-SS-A, SS-B antibod-

[1]Department of Neurology, Osaka Saiseikai Nakatsu Hospital, Japan, [2]Department of Pediatrics, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Japan, [3]Department of Neurology, Kanazawa Medical University, Japan and [4]Department of Neurology, Osaka Redcross Hospital, Japan
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Correspondence to Dr. Makio Takahashi, ta@kuhp.kyoto-u.ac.jp

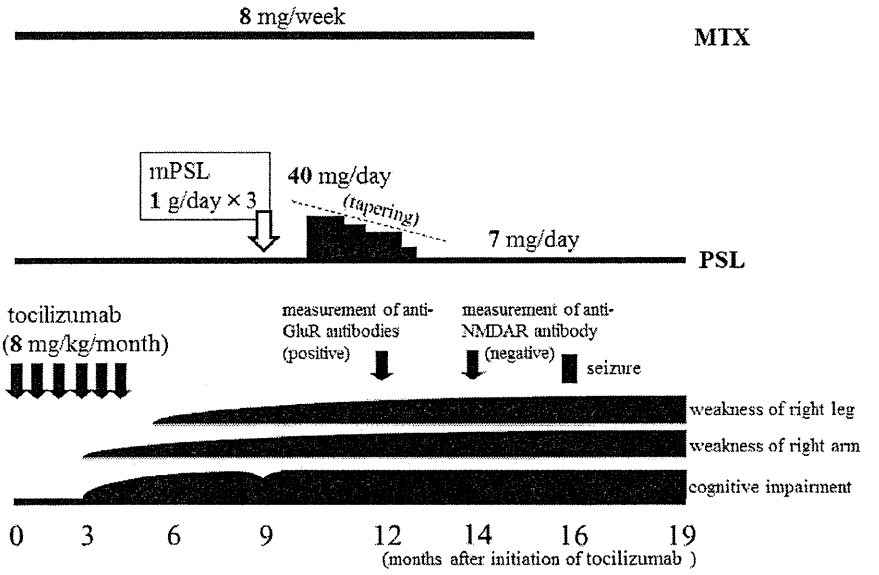

Figure 1. Schematic diagram of the patient's clinical course and treatment in the present case. The X axis indicates the number of months after the initiation of tocilizumab. MTX: methotrexate, PSL: prednisolone, mPSL: methylprednisolone, GluR: glutamate receptor, NMDAR: N-methyl-D-aspartate receptor

ies, MPO-ANCA or PR3-ANCA antibodies were detected. A cerebrospinal fluid (CSF) examination revealed slight lymphocytic pleocytosis (6/μL) and an elevated protein concentration (57 mg/dL). No bacteria were cultured in the CSF, and viral studies were negative, including polymerase chain reaction for herpes simplex virus, human herpes virus-6 and JC virus DNA. No malignancy was detected on esophagogastroduodenoscopy, colonoscopy or a whole-body CT scan.

Fluid-attenuated inversion recovery (FLAIR) MRI of the brain revealed high intensity lesions within the left frontoparietal and bilateral temporal white matter seven months after the administration of tocilizumab (Fig. 2a). These lesions were partially contrasted with gadolinium. ^{99m}Tc-ethylcysteinate dimer SPECT showed a decreased uptake in both the lesions observed on MRI and bilateral limbic areas (data not shown).

A needle brain biopsy of the right temporal lobe lesion adjacent to the lateral ventricles showed definitive perivascular lymphocytic infiltration and abundant reactive astrocytes (Fig. 2a, arrow, Fig. 2c). Immunohistochemical staining with lymphocyte markers showed perivascular inflammatory infiltrates of both T- (CD3) and B- (CD20) cells (Fig. 2d, e), while fibrinoid necrosis, characteristic of RA associated angiitis, was absent, thus indicating nonspecific encephalitis. The administration of methylprednisolone pulse therapy (1 g/day for three days) and subsequent oral steroids (PSL, tapered from 40 mg/day) temporarily ameliorated the patient's symptoms; however, his condition deteriorated (Fig. 1). Furthermore, he experienced recurrent generalized tonic-clonic seizures 16 months after treatment with tocilizumab. An interictal EEG showed periodical lateralized epileptiform discharges in the right hemisphere. MRI performed nine months later demonstrated the disappearance of enhancement in the left parietal and right temporal white matter lesions, although new lesions were observed in the right frontal lobe in addition to marked atrophy in the bilateral mesial temporal areas, suggesting limbic encephalitis (Fig. 2b). Autoantibodies against the N- and C-termini of NMDA type GluRε2 (homologs to NR2B) were detected in both the serum and CSF collected 12 months after the initiation of tocilizumab; the antibody titer was higher in the CSF than in the serum. The IL-6 level was simultaneously elevated (35 pg/mL) in the CSF. However, anti-NMDA receptor (NMDAR) antibodies were negative in the CSF collected 14 months after the administration of tocilizumab using a cell-based assay with human embryonic kidney 293 cells (Fig. 1).

The patient suffered from recurrent infections; therefore, only low-dose PSL (7 mg/day) was continued. He died of aspiration pneumonia 19 months after the introduction of tocilizumab. An autopsy was not allowed.

Discussion

Tocilizumab is a humanized monoclonal antibody against IL-6R that was introduced for the treatment of adult RA in 2008 in Japan, 2009 in Europe and 2010 in the U.S.A. More recently, tocilizumab has been shown to be effective for neuromyelitis optica (NMO) (4). In general, tocilizumab attenuates plasma cell differentiation and subsequent autoantibody production, such as that of aquaporin 4 antibodies in patients with NMO (4, 5). It also suppresses IL-21, which is primarily derived from effector/memory CD4-T cells. IL-21

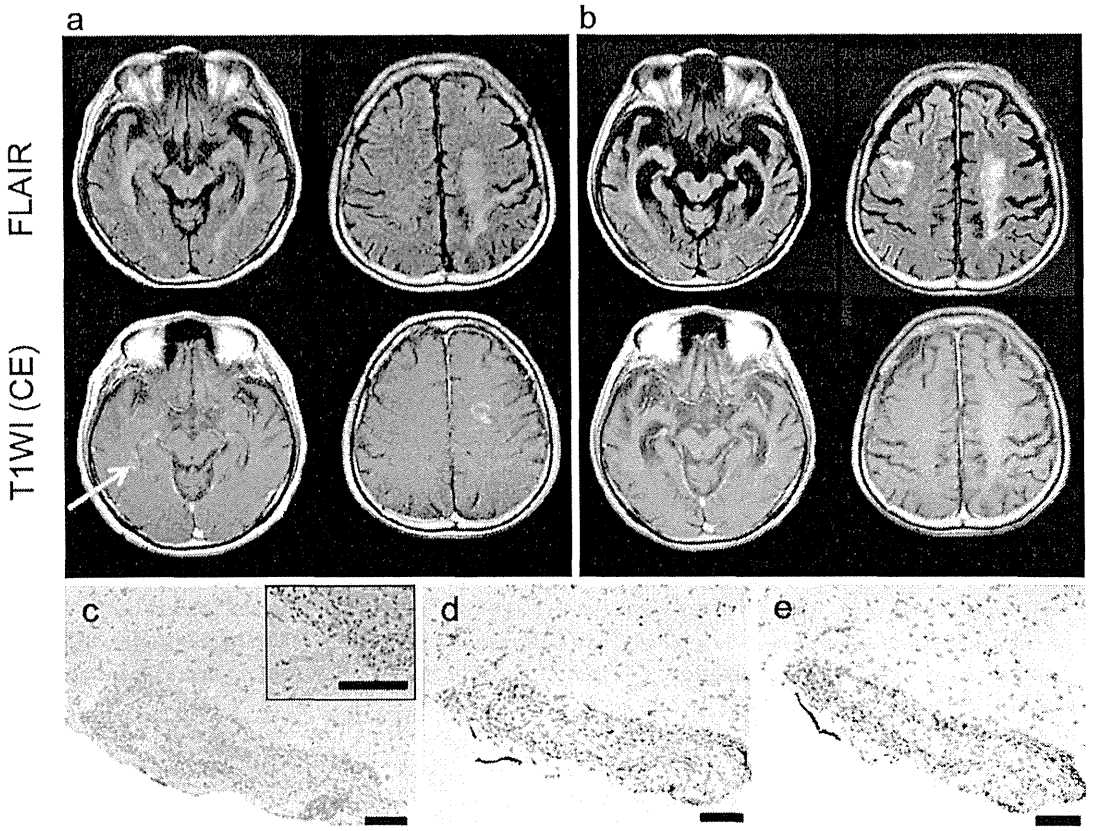

Figure 2. **An axial view of FLAIR (upper) and T1-weighted contrast (lower) MRI performed at seven months (a) and 16 months (b) after tocilizumab treatment. FLAIR-MRI revealed high-intensity lesions reflecting leukoencephalopathy within the left frontoparietal, right frontal and bilateral temporal areas (a). Gadolinium-enhanced areas on T1-weighted MRI were partially observed within the lesions. Compared to the image obtained at seven months (a), progressive brain atrophy was conspicuous at 16 months, especially in the bilateral mesial temporal areas (b). A needle brain biopsy of the right temporal white matter adjacent to the lateral ventricles performed at 10 months after the initiation of tocilizumab (Fig. 1a, arrow). The microscopic findings of the obtained tissue showed definitive perivascular lymphocytic infiltration (c) with reactive astrocytes (Hematoxylin and Eosin staining) (c, inset). Immunohistochemical staining with T-(CD3) (d) and B-(CD20) cell (e) markers revealed perivascular inflammatory infiltrates of both T- and B-cells. The scale bar indicates 25 μm (c, inset) and 50 μm (d, e).**

plays a pivotal role in the differentiation of plasma cells and production of autoantibodies in patients with RA. Tocilizumab also inhibits IgG4 (not IgG1)-class anti-CCP antibodies by blocking the effects of IL-6 on IL-21 production induced by CD4-T-cells (6). IL-6 exhibits ambivalent effects with respect to inflammation and neurotrophic repair depending on the pathological context in the central nervous system (CNS) (7). Therefore, tocilizumab potentially has both positive and negative effects on the CNS.

Notably, tocilizumab-induced leukoencephalopathy was described in the case of a 72-year-old woman with RA who developed cognitive impairment 40 months after the initiation of tocilizumab (1). FLAIR-MRI demonstrated the dissemination of high-intensity lesions in the bilateral cerebral white matter. The patient's clinical symptoms and MRI abnormalities persisted for five months after the discontinuation of tocilizumab. Unlike that observed in this reported case, which lacked a pathological study, the present patient exhibited progressive dementia, weakness of the extremities and generalized tonic-clonic seizures. MRI of the brain demonstrated both multifocal encephalopathy lesions and bilateral mesial temporal atrophy.

TNF-α antagonists, such as etanercept and infliximab, may cause demyelinating disorders of the CNS and encephalopathy (8). These drugs were administered before the introduction of tocilizumab in the present case. Although several cases of etanercept-related encephalopathy have been previously reported (2), it is unlikely that etanercept caused encephalopathy after at least 16 months of use in our patient. Furthermore, to our knowledge, no cases of encephalopathy induced by adalimumab have been reported. Therefore, we suspect tocilizumab, the last biological agent used,

to be the trigger for the development of encephalopathy in this case (Fig. 1).

Regarding MTX, which was used in the present case in combination with tocilizumab, rare case reports have shown that low doses of this drug can cause blood brain barrier (BBB) disruption and subsequent leukoencephalopathy in RA patients (9). We postulate that MTX disrupted the BBB, which then allowed tocilizumab to exert toxic effects on the CNS.

Furthermore, the detection of autoantibodies against intrathecal GluRε2 in this case warrants comment. Tocilizumab attenuates autoantibody production (4, 10); however, it may also augment serum IL-6 via the suppression of IL-6R signaling (10). Salsano et al. reported a case of autoinflammatory encephalopathy in which the patient exhibited an upregulated IL-6 level in the CSF and an augmented intrathecal IL-6 level that was not suppressed by tocilizumab treatment (11). On the other hand, the serum IL-6 levels increase in RA patients following the administration of tocilizumab for at least two weeks, while RA symptoms continue to be ameliorated (10). Therefore, the temporarily augmented serum IL-6 levels induced by tocilizumab may allow IL-6 to spread into the brain parenchyma via a disrupted BBB, which may subsequently induce the secondary production of intrathecal anti-GluRε2 antibodies and limbic encephalitis.

Among several subtypes of GluRs, NMDA-type GluRs play key roles in synaptic plasticity related to learning and memory. These molecules exhibit a heterotetramer complex structure composed of NR1 and NR2/3 subunits. Antibodies against the glutamate NR1 and NR2A/NR2B subunits of NMDAR, known as anti-NMDAR antibodies, were originally reported in cases of ovarian teratoma-associated limbic encephalitis (12). Because antibodies against GluRε2 (NR2B) are detected in several diseases, including reversible autoimmune limbic encephalitis and other forms of encephalitis/encephalopathy, the presence of GluRε2 antibodies is thought to be less specific than that of NMDAR (13). Furthermore, cases involving the development of anti-NMDAR encephalitis following TdaP-IPV booster vaccination (14) or Guillain-Barré syndrome (15) have been reported. These examples imply that the production of either anti-NMDAR or anti-GluR antibodies can be induced via host immunomodulatory reactions and by drugs, such as tocilizumab.

To date, biological agents, including tocilizumab, have been increasingly used for the treatment of several inflammatory autoimmune disorders. However, strong suppression of specific cytokine receptors, such as IL-6R, may perturb the balance of the immune system under a disrupted BBB, thus resulting in the development of autoimmune encephalitis/encephalopathy. Therefore, careful attention should be paid to monitoring the development of encephalopathy under treatment with these biological agents due to their possible adverse effects.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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LETTER TO THE EDITOR

Another case of respiratory syncytial virus-related limbic encephalitis

Kengo Moriyama · Yukitoshi Takahashi · Takashi Shiihara

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Dear Sir,

We read the article entitled "Respiratory syncytial virus-related encephalitis: magnetic resonance imaging findings with diffusion-weighted study" in your journal with great interest [1]. In the article, Park et al. reviewed the medical records of 3,856 patients, diagnosed with respiratory syncytial (RS) virus bronchiolitis and identified three cases of RS virus-related encephalitis, including the first reported case of RS virus-related limbic encephalitis. This was the case of a 3-year-old boy in whom the RS virus was detected in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR). In that case, limbic encephalitis could have been caused by a direct invasion of the RS virus. Brain magnetic resonance imaging (MRI) revealed subtle bilateral hippocampal enlargement with increased signal intensity on fluid-attenuated inversion recovery (FLAIR) images; however, there was no diffusion abnormality on diffusion-weighted imaging (DWI).

We would like to report another case of respiratory syncytial virus-related limbic encephalitis, where anti-*N*-methyl-*D*-aspartate receptor (NMDAR) antibodies were detected. A 3-year-old girl developed fever, 10 days before admission, which persisted for 4 days. Thereafter, she developed convulsions for 1 h, after which, she was admitted to our hospital. The day of admission was designated as day of illness (DOI) 0. RS virus infection was found to be prevalent in our area for a few weeks prior to this presentation. The patient did not have any history of neurological disorders, overt RS virus infection, or any other contributory family history. The findings of CSF examination were unremarkable, except for the presence of mild pleocytosis: white blood cell count 8/μL and total protein level 24 mg/dL. The patient's nasopharyngeal aspirate was examined using a rapid RS virus antigen detection test; the test results were positive. Subsequently, the results of PCR were positive for RS virus, whereas those of PCR using CSF were negative [2]. Electroencephalography showed a generalized high-voltage slow wave. The patient showed bizarre behaviors and complex partial seizures. On DOI 1, brain MRI did not show any apparent abnormality. On DOI 6, follow-up brain MRI revealed amygdalar and hippocampal lesions consistent with a diagnosis of limbic encephalitis (Fig. 1). Signal abnormalities were evident not only on FLAIR images but also on DWI. There were no signs of neoplasms such as ovarian tumor on imaging studies. Enzyme-linked immunosorbent assay indicated significantly elevated levels of antibodies for the peptides NR2B and NR1, which are basic NMDAR components, in CSF on DOI 0 and in serum specimens on DOI 1 [3]. CSF titers of NR2B and NR1 on DOI 0 were higher than serum titers on DOI 1; however, by DOI 20, CSF and serum titers of these peptides normalized. The patient's condition almost normalized, with alleviation of hyperactivity, and she was discharged on DOI 29. On DOI 44, her developmental quotient was 83. On DOI 57, brain MRI revealed that the amygdalar and hippocampal lesions had reduced in size and did not have restricted diffusion. Nine months after symptom onset, she still experienced monthly seizures.

K. Moriyama (✉) · T. Shiihara
Department of Neurology, Gunma Children's Medical Center,
779 Shimohakoda, Hokkitsu-machi, Shibukawa,
Gunma 377-8577, Japan
e-mail: medicalkengo@yahoo.co.jp

Y. Takahashi
National Epilepsy Center, Shizuoka Institute of Epilepsy
and Neurological Disorders, Aoi-ku, Shizuoka, Japan

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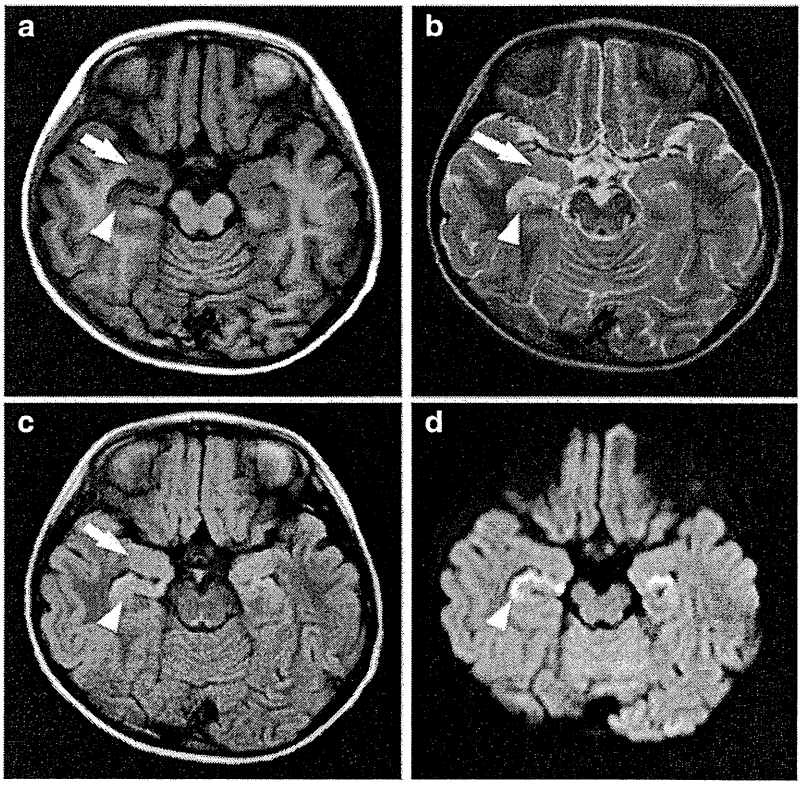

Fig. 1 Axial magnetic resonance imaging using a 1.5 T image showing the amygdalar (*arrow*) and hippocampal (*arrow head*) lesions on both sides, on day of illness 6. Low signals on (**a**) a T1-weighted image (repetition time[TR]/echo time[TE]/inversion time[TI] 2464/15/1,000 ms) and high signals on (**b**) a T2-weighted image (TR/TE 4383/120 ms), (**c**) a FLAIR image (TR/TE/TI 11000/140/2,800 ms), and (**d**) a diffusion-weighted image (TR/TE 2860/78 ms); the high intensity signals for the hippocampus are clearly visible on the diffusion-weighted image (**d**)

Unlike the report by Park et al., in our patient, the RS virus was not detected in CSF by PCR, and NMDAR antibodies were detected in CSF and serum. Therefore, the cause of limbic encephalitis in our patient was not direct invasion of the RS virus, but more likely, a parainfectious immune-mediated response. MRI signal abnormalities were evident not only on FLAIR but also on DWI. Park et al. speculated that diffusion abnormalities on DWI-related biological structures undergo irreversible structural changes. The MRI signal pattern may reflect the pathophysiological difference or disease severity itself. There have been only two reported cases of RS virus-related limbic encephalitis; therefore, we are far from a conclusion. Future studies on infectious pathogens and various auto-antibodies in limbic encephalitis may provide additional insights.

Conflict of interest We declare that we have no conflict of interest.

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Chronic periodic lateralised epileptic discharges and anti-N-methyl-D-aspartate receptor antibodies

Eisuke Sakakibara [1], Yukitoshi Takahashi [2], Yoshiko Murata [3], Go Taniguchi [1], Daichi Sone [3], Masako Watanabe [3]

[1] Department of Neuropsychiatry, The University of Tokyo Hospital, Tokyo
[2] National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka
[3] National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

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ABSTRACT – Periodic lateralised epileptiform discharges (PLEDs) are uncommon transient electroencephalographic findings accompanied by acute brain lesions. A small proportion of PLEDs persist for more than three months and are called "chronic" PLEDs, the pathophysiology of which is still debated. Herein, we report a man with right hemispheric PLEDs which lasted for more than 14 months and mild left hemispatial neglect after he experienced status epilepticus. Although MRI was normal, positron emission tomography revealed right temporo-parieto-occipital hypometabolism, which coincided with the source area of PLEDs estimated by magnetoencephalography. In addition, levels of anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies and granzyme B were found to be high in the cerebrospinal fluid. Following two courses of steroid pulse therapy, the patient's left spatial neglect improved and the PLEDs were partially resolved. These findings suggest that the chronic PLEDs present in this case were an interictal phenomenon and that their pathophysiology involved autoimmune processes.

Key words: status epilepticus, magnetoencephalography, steroid pulse therapy, left hemispatial neglect

Correspondence:
Eisuke Sakakibara
Department of Neuropsychiatry,
The University of Tokyo Hospital,
7-3-1 Hongo, Bunkyo-ku,
Tokyo 113-8655, Japan
<sakakibara-tky@umin.ac.jp>

Periodic lateralised epileptiform discharges (PLEDs) are uncommon electroencephalographic findings characterised by repetitive focal complexes that contain one or more sharp-wave components of approximately 0.5-3 Hz in frequency (Chatrian *et al.*, 1964).

Most PLEDs are relatively transient, appearing within 24 to 72 hours after the onset of acute brain lesions and resolving in a few days or weeks (Chatrian *et al.*, 1964; García-Morales *et al.*, 2002). However, a small portion of PLEDs persist for more than three months and are differentially termed "chronic" PLEDs, the underlying cause of which appears to differ (Westmoreland *et al.*, 1986; Fitzpatrick and Lowry, 2007). Although more than 80% of patients with PLEDs experience clinical

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seizures or status epilepticus, the pathophysiology of PLEDs is still a subject of debate and it remains unclear whether they can be characterised as ictal phenomena (Fitzpatrick and Lowry, 2007). Here, we report a man with chronic right hemispheric PLEDs for more than 14 months with elevated levels of anti-*N*-methyl-d-aspartate (NMDA) receptor antibodies and granzyme B in his cerebrospinal fluid (CSF). We administered two courses of steroid pulse therapy, which partially resolved the PLEDs and improved subtle neurocognitive deficits. In the light of these findings, the pathophysiology of chronic PLEDs is briefly discussed.

Case study

The patient, a 54-year-old man, experienced monthly seizures with loss of consciousness from the age of 10. Phenytoin reduced the patient's seizure frequency to one a year. The patient graduated from a university, lived alone, and was employed as an office worker. An EEG recorded when the patient was 43 revealed no epileptic discharge, but registered sporadic, diffuse theta waves (4-7 Hz) and high-voltage slow waves (3 Hz) with right fronto-centro-parietal dominancy. After being seizure-free for a number of years, the patient discontinued his medication.

When the patient was 52 years old, a cluster of seizures culminating into status epilepticus occurred and he was brought to a hospital. Left hemiparesis was observed between ictus and he was intubated and sedated for four days. Seizures recurred after extubation and a 1,000 mg of valproate was started. MRI, 12 days after admission, revealed cortical thickening and hyperintensity on fluid-attenuated inversion recovery (FLAIR) in the right temporal, parietal, and occipital lobes (*figure 1A*). Seizures were controlled by administering 200 mg of carbamazepine and 3,000 mg of levetiracetam. During the follow-up period, right hemispheric PLEDs emerged on an EEG taken five months after the status.

The patient was referred to our hospital 19 months after the status with major complaints of sleepiness and loss of appetite. Upon admission, the man appeared untidy, and put all of his valuables and what appeared to be useless rubbish into a dirty sack. He also presented with mild left hemispatial neglect. Laboratory tests were normal. Cessation of valproate improved the patient's sleep patterns and appetite. An EEG showed intermittent PLEDs prevailing for more than 50% of the total EEG recording (*figure 2A*). In addition, a hypermotor seizure occurred during the EEG, at which time PLEDs disappeared several seconds before the onset of a clinical seizure (*figure 2C*). FLAIR and diffusion-weighted MRI sequences revealed no significant abnormalities. However, fluorodeoxyglucose positron emission tomography (FDG-PET) showed right temporo-parieto-occipital hypometabolism, which was consistent with the source area of the PLEDs, as estimated by magnetoencephalography (MEG) (*figure 1B, 1C, and 1D*). No signs of inflammation were found in the CSF test and a systemic workup aimed at tumour identification, including whole-body FDG-PET and serological tumour markers, was negative. In addition, autoantibodies associated with systemic lupus erythematosus and thyroiditis tested negative. Upon further examination, we found that anti-NMDA receptor (anti-GluR2B and anti-GluR1) antibodies, as well as granzyme B, were strongly elevated in the CSF, compared with disease controls (Takahashi *et al.*, 2009).

Based on these findings, two courses of steroid pulse therapy (1,000 mg/day of methylprednisolone for three days) were performed, which improved the patient's left hemispatial neglect (*figure 3*) and caused the patient's PLEDs to dissolve into periodic delta activity (*figure 2C*).

Written informed consent was obtained from the patient for this case report.

Discussion

Chronic PLEDs are usually found in patients with prolonged partial seizure disorders, and are associated with sustained structural brain abnormalities (Westmoreland *et al.*, 1986). In agreement with previous reports, the patient in this case presented with chronic epilepsy, however, the patient demonstrated no structural brain abnormalities.

As previously mentioned, it is still unclear whether PLEDs represent ictal activity (Fitzpatrick and Lowry, 2007). Based on the finding that the onset of PLEDs is accompanied by ipsilateral hypermetabolism in PET studies, some have argued that these discharges represent ictal activity, comparable to that of partial status epilepticus (Handforth *et al.*, 1994). Others, however, consider that PLEDs reflect acute cerebral damage and are not necessarily related to seizures (García-Morales *et al.*, 2002). It has been proposed that ictal/interictal differences should be considered as a continuum rather than a discrete dichotomy, with PLEDs stretching across the entire ictal-interictal continuum (Chong and Hirsch, 2005). Because PLEDs accompanied by rhythmic discharges (PLEDs plus) are more frequently followed by seizures than those without rhythmic discharges (PLEDs proper), the former are placed towards the ictal end and the latter towards the interictal end of the spectrum (Reiher *et al.*, 1991).

A couple of points should be discussed regarding the nature of PLEDs observed in the present case. First, the

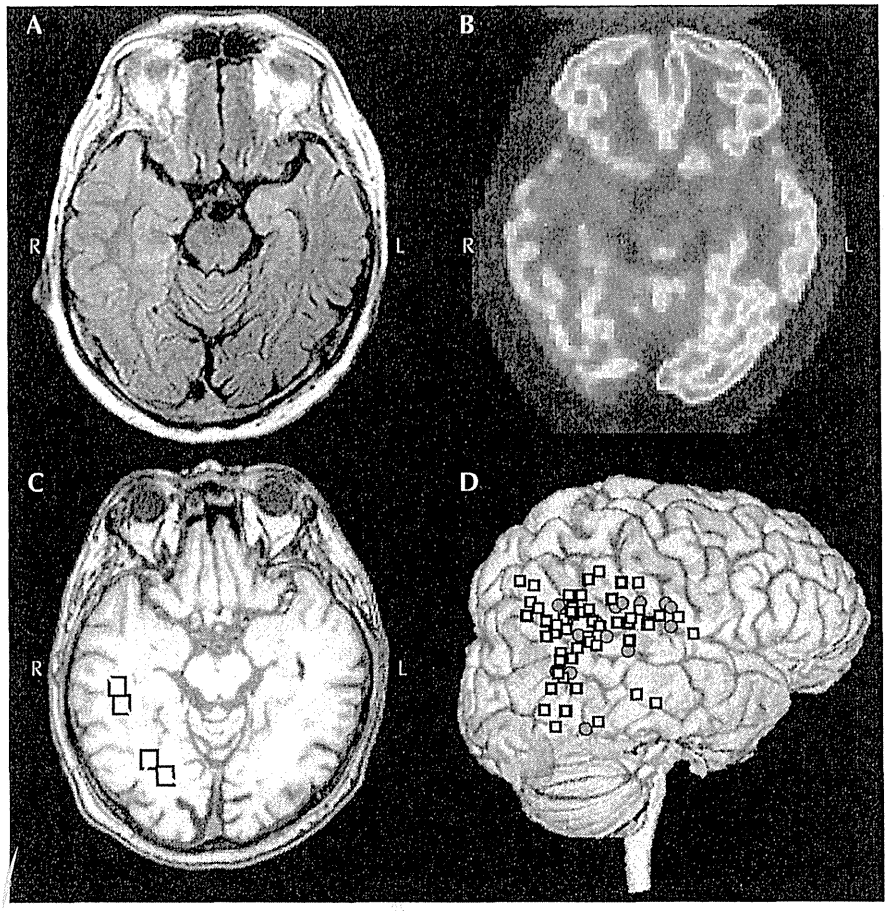

Figure 1. (A) Axial fluid-attenuated inversion recovery MRI of the brain, acquired 12 days after the onset of status epilepticus. Thickening and hyperintensity were observed in the right temporo-parieto-occipital cortex. (B) Fluorodeoxyglucose positron emission tomography and spike dipoles of periodic lateralised epileptiform discharges (PLEDs) estimated by magnetoencephalography, superimposed on T1-weighted MR images obtained upon referral to our hospital (C, D).
Yellow squares represent dipoles with a goodness of fit of more than 90%. Green circles represent dipoles with a goodness of fit of more than 80%. The source area of PLEDs roughly coincided with the hypometabolic region.

patient presented with mild left hemispatial neglect. Meador and Moser (2000) described left hemispatial neglect to be a possible sign of negative seizures and reported a patient with PLEDs in the left parietal region who experienced negative symptoms including right hemiparesis, aphasia, apraxia, and severely depressed mood, which were improved with phenobarbital. Because the negative symptom in the present case was far milder than the aforementioned case, it might be better interpreted as a functional impairment caused by neuropathology underlying chronic epileptiform discharges.

The present case exhibited clinical seizures. However, observed PLEDs were unaccompanied by rhythmic discharges. Moreover, PLEDs disappeared several seconds before the onset of a clinical seizure. This pattern is different from the reported progression of PLEDs proper to PLEDs plus to seizures, and supports the hypothesis that the recorded PLEDs were interictal discharges (Reiher *et al.*, 1991).

In the present case, PET studies disclosed hypometabolism rather than hypermetabolism in the right temporo-parieto-occipital region, which roughly coincided with the localisation of the source dipole of the PLEDs estimated by MEG. This finding is similar to a previous study of a patient who experienced recurrent PLEDs due to a metastatic brain tumour and was investigated using MEG and PET (Hisada *et al.*, 2000). Hypometabolism is indicative of an interictal brain state during PET. However, lack of concurrent EEG recordings restrict the significance of the PET findings as conclusive evidence that observed PLEDs were interictal phenomenon, since PLEDs might have resolved during a PET scan.

By combining clinical, EEG, and PET findings together, the chronic PLEDs recorded in this case apparently

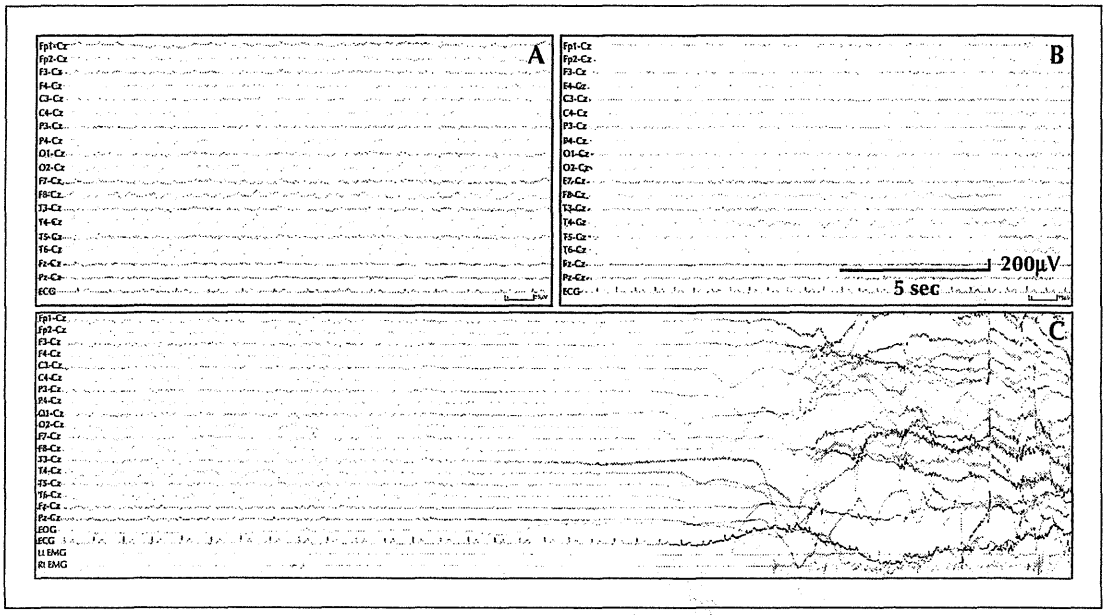

Figure 2. (A) EEG tracing 19 months after the status epilepticus. Right hemispheric periodic complexes (1.0-1.5 Hz) were observed with the highest voltage of the sharp-wave components recorded at T4 and T6 using the international 10-20 EEG system. Because the A2 reference was contaminated by periodic lateralised epileptiform discharges (PLEDs), the midline (Cz) reference was used. (B) EEG after two courses of steroid pulse therapy; sharp-wave components of the PLEDs disappeared and only right hemispheric periodic delta waves could be observed. (C) Seizure onset; the interval between PLEDs became longer and finally disappeared about 10 seconds before the onset of the clinical seizure.

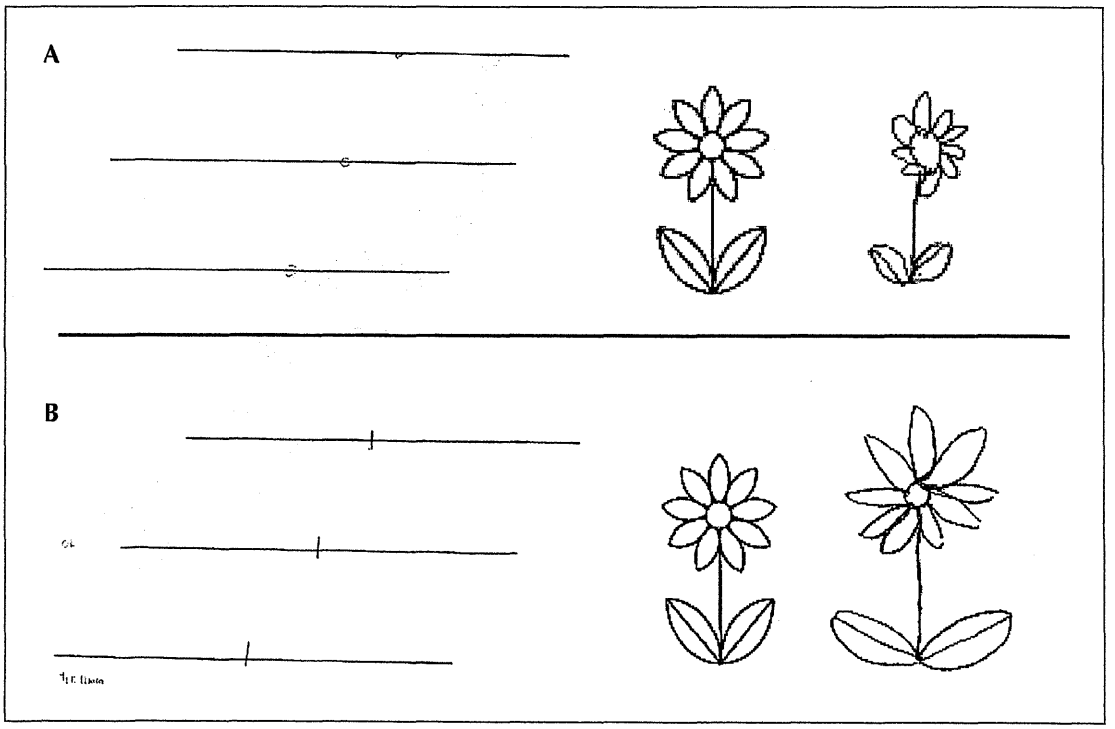

Figure 3. Improvement of left hemispatial neglect after steroid pulse therapy. The patient was asked to mark the centre of three horizontal lines (left) and to copy a picture of a flower (right).
(A) Test result before the two courses of steroid pulse therapy. (B) Test result after the steroid pulse therapy.

correspond to the interictal end of the ictal-interictal continuum.

What is notable in this case was the positive finding of anti-NMDA receptor antibodies in the CSF. Anti-NMDA receptor antibodies have received attention lately because of the recent establishment of anti-NMDA receptor encephalitis as a clinical entity associated with ovarian teratoma (Dalmau *et al.*, 2011). Rasmussen's encephalitis is also accompanied by anti-NMDA receptor (anti-GluR2B) antibodies (Takahashi *et al.*, 2009). Moreover, although rare, PLEDs can be accompanied by the presence of anti-NMDA receptor antibodies (Labate *et al.*, 2009) and Rasmussen's encephalitis (Fitzpatrick and Lowry, 2007).

The causative role of anti-NMDA receptor autoantibodies in the induction of status in the present case is equivocal; although epileptic status and cortical thickening are common in patients with encephalitis, the clinical course in the current case was dissimilar to that of patients with anti-NMDA receptor or Rasmussen's encephalitis. In addition, since the patient had been affected by epilepsy for a long period of time, the withdrawal of antiepileptic medication may have caused the status.

Granzyme B is a serine protease secreted chiefly from cytotoxic T lymphocytes, which induces DNA fragmentation and apoptosis in target cells. Granzyme B in the CSF of patients with Rasmussen's encephalitis is reported to be elevated, and is considered to be involved in the autoimmune pathophysiology of the disease (Takahashi *et al.*, 2009). The existence of anti-NMDA autoantibodies and granzyme B in the CSF may be a sign of cytotoxic T-cell-mediated neuronal injury and fragmentation of neuronal molecules including glutamine receptors, which could cause the production of autoantibodies against them (Takahashi *et al.*, 2009). In the present case, the effectiveness of steroid pulse therapy indicates that reversible autoimmune processes were involved in the pathology that caused both chronic epileptiform discharges and the subtle neurocognitive deficit. □

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The authors have no conflicts of interests to disclose.

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CASE REPORT

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LIMBIC ENCEPHALITIS ASSOCIATED WITH RELAPSING POLYCHONDRITIS RESPONDED TO INFLIXIMAB AND MAINTAINED ITS CONDITION WITHOUT RECURRENCE AFTER DISCONTINUATION: A CASE REPORT AND REVIEW OF THE LITERATURE

TAKESHI KONDO[1], MAMIKO FUKUTA[2], AYUMU TAKEMOTO[3], YUICHIRO TAKAMI[3], MOTOKI SATO[3], NORIYUKI TAKAHASHI[1], TOMIO SUZUKI[3], JUICHI SATO[1], NAOKI ATSUTA[4], GEN SOBUE[4], YUKITOSHI TAKAHASHI[5] and NOBUTARO BAN[1]

[1]*Department of General Medicine/Family & Community Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[2]*Center for Medical Education, Nagoya University Hospital, Nagoya, Japan*
[3]*Department of General Medicine, Nagoya University Hospital, Nagoya, Japan*
[4]*Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[5]*Department of Pediatrics, National Epilepsy Center, Shizuoka, Japan*

ABSTRACT

Central nervous system (CNS) manifestations are rare complications of relapsing polychondritis (RP). The majority of patients respond well to glucocorticoid therapy, but need to maintain it. Some patients are refractory to initial glucocorticoid therapy and to additional immunosuppressants, and end up with an outcome worse than at therapy initiation. The standardized therapeutic protocol for this condition has not been established. The effects of anti-tumor necrosis factor (TNF) -α agents have been reported recently. We experienced a patient with RP and limbic encephalitis who was refractory to initial high-dose glucocorticoid, but subsequently responded to infliximab and did not show deterioration of signs and symptoms after stopping therapy. We report this case together with a systematic literature review. This is the first case report of RP with CNS manifestations successfully treated by an anti-TNF-α agent without recurrence after discontinuation.

Key Words: relapsing polychondritis, limbic encephalitis, infliximab, anti-tumor necrosis factor-alpha agent, therapy discontinuation

INTRODUCTION

Relapsing polychondritis (RP) is an uncommon disorder of unknown etiology that is characterized by recurrent and progressive inflammation of cartilaginous structures. A minority of patients with RP develop central nervous system (CNS) manifestations,[1)] and limbic encephalitis has also been reported.[1-5)] Glucocorticoid has been used as the first-line therapeutic agent,[1-22)] but a standardized second-line therapeutic protocol for RP with CNS manifestations has not

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Corresponding author: Takeshi Kondo, MD
Department of General Medicine/Family & Community Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan
Phone/Fax: +81-52-744-2951, E-mail: kondo@med.nagoya-u.ac.jp

been established. The effects of anti- tumor necrosis factor (TNF) -α agents have been reported recently.[5,9] We report a patient with limbic encephalitis associated with RP who was refractory to initial high-dose glucocorticoid therapy, but subsequently responded to infliximab and discontinued therapy without recurrence. We also reviewed cases of RP with CNS manifestations using PubMed with regard to clinical manifestations and treatment.

CASE PRESENTATION

A 58-year-old Japanese male architect was brought to our institution by his wife, presenting with amnesia, disorientation, emotional liability and urinary incontinence. One year prior to admission, he had bilateral ear pain with swelling and erythema which improved without any treatment over a 4-week period. Nine months prior to admission, he experienced iritis and scleritis in addition to recurrent pain in bilateral auricles. Subsequent biopsy of the left auricle revealed infiltration of inflammatory cells in the perichondrium (Fig. 1). Diagnosis of RP was made based on McAdam's criteria, modified by Damiani and Levine.[23,24] No other organs were affected. Inflammation of bilateral auricles disappeared without any treatment, while iritis and scleritis were controlled by topical glucocorticoid therapy. Around 2 months prior to admission, he showed amnesia with gradual progression. One month prior to admission, he developed difficulty with drawing architectural drafts and finding his way home, together with emotional liability and urinary incontinence. Past medical history revealed well-controlled diabetes mellitus by diet and dipeptidyl peptidase-4 inhibitor (HbA1c was 6.4 to 6.7%).

On admission, his body temperature was 36.7°C, blood pressure was 112/66 mmHg and heart rate was 68 beats per minute. Physical examination revealed flared ears. Head, eye, ear, nose, chest and abdominal examinations were unremarkable. Neurological examination revealed poor tandem gait and poor finger-nose-finger test, but other examinations such as the cranial nerve, sensory and motor systems were unremarkable. He was euphoric and disoriented. His Mini-Mental States Examination (MMSE) result was 16 out of 30. Complete blood cell count, serum chemistry screening and endocrine function were unremarkable. Antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, anti-thyroid peroxydase antibody, anti-thyroglobulin antibody, urinalysis and serological tests for human immunodeficiency virus (HIV)

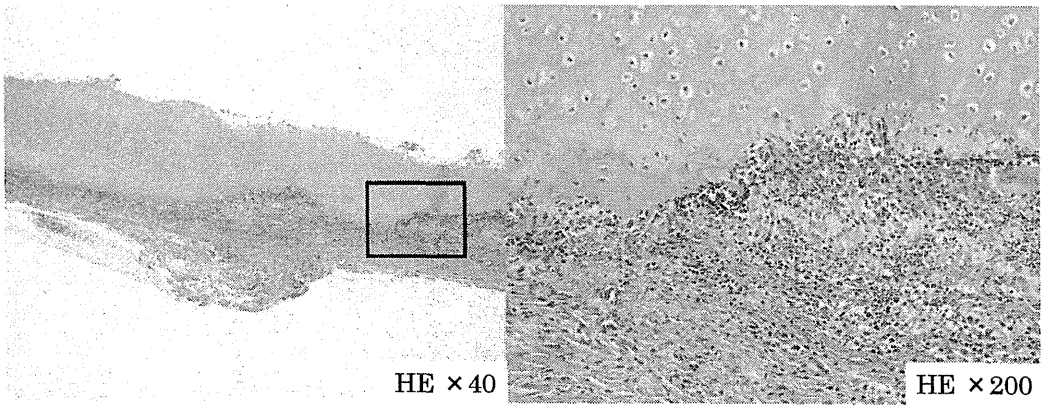

Fig. 1 Histopathological examination of ear biopsy (hematoxylin-eosin stain) showed infiltration of inflammatory cells (histiocytes, lymphocytes, neutrophils and eosinophils) in perichondrium and chondrium.

and treponema pallidum were all normal or negative. Cerebrospinal fluid (CSF) analysis showed 33 cells/μl with 32 polymorphonuclear leukocytes, glucose 81 mg/dl and protein 92 mg/dl. CSF smear for Gram stain and acid-fast organisms stain were negative. CSF cultures for bacteria and *Mycobacterium tuberculosis* and polymerase chain reaction of *Herpes simplex virus* and cytology were also negative. Both anti-N-methyl-D-aspartate type glutamate receptor (GluR) N2B antibody and anti-GluR δ2 antibody were positive in CSF, but neither were positive in serum.

Whole body fluorine-18 fludeoxyglucose positron emission tomography ([18F]FDG-PET) with CT to detect tumor revealed no abnormal uptake. Comparing current brain magnetic resonance imaging (MRI) result with the previous ones indicated limbic system atrophy resulting in ventricular enlargement (Fig. 2-A, B). Diffusion weighted image, fluid-attenuated inversion recovery image (FLAIR) and gadolinium enhancement showed no abnormality. Electroencephalogram showed diffuse dominant theta waves with no spike.

Considering his clinical symptoms like emotional lability and amnesia, limbic system atrophy in MRI and increased number of CSF cells limbic encephalitis was diagnosed. Because other causes such as HIV encephalitis, herpes simplex encephalitis, tumor-associated limbic encephalitis or Hashimoto encephalopathy were ruled out, limbic encephalitis associated with RP was diagnosed, clinically. A course of intravenous 1 g methylprednisolone for 3 days was administered, followed by oral prednisolone 1 mg/kg per day. His cognitive function improved temporarily, but worsened again (Fig. 3). Subsequently infliximab 3 mg/kg was added to the prednisolone. His head MRI had no change but MMSE score was improved gradually, ataxia disappeared through 4 doses of infliximab over a 3-month period, and problematic behavior disappeared. Because of his stable condition as well as the high cost of infliximab, he and his wife refused further infliximab therapy. His condition continued to be stable without infliximab. Prednisolone was tapered down over a 16-month period and finally stopped. The patient was followed up for an additional 9 months after stopping prednisolone without recurrence (Fig. 3). At the end, he could continue active daily living independently, but could not resume his work.

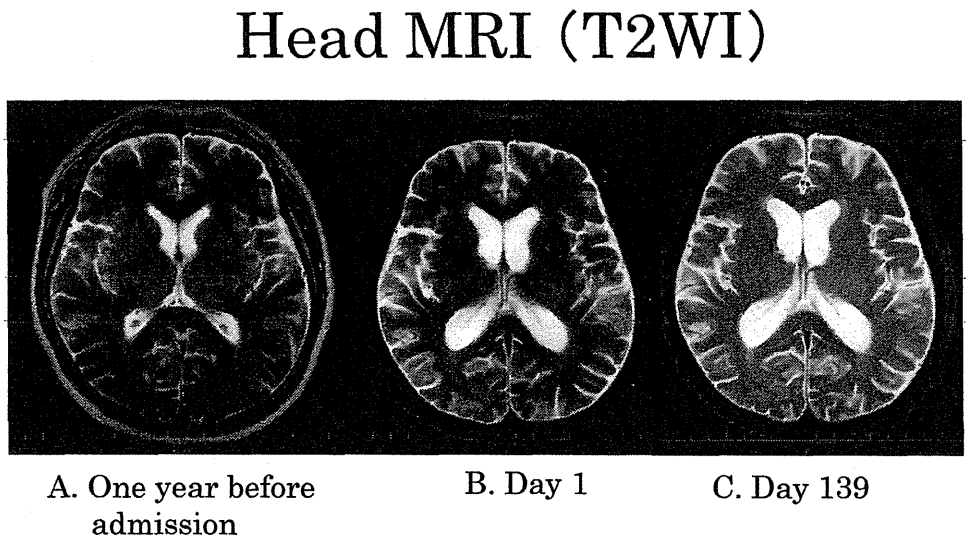

Fig. 2 (A) T2WI one year before admission; (B) T2WI of Day 1 showed ventricular enlargement compared to one year before admission; (C) there was no change after 6 months.

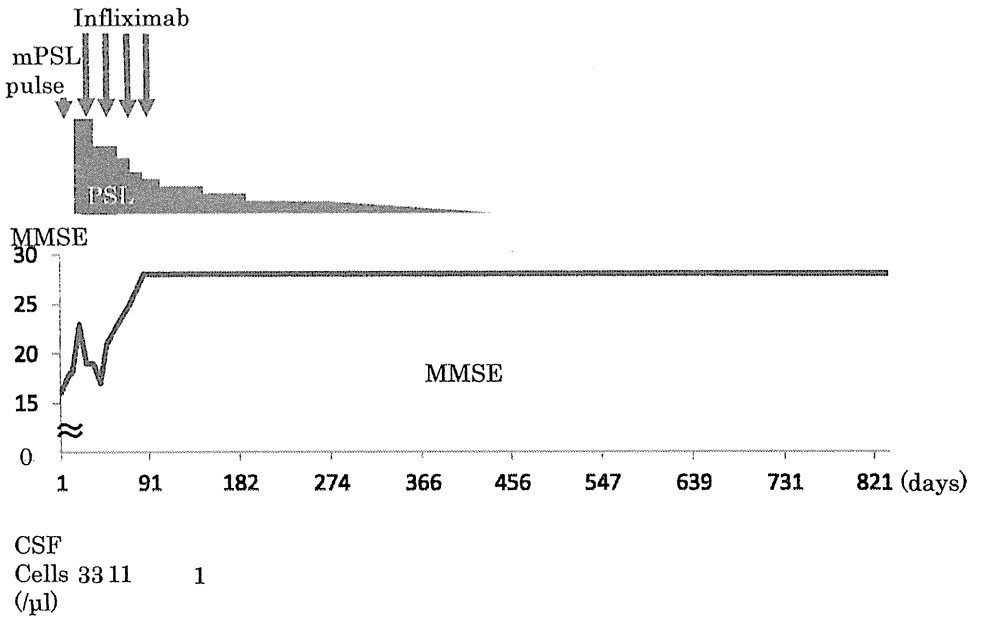

Fig. 3 Clinical course. Cognitive function improved temporarily after methylpredonisolone pulse, but worsened again. MMSE score was improved gradually after infliximab.

DISCUSSION

RP, a rare episodic and progressive inflammatory disease presumed to have autoimmune etiology, was first described in 1923.[25] RP affects cartilage in multiple organs, such as the ear, nose, larynx, trachea, bronchi, and joints.[25] In addition, it can affect proteoglycan-rich tissues such as the eyes, aorta, heart and skin.[25] The diagnosis of RP is usually made on the basis of clinical findings.[25] McAdam criteria[23] modified by Damiani and Levine,[24] which is commonly used as a criterion to confirm the diagnosis of RP, consists of: a) at least 3 of 6 clinical criteria (bilateral auricular chondritis, nonerosive seronegative inflammatory polyarthritis, nasal chondritis, ocular inflammation, respiratory chondritis and audiovestibular damage); b) 1 or more of the previously-mentioned clinical criteria and biopsy confirmation of cartilage inflammation; or c) chondritis at 2 or more separate anatomic locations with response to steroids and/or dapsone. This case fits criterion b).

RP with CNS manifestations is rare.[8,22] We searched MEDLINE in March 2014 using ("Polychondritis, Relapsing" [Mesh] OR "Relapsing polychondritis") AND ("Encephalitis" [Mesh] OR "Limbic Encephalitis" [Mesh] or encephalitis or encephalopathy or "Limbic Encephalitis" OR "Meningoencephalitis" [Mesh] OR Meningoencephalitis or "nervous system") as keywords. We retrieved a total of 54 articles, 26 of them including 31 cases that met inclusion criteria (case report or case series written in English or Japanese) (Table 1).[1-22,26-28]

As shown in Table 1, 28 out of 31 patients have been treated with a high dose of glucocorticoid.[1-22] Twenty-two out of those 28 patients had symptoms which were well-controlled by initial therapy, but only one could discontinue glucocorticoid therapy.[19] Six patients were refractory to initial glucocorticoid therapy.[3,4,7,9,11,12] Additional therapy (cyclophosphamide, intravenous immune globulin, tacrolimus, plasmapheresis, methotrexate and cyclosporin) showed no remarkable effect

Table 1 Abbreviations: T2WI, T2 weighted image. mPSL, methylpredonisolone. PSL, predonisolone. AZP, azathioprine. MONO, monocytes. PMN, polymorphonuclear leukocytes. CYC, cyclophosphamide. MTX, methotrexate. IVIG, intravenous immunoglobulin. nr, not reported.
Cases filled in red were refractory to initial glucocorticoid therapy. Cases filled in blue had good response to initial glucocorticoid therapy. Other patients received no treatment or the results were unknown.[5,7,21,27,28,30]
*The clinical course after the second pulse is not shown.

Year	Age	Sex	Associated neurologic disorders (most patients had fever, headache or meningeal irritation signs)	CSF Leucocytes (/mm 3)	MRI	Treatment	neurological response to initial therapy	neurological response at end of follow up	Outcome	treatment successfully discontinued
this case	58	M	amnesia, cognitive impairment, emotional liability, urinary incontinence, euphoria	33 (32 PMN and 1 MONO)	ventricular enlargement	mPSL 1 g/day 3 days→ PSL 1 mg/kg/day→ +infliximab→PSL →stopped	transitory	good	alive	yes
2011 [9]	57	M	generalized seizure, confusion	700 (MONO 686)	T2WI high, gadolinium-enhanced	high dose i.v. mPSL→ high dose i.v. mPSL+CYC →PSL+CYC→ PSL+MTX→infliximab	transitory	good	alive	no
2011 [7]	52	M	amnesia, gait disorders and urinary incontinence, acalculia	231 (PMN 161, MONO 69)	ventricular enlargement	mPSL 500 mg+IVIG 30 g/day 5 days→ PSL 20 mg/day→ Steroid Pulse	transitory	good or transitory*	alive	no
2009 [3]	62	M	delirium, hallucinations, agitation, disinhibition, cognitive impairment, seizure, disturbed consciousness, recurrent clonic convulsion	39 (MONO 23)	FLAIR high	iv mPSL 3 days a week 3 weeks→iv mPSL 3 days a week 4 weeks→ PSL 20 mg/day+tacrolimus 3 mg/day	transitory	worsend	alive	no
2008 [12]	51	M	coordination disorder, distractibility, emotional lability, insomnia, nocturnal myoclonic jerks, perseveration, attention and concentration deficits, confusion, speech latency, word-finding difficulty, myoclonus	39 (MONO 59)	high signal abnormalities	PSL 80 mg/day→ Cyclophosphamide 150 mg/day	worsened	worsend	died (after 10 months of neurological onset)	no
2011 [4]	73	M	transitory loss of consciousness, confusion, disorientation, confabulation, aphasia, hallucinations, cognitive impairment	89 (MONO 89)	FLAIR high, T2 high	mPSL1500 mg 3 days→ 3500 mg→ mPSL po 24 mg/day→ mPSL 1500 mg+ plasmapheresis→+IVIG	transitory	worsend	died (after 5 month of disease onset)	no
2009 [11]	67	F	bradykinesia, disturbed consciousness, reduced willingness, walking disorder	73 (MONO 73)	FLAIR high	mPSL 1000 mg/day 3 days→PSL 40 mg/day→ PSL 60–50 mg/day +MTX 6–8 mg/w+CyA 100–200 mg/day	transitory	worsend	died (after 6 months of neurological onset)	no
1992 [29]	73	F	decreased consciousness, slow in mention, right eyelid paresis, slight unilateral facial weakness	nr	nr	PSL 100 mg/day→ +Cyc 100 mg/day→ PSL 5 mg/day→both stopped	good	good	alive	yes
2011 [7]	44	M	amnesia, irritated, anxious	190 (PMN17 MONO 171)	T2WI high	mPSL 200 mg 5 days→ 120 mg/day one week→ PSL 60 mg/day +AZP 100 mg/day→PSL 25 mg/day+AZP 100 mg/day	good	good	alive	no
2011 [5]	44	F	anxiety, insomnia	70 (PMN 28 MONO 42)	normal	mPSL 500 mg iv→mPSL 120 mg/day→+AZP	good	good	alive	no
2011 [8]	68	F	dysarthria, disorientation, impaired language function, agraphia	100 (PMN 33, MONO 67)	high intensity	mPSL 1 g 3 days→ PSL 1 mg/kg/day→10 mg/day	good	good	alive	no
2010 [10]	70	M	confusion, hallucinations	38	T2WI high, gadolinium enhancement	mPSL 1 g 3 days→ PSL 1 mg/kg/day→15 mg/day	good	good	alive	no
2008 [13]	66	F	bradykinesia, somnolence, urinary incontinence, mutism, disorientation	90	T1WI low, T2WI high, FLAIR high	mPSL 1000 mg/day 3 days	good	good	alive	no

2008 [12]	68 M	comprehension problems, emotional lability, confusion, language problems, amnesia, executive dysfunction, visuospatial impairment, mild anomia	4 (MONO 2)	T2WI high	PSL 80 mg/day	good	good	alive	no
2007 [14]	40 M	confusion, somnolence	1500 (PMN 1245)	T2WI high, FLAIR high	intravenous steroid therapy	good	good	alive	no
2007 [26]	64 M	amnesia, disorientation, acalculia, reduced willingness	14 (MONO 14)	T2WI high, FLAIR high	PSL 30 mg po→ PSL 20 mg/day po	good	good	alive	no
2006 [15]	71 F	confuse, aphasia, weakness of right extremities	110 (MONO 100)	enhanced	hydrocortisone 200 mg/day→ PSL 60 mg/day→ PSL 20 mg/day	good	good	alive	no
2004 [17]	38 M	right-side weakness, diplopia, right side hemipregia, with hyperreflexia and clonus at the ankle, confuse	nr	T2WI high	corticosteroid therapy→ PSL 1 mg/kg/day+AZP	good	good	alive	no
2004 [3]	45 M	confusion, euphoria, hyperactive behavior, disorientation, amnesia, fever, inappropriately jocular affect, disjointed speech, confabulation, attention deficits	8000 (MONO 7520)	T2WI high	high dose mPSL→ PSL 40 mg/day	good	good	alive	no
2004 [10]	49 M	disorientation, somnolent, ataxic, disorientation, gait disorder	145 (PMN 55 MONO 81)	T2WI high	1 g mPSL 3 days→ PSL 40 mg/day a week→ 20 mg→10 mg/day+ 200 mg hydroxychloroquine per day	good	good	alive	no
2004 [1]	57 M	amnesia, anxiety, depressive state	119 (MONO 105)	T2WI high, FLAIR high, gadolinium enhanced	mPSL 1 g/day 3 days 2 course →60 mg/day	good	good	alive	no
2004 [2]	62 M	acalculia, confusion, euphoria, amnesia	24000 (MONO 21360)	T2WI high, FLAIR high	methylprednisone pulse→ PSL 40 mg/day po	good	good	alive	no
1995 [18]	36 M	horizontal diplopia	5 (5 MONO)	T2WI high, gadolinium enhancement	PSL 20 mg taper over 2 weeks→ 30 mg/day→3 months→ 10 mg/day	good	good	alive	no
1991 [20]	64 M	change in mental status, hallucination	100 (2PMN, 96 MONO)	nr	PSL 100 mg iv→ 60 mg/day→ +Cyclophosphamide 125 mg/day	good	good	alive	no
1983 [22]	58 F	unsteady in walking, confused, hallucination, disorientation, nystagmus, facial weakness	nr	nr	PSL 80 mg/day→ dapson 200 mg/day	good	good	alive	no
2012 [6]	60 M	acalculia, dyslexia, right left agnosia, mild right hemiplesia	138 (MONO 128 PMN 10)	FLAIR high, enhanced	PSL iv→PSL po 20 mg	good	good	improved	no
1984 [21]	51 M	left facial weakness, ataxia, dementia, confuse	normal	nr	steroid	no	no	alive	no
2011 [7]	54 M	bipolar disorder, fmemory loss, hallucinations, amnesia, disorientation, insomnia, irritability	800 (MONO 800)	T2WI high	mPSL 1000 mg iv 3 days→ PSL 80 mg/day+AZP	nr	good	alive	no
2009 [5]	29 M	nr	32 (PMN 32)	T2WI high, FLAIR high	oral steroid→ azathioprine+adalimumab	nr	nr	alive	no
2000 [28]	75 F	tremor	nr	T2WI high	nr	nr	nr	alive	no
2008 [30]	61 M	convulsions, dicreased interest, slurred speech, hallucinations, somnolent, rigidity	312 (MONO 299)	T2WI high, FLAIR high, gadolinuim enhancement	no treatment (supportive therapy alone)	good	good	alive	no
2006 [27]	53 M	cognitive impairment, difficulties with problem solving, amnesia, uncharacteristically aggressive and abusive behavior, disorientation, psychomotor dysfunction	nr	DWI high	palliative care	no (no treatment)	no (no treatment)	died (after 18 months *from onset*)	no

and 3 patients died.[3,4,7,11,12] Only one who was treated with infliximab[9] had a good outcome, so we chose infliximab as a second-line agent.

This is the first case report of RP with CNS manifestations treated with an anti-TNF-α agent who did not show deterioration of signs and symptoms after stopping therapy.

Infliximab may be a good choice for RP with CNS manifestation refractory to initial glucocorticoid therapy.[9] Infliximab has a large molecular weight, so it is impossible for it to permeate the blood-brain barrier. Then why does it work? One potential explanation is that breakdown of the blood-brain barrier by inflammation may permit infliximab to access cerebral parenchyma, resulting in the suppression of TNF-α mediated inflammatory processes.[29] Although theoretically it may be reasonable to stop infliximab when neurologic symptoms are stable, if breakdown of the blood-brain barrier by inflammation is important for the effect of infliximab, it would be wise to closely observe the clinical course when discontinuing infliximab.

CONCLUSION

Anti-TNF-α agents may be a treatment of choice for RP with CNS manifestations refractory to initial glucocorticoid therapy. In addition, anti-TNF-α agents may be discontinued, but it would be prudent to closely observe the clinical course when stopping infliximab.

The authors declare no conflict of interest associated with this article.

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