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【 CASE REPORT 】

Temporal Changes on ^{123}I-Iomazenil and Cerebral Blood Flow Single-photon Emission Computed Tomography in a Patient with Anti-N-methyl-D-aspartate Receptor Encephalitis

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Abstract:

A 45-year-old man was admitted due to tonic seizures, aphasia, disturbance of consciousness, and abnormal behavior. Because cerebral magnetic resonance imaging findings were normal and mild cerebrospinal fluid (CSF) pleocytosis was observed, autoimmune encephalitis was suspected. The presence of anti-N-methyl-D-aspartate (NMDA) receptor antibodies in the CSF was subsequently confirmed. ^{123}I-Iomazenil and cerebral blood flow single photon emission computed tomography (SPECT) revealed an abnormal uptake in the left frontotemporal region. Multimodal immunotherapy was administered, which remarkably improved the level of consciousness. Progressive reversibility of SPECT findings with clinical improvement suggested that the disorder-related functional deficits had been caused by anti-NMDA receptor antibodies.

Key words: anti-NMDA receptor encephalitis, cerebral blood flow SPECT, ^{123}I-Iomazenil SPECT

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Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is associated with antibodies against the GluN1 (NR1) and GluN2 (NR2) subunits of the NMDA receptor. Most patients develop a multistage illness that progresses from psychosis, memory deficits, aphasia, movement disorder, and seizures into a state of unresponsiveness with disturbance of consciousness (1). In these patients, cerebral magnetic resonance imaging (MRI) typically reveals only slight to mild signal abnormalities. In cases of anti-NMDA receptor encephalitis, it is difficult to consider this disorder due to the lack of specific diagnostic biomarkers other than anti-NMDA receptor antibodies. However, single-photon emission computerized tomography (SPECT) can reveal functional abnormalities in anti-NMDA receptor encephalitis, even in cases in which structural abnormalities are not observed on cerebral MRI (2).

We herein report a case of anti-NMDA receptor encephalitis in which the modalities of ^{123}I-iomazenil and cerebral blood flow (CBF) SPECT were useful in determining the affected site.

Case Report

A 45-year-old Japanese man had been repeatedly experiencing difficulties with his right upper limb movement and speech. He was referred to our hospital soon after experiencing a tonic seizure followed by aphasia and motor paresis of the right upper limb and exhibiting abnormal behavior.

On admission, the patient's body temperature was 37.4℃, blood pressure was 147/98 mmHg, and pulse was 90 beats/min with a regular rhythm. The patient's blood cell counts were normal. Inflammatory markers, such as erythrocyte sedimentation rate (33 mm/h) and C-reactive protein levels (2.36 mg/dL), were mildly elevated. A serum biochemical

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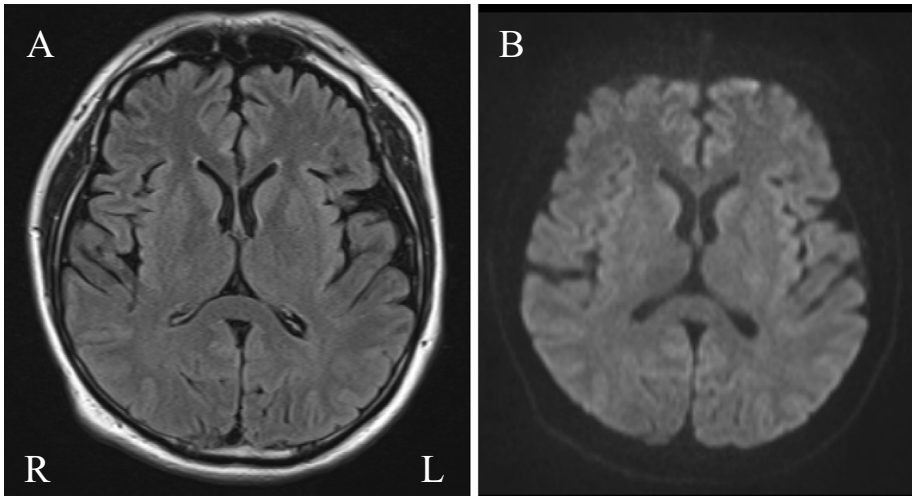

Figure 1. Cerebral magnetic resonance imaging (MRI) findings. Cerebral MRI fluid attenuated inversion recovery (FLAIR, A) and diffusion-weighted imaging (DWI, B) images on day 1 did not reveal any abnormalities in the brain. These abnormalities could not even be observed in the left frontotemporal region, in which electroencephalographic abnormalities had been confirmed. R: right side, L: left side

analysis revealed mildly elevated levels of liver enzymes (alanine aminotransferase, 47 IU/L; γ-glutamyl transpeptidase, 78 IU/L), creatine kinase (834 IU/L), glucose (198 mg/dL), and HbA1c (8.6%). No antinuclear antibodies or any other serum autoantibodies were detected. The initial cerebrospinal fluid (CSF) analysis revealed an initial pressure of 170 mmH_2O, a mildly elevated mononuclear cell count (14 cells/mm^3), and normal total protein levels (35 mg/dL). Laboratory tests revealed the absence of β-D-glucan, *Aspergillus*, *Cryptococcus*, and *Candida* antigens in the CSF. Serum and CSF anti-viral antibody titers, such as those of antibodies against herpes simplex virus type 1, were normal.

Cerebral MRI performed on admission, including fluid attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI), revealed no abnormal signal intensities (Fig. 1). Successive cerebral MRI was performed at multiple time points during hospitalization; however, no marked changes in the signal nor any atrophic changes appeared. An electroencephalogram (EEG) on day 3 showed paroxysmal multiple sharp waves over the left frontal and temporal regions (Fig. 2A). The T3-C3 and C3-Cz electrode pairs showed phase reversal on a bipolar montage at 20 seconds from the time point of Fig. 2A (Fig. 2B). Simultaneous video monitoring revealed the patient's oral automatism, indicating that the C3 region was an epileptic focus. Whole-body computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) revealed no signs of malignancy. On day 14, CBF SPECT was performed, which revealed increased cerebral perfusion in the left frontotemporal region (Fig. 3A).

The empiric administration of acyclovir and meropenem was started; however, disturbance of consciousness (Glasgow Coma Scale E4V2M4) appeared on day 19, followed by frequent seizures (Fig. 4) that seemed to be secondarily generalized to tonic-clonic seizure based on the clinical features and EEG findings. Intractable seizures were treated with antiepileptic drugs, such as carbamazepine, valproic acid, and levetiracetum. In addition, intravenous midazolam administration was performed for status epilepticus. Autonomic disturbances were also present, and hypertensive crisis and tachycardia were observed. Based on the results of previous radiological and serological examinations, it was deemed unlikely that the patient had a paraneoplastic neurological syndrome. A CSF analysis on day 21 revealed an elevated cell count (28 cells/mm^3) but a normal total protein level. ^{123}I-Iomazenil SPECT on day 26 revealed a markedly decreased uptake in the left frontotemporal region (Fig. 3D).

On days 26 and 33, methylprednisolone pulse therapy (mPSL, 1 g/day for 3 successive days, two courses) was administered because an autoimmune neurological syndrome was suspected. Subsequently, plasmapheresis was performed on day 38. After receiving these immunotherapies, the patient's level of consciousness gradually improved (Fig. 4). The frequency and duration of tonic seizures decreased. In addition, the presence of anti-NMDA receptor antibodies in the patient's CSF specimen was confirmed with a cell-based assay using human embryonic kidney 293 cells co-transfected with GluN1 and GluN2 (3). Acyclovir and meropenem administration was discontinued when viral and bacterial infections were ruled out. On day 54, the further reduction in the ^{123}I-iomazenil uptake was observed (Fig. 3E). Furthermore, the increased perfusion in the left frontotemporal region became less apparent by day 68 (Fig. 3B).

On day 68, high-dose intravenous immunoglobulin therapy (IVIg, 0.4 g/kg body weight/day for 5 successive days) was started, followed by oral prednisolone administration (Fig. 4). This multimodal immunotherapy markedly amelio-

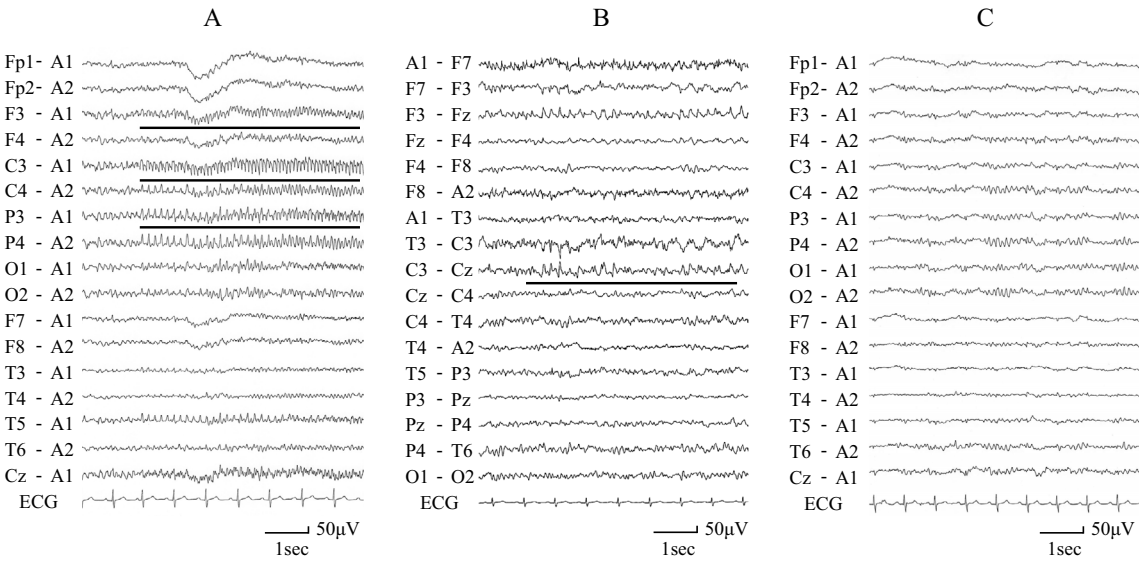

Figure 2. **Electroencephalography (EEG) recordings before and after the immunotherapy. EEG recordings on day 3 (A, B) and day 125 (C). EEG on day 3 revealed paroxysmal multiple sharp waves over the left frontal and temporal regions (A). The T3-C3 and C3-Cz electrode pairs showed phase reversal on a bipolar montage at 20 seconds after the time point of A (B). Following immunotherapies with intravenous methylprednisolone, plasmapheresis, and subsequent intravenous immunoglobulin (IVIg), regular alpha rhythms without epileptic discharges were observed on an EEG (C).**

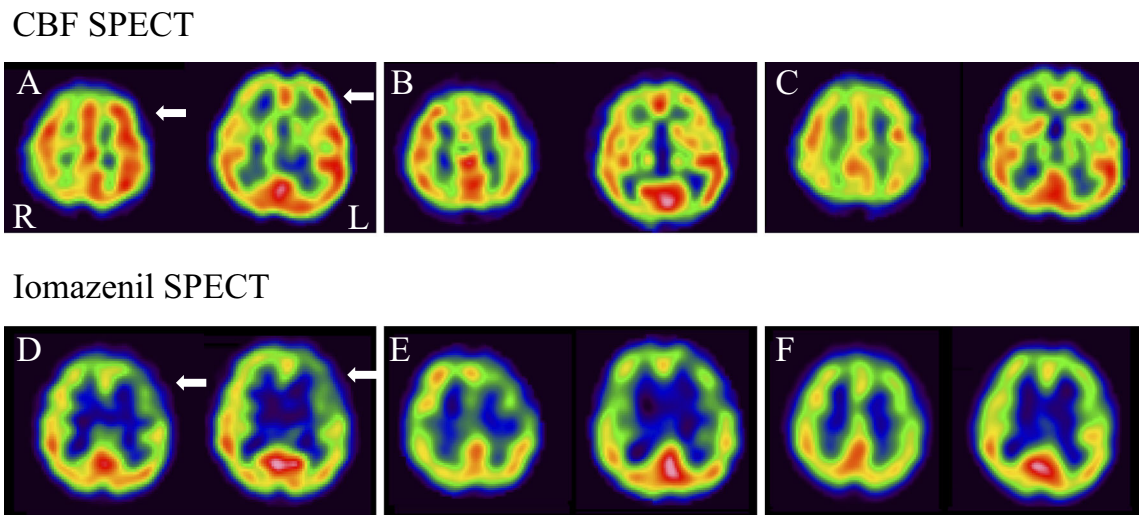

Figure 3. **Chronological changes in cerebral blood flow (CBF) and ^{123}I-iomazenil single photon emission computed tomography (SPECT). Upper panels: CBF SPECT findings obtained before and after immunotherapy. Technetium-99m-ethyl cysteinate dimer (^{99m}Tc-ECD) SPECT indicating the CBF revealed increased cerebral perfusion in the left frontotemporal region on admission (A, arrows, day 14). However, the laterality of perfusion became less apparent in the middle (B, day 68) and after (C, day 109) immunotherapy. Lower panels: ^{123}I-iomazenil SPECT findings obtained before and after immunotherapy. ^{123}I-Iomazenil SPECT indicating the distribution of benzodiazepine receptors in the brain revealed a reduced uptake in the left frontotemporal region on admission (D, arrows, day 26) and further deterioration at one month after admission (E, day 54). After immunotherapies with plasmapheresis and subsequent intravenous immunoglobulin (IVIg), the reduced uptake became less remarkable (F, day 115). R: right side, L: left side**

rated the disturbance of consciousness in the patient. Oral prednisolone was gradually tapered by 5 mg per week. A CSF analysis on day 97 revealed a decreased cell count (2 cells/mm^3). CBF SPECT on day 109 revealed no obvious laterality (Fig. 3C). The anti-NMDA receptor antibodies in the CSF were re-evaluated on day 112 when the patient's

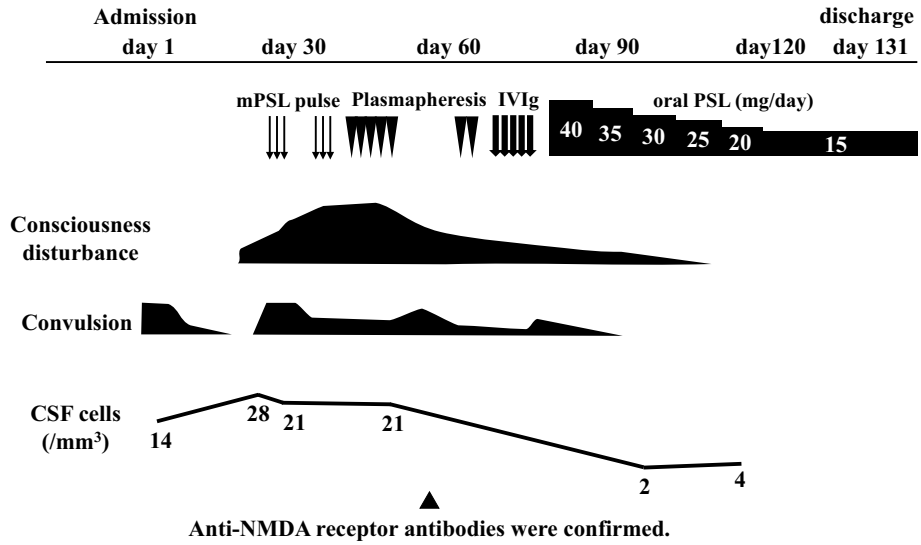

Figure 4. **Clinical course of the present case. Medical records and chronological changes in the symptoms and cerebrospinal fluid (CSF) cell counts after admission are shown. Multimodal immunotherapy ameliorated symptoms and CSF pleocytosis. IVIg: intravenous immunoglobulin, mPSL: methylprednisolone, NMDA: N-methyl-D-aspartate, PSL: prednisolone**

neurological deficits had almost recovered, and their absence was confirmed by a cell-based assay. On day 115, the reduced uptake of ^{123}I-iomazenil in the left frontotemporal region became less remarkable (Fig. 3F). An EEG on day 125 showed regular alpha rhythms without epileptic discharges (Fig. 2C). On day 131, the patient was discharged and returned home without any residual symptoms. He returned to his previous job without experiencing any difficulties. Oral prednisolone was discontinued, and no recurrence was confirmed for the following three years.

Discussion

Severe intractable tonic seizures and abnormal behavior due to anti-NMDA receptor encephalitis were observed in the present case and were successfully treated by multimodal immunotherapy. To make a definite diagnosis of autoimmune encephalitis, developing a test for autoantibodies that could explain the clinical characteristics is considered to be especially important. In order to develop a syndrome-based diagnostic approach to autoimmune encephalitis, Graus et al. formulated a set of guidelines. The present case met the diagnostic criteria for probable anti-NMDA receptor encephalitis based on these guidelines (4). In cases where autoimmune encephalitis is suspected and the possibility of infection has been ruled out, it is prudent to start immunotherapy to treat the patient.

It has been proposed that the primary pathomechanism of anti-NMDA receptor encephalitis involves anti-NMDA receptor antibodies (1). More than 75% of all patients with anti-NMDA receptor encephalitis show substantial recovery with a decline in antibody titers. Anti-NMDA receptor antibodies cause a titer-dependent, rapid, and reversible loss of surface NMDA receptors owing to antibody-mediated capping and internalization, resulting in the abrogation of the NMDA receptor-mediated synaptic function (1, 5).

Previous studies have reported that, in cases of anti-NMDA receptor encephalitis, CBF SPECT reveals variable multifocal cortical and subcortical abnormalities (increased or decreased cerebral perfusion) that might change during the disease course, although some cases showed normal CBF findings (6, 7). In the present case, CBF SPECT revealed reversible increased cerebral perfusion in the left frontotemporal region. The increased regional cerebral perfusion on CBF SPECT likely reflected transient hyperemia due to the occurrence of seizures (nonspecific postictal hyperperfusion) or status epilepticus (Fig. 3A-C).

However, to our knowledge, the use of ^{123}I-iomazenil SPECT in cases of anti-NMDA receptor encephalitis has not been reported. In the present case, ^{123}I-iomazenil SPECT revealed a reversible decrease in the radiotracer uptake in the left frontotemporal region. An interictal examination with ^{123}I-iomazenil SPECT has been used to detect epileptogenic foci in patients with focal epilepsy (8). ^{123}I-Iomazenil SPECT was developed to visualize the distribution of central benzodiazepine receptors coupled with $GABA_A$ receptors, which are present on inhibitory neurons. Although the precise functional association between NMDA and $GABA_A$ receptors is unclear, a previous study using mouse hippocampal slices showed that NMDA receptor activation enhances the GABAergic transmission (9). Therefore, anti-NMDA receptor antibodies may reduce the activity of GABAergic transmission. Thus, the partial reversibility of the decreased ^{123}I-iomazenil radiotracer uptake and a lack of MRI abnormalities in this case suggested that functional deficits due to anti-NMDA receptor antibodies might cause this disorder. According to a previous study using cultured rat hippocampal neurons, anti-NMDA receptor antibodies specifically af-

fected NMDA receptors without any demonstrable effect on $GABA_A$ receptors (10).

It was also reported that tumor necrosis factor-α (TNF-α) induced by inflammation causes internalization of benzodiazepine receptors (11). The immunopathogenesis of anti-NMDA receptor encephalitis has been proposed to be caused by a B cell-mediated rather than a T cell-mediated mechanism (12, 13). However, regarding T cell involvement TNF-α, a T cell-producing cytokine, has also been reported to increase slightly in CSF of patients with anti-NMDA receptor encephalitis (14). The SPECT findings of decreased benzodiazepine receptors at the acute stage of this case might be due to TNF-α induction. On ^{123}I-iomazenil SPECT performed on day 115 (Fig. 3F), the uptake became less remarkable, indicating improvement in inflammation and the reduction in TNF-α production by immunotherapies. The partial reversibility of the ^{123}I-iomazenil SPECT findings might be mediated by the amelioration of anti-NMDA receptor antibody-associated neuroinflammation. Since the combined immunotherapies were successful on this case, the reversibility of functional abnormality might be supported by chronological changes in the hypodistribution on ^{123}I-iomazenil SPECT.

Cerebral MRI abnormalities have been found in nearly 50% of cases with anti-NMDA receptor encephalitis (1). Because some cases of anti-NMDA receptor encephalitis show no cerebral MRI abnormalities, ^{123}I-iomazenil and CBF SPECT analyses must be used to examine the affected site and assess the effectiveness of treatment.

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

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