INTERNAL MEDICINE

□ CASE REPORT □

An Atypical Case of Anti-NMDA Receptor Encephalitis: Predominant Parkinsonism and Persisting Micrographia without Oro-facial Dyskinesia

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Abstract

We describe the case of a 46-year-old man with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis with prominent parkinsonism. The patient presented with psychiatric symptoms followed by epileptic seizure and parkinsonism including micrographia. Magnetic resonance imaging (MRI) revealed lesions in the bilateral medial temporal lobes and basal ganglia on fluid-attenuated inversion recovery images. His symptoms and MRI findings were ameliorated by immunotherapy but then relapsed. After retreatment, his parkinsonism gradually improved except for the micrographia. This is an atypical case of anti-NMDAR encephalitis in that the patient showed prominent and refractory parkinsonism, thus indicating that the clinical diversity of anti-NMDAR encephalitis is greater than expected.

Key words: parkinsonism, micrographia, anti-NMDA receptor antibody, limbic encephalitis, basal ganglia, relapse

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune limbic encephalitis associated with antibodies against heteromers of the NR1 and NR2 subunits of cell-surface NMDARs, and it shows clinical features such as behavioral changes, memory deficit and involuntary movement (1-3). Movement disorders such as choreoathetosis, parkinsonism and myoclonus have been identified in 70-90% of anti-NMDAR encephalitis cases (3, 4), of which choreoathetosis, especially in the orofacial and upper limbs, is observed most frequently (1, 4); in contrast, parkinsonism, demonstrating such symptoms as rigidity and micrographia, is a rare manifestation.

We herein describe an atypical case of relapsing anti-NMDAR encephalitis with parkinsonism, which persisted for a long duration despite improvement of the encephalitis.

Case Report

A 46-year-old right-handed man without any previous medical history developed recurring paroxysmal symptoms, such as vertigo, nausea, palpitation, and olfactory hallucination, followed by an abnormal sensation in his right leg. Subsequently, hypophonia and micrographia emerged. Somatoform disorder was suspected during an evaluation by a psychiatrist. However, the symptoms did not improve with the administration of benzodiazepine and a selective serotonin reuptake inhibitor. Five months after onset, the patient was admitted to our hospital with a suspicion of encephalopathy. On admission, other than a body temperature of 37.8 ℃, he showed normal vital signs. Physical examination showed no abnormalities except for pigment deposition on the abdomen. A neurological examination revealed a mild disturbance in consciousness, miosis with decreased light reflexes, and normal deep tendon reflexes. There was no pathological reflex. The patient presented with a masked facial expression and spoke in a whispery monotone. Muscle

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tonus of the neck and extremities was initially normal, but rigidity of the left arm and leg emerged 2 weeks after admission. Tonic seizure was also observed intermittently, lasting a few minutes and recovering through a postictal stupor state.

The hematological findings were normal, including autoantibodies related to various connective tissue disorders. Anti-thyroglobulin, thyroid peroxidase and thyroid microsomal antibodies were slightly elevated, but the thyroid function was normal. A cerebrospinal fluid (CSF) analysis showed slight elevations of the protein level (93 mg/dL) and IgG index (0.81), with a normal cell count and glucose level. The oligoclonal IgG bands were positive. Herpes viral DNA was not detected in the CSF. The serum and CSF were negative for anti-neuronal autoantibodies, such as those against Hu, Yo, Ri, amphiphysin, Ma2 and recoverin, and for antibodies related to autoimmune limbic encephalitis, such as those against the voltage gated potassium channel (VGKC), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), gamma-aminobutyric acid B receptor (GABABR) and metabotropic glutamate receptor 1 (mGluR1) and 5 (mGluR5), as well as for antibodies targeting the amino terminus of alpha-enolase (NAE), a diagnostic marker for Hashimoto's encephalopathy. Antibodies against NR1/NR2 heteromers of NMDAR were detected in the CSF (titer: 1/80), but not in the serum.

An electroencephalogram (EEG) showed a periodic sharp wave at intervals of approximately 1.5-2 s, mainly in the right temporal region, which resembled periodic lateralized epileptiform discharges. The background activity was a posterior dominant 10-Hz alpha wave. Magnetic resonance imaging (MRI) of the brain revealed high signal intensities in the bilateral medial temporal lobes and basal ganglia, predominantly on the left side, on fluid-attenuated inversion recovery (FLAIR) images without gadolinium enhancement, as well as mild swelling of the head of the caudate nucleus and medial temporal lobe on the left side [Fig. 1(A) a-c]. The tonic seizure was diagnosed to be a complex partial seizure due to temporal lobe epilepsy, based on the clinical features and EEG and MRI findings. ^{99m}Tc single photon emission computed tomography (SPECT) showed hypoperfusion in the cerebellum and bilateral basal ganglia, which was especially severe in the left caudate nucleus [Fig. 1(B) a]. No tumors or inflammatory lesions were found during a comprehensive tumor screening using repeated contrast enhanced CT and a urogenital examination for testicular tumors. Thus, the patient was diagnosed with anti-NMDAR encephalitis without tumors, presenting with complex partial seizure and parkinsonism.

Anti-epileptic drugs, steroids (three cycles of steroid pulse therapy with methylprednisolone 1 g/day for 3 days, followed by oral prednisolone that was subsequently tapered off) and intravenous immunoglobulin (IVIG, 400 mg/kg/day for 5 days) were administered (Fig. 2). The epileptic seizures and rigidity of the left arm and leg disappeared, and the EEG findings normalized after the steroid pulse therapy. One month after therapy initiation, the anti-NMDAR antibody titer in the CSF decreased to 1/40. Parkinsonism, characterized by a small-step gait, and hypophonia improved gradually with rehabilitation. However, the micrographia continued, even after discharge.

On a neurological examination 5 months after the initial therapy (11 months after onset), micrographia was recognized in both hands, but it was more evident in the right hand (Fig. 3). Handwritten characters gradually shrank with writing progression but slightly improved at the beginning of each new line. There was no difference in character size between spontaneous writing and transcription of the examiner's handwriting, and the handwriting sample size and direction did not influence the character size. Micrographia was found to be mild when the patient drew figures, such as a double pentagon. On FLAIR images from brain MRI, high signal intensities became less prominent [Fig. 1(A) d-f]. Mild atrophy of the head of the caudate nucleus and medial temporal lobe on the left side was also observed.

After an additional 2 months (13 months after the initial episode), the patient complained of an abnormal sensation similar to insects moving inside and through his left arm, as well as anxiety and frustration. He was therefore readmitted to our hospital. A neurological examination on admission revealed worsening of the micrographia in both hands and other parkinsonism features, such as a masked facial expression, hypophonia, a small-step gait and freezing. Rigidity of the neck and extremities was not detected. Handwritten characters showed a marked initial reduction in size compared with written samples (Fig. 4). The severity of micrographia was not influenced by the transcription content, including Kanji, Hiragana, and Katakana characters, upper- and lowercase alphabet letters, numbers and symbols. Visual and auditory cues did not improve the handwriting.

In the CSF, the IgG index was elevated to 0.69, while the anti-NMDAR antibody titer decreased to 1/20. Brain MRI showed recurrent high signal intensities on FLAIR images of the bilateral medial temporal lobes and head of the caudate nucleus, predominantly on the right side [Fig. 1(A) g-i]. Hypoperfusion of the basal ganglia on SPECT was detected mainly on the left side [Fig. 1(B) b]. A relapse of anti-NMDAR encephalitis was diagnosed, and three cycles of steroid pulse therapy were administered, followed by the oral administration of azathioprine to prevent relapse. Azathioprine was subsequently discontinued due to liver dysfunction and replaced by prednisolone. The abnormal sensation in the left arm and parkinsonism symptoms, except for the micrographia, improved gradually. The high intensity lesions on MRI disappeared [Fig. 1(A) j-l], but hypoperfusion of the left basal ganglia remained on SPECT. Encephalitis has not relapsed for over one year in this case, despite tapering of the oral prednisolone.

Discussion

This anti-NMDAR encephalitis case without tumors was

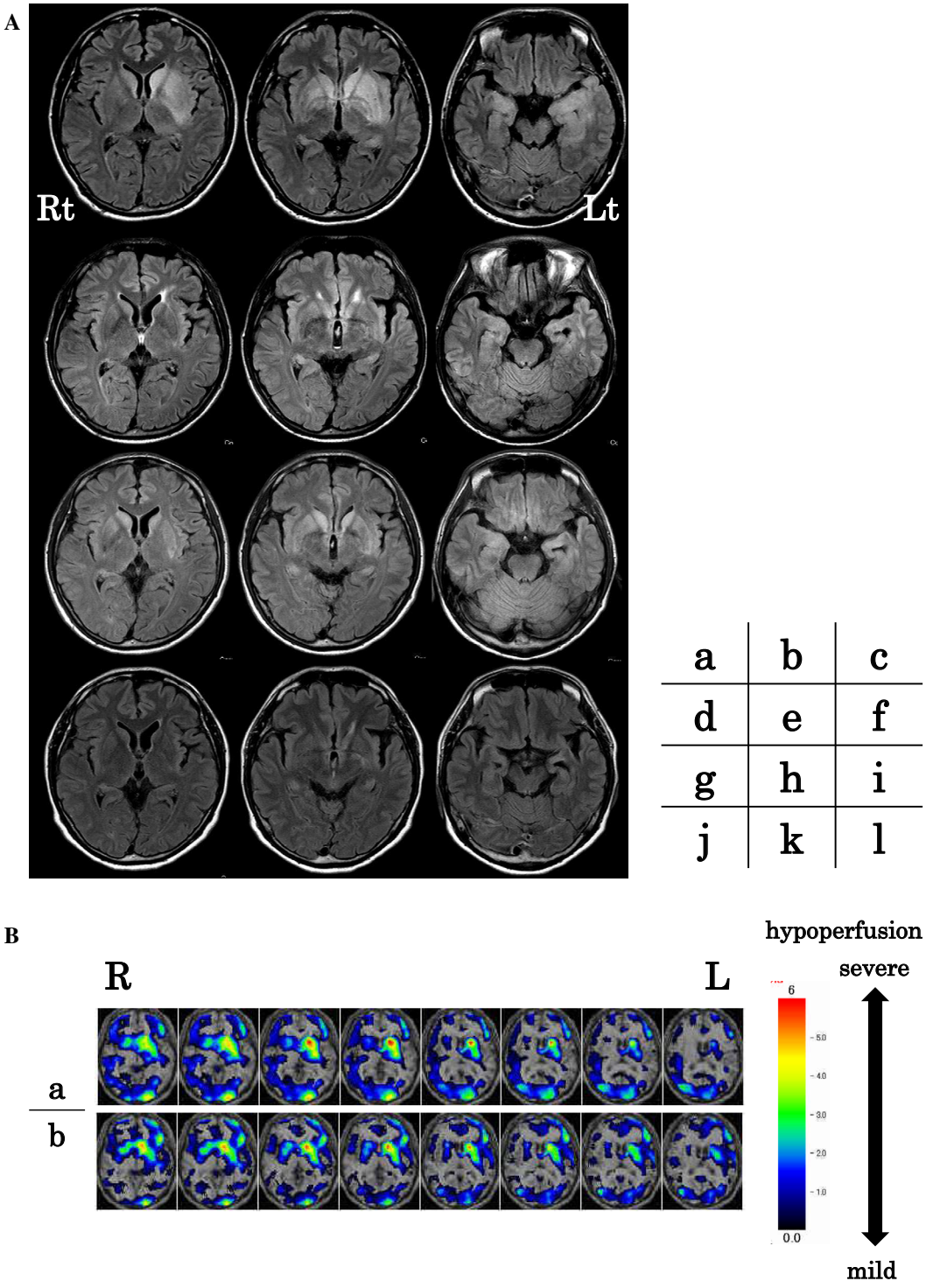

Figure 1. **(A) MRI FLAIR images obtained at admission and during the therapeutic course. (B) ^{99m}Tc SPECT performed at onset and at relapse of the encephalitis. (A) Magnetic resonance imaging (MRI) on admission showed high signal intensities in the bilateral medial temporal lobes and basal ganglia, predominantly on the left side, on fluid-attenuated inversion recovery (FLAIR) images (a-c), as well as mild swelling of the head of the caudate nucleus and medial temporal lobe on the left side. After treatment with steroid pulse therapy and intravenous immunoglobulin (IVIG), the high signal intensities became less prominent, and the head of the caudate nucleus and medial temporal lobe on the left side turned slightly atrophic (d-f). Recurrent high signal intensities in the bilateral medial temporal lobes and the head of the caudate nucleus, predominantly on the right side, were observed at relapse (g-i). The high signal intensities disappeared after re-treatment (j-l). (B) ^{99m}Tc single photon emission computed tomography (SPECT) at onset revealed hypoperfusion in the bilateral basal ganglia, which was most severe in the left caudate nucleus (a). At relapse, severe hypoperfusion in the left basal ganglia was still observed (b).**

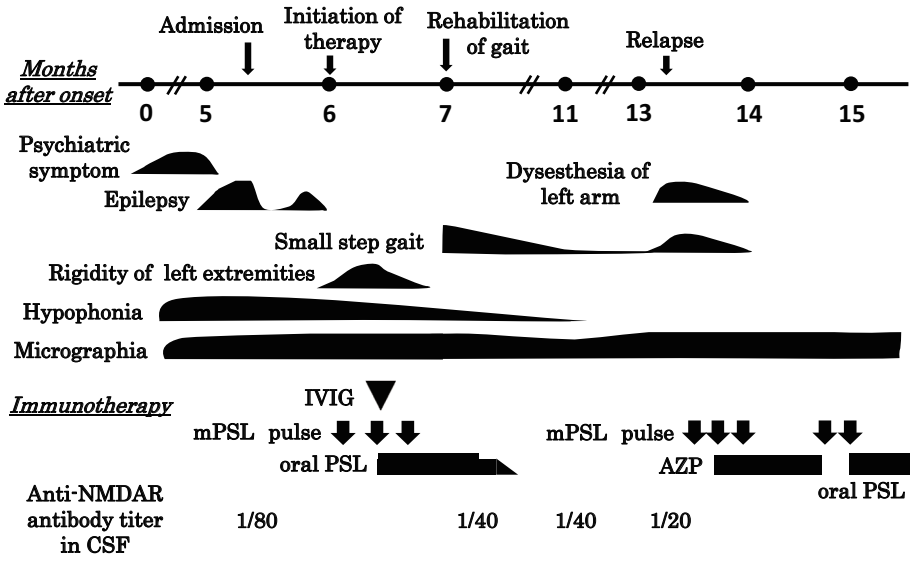

Figure 2. **The clinical course. Immunotherapy was effective for treating all symptoms except micrographia, both at onset and at relapse. The anti-NMDAR antibody titer in the CSF decreased continuously during the therapeutic course despite relapse. PSL: prednisolone, IVIG: intravenous immunoglobulin, AZP: azathioprine, NMDAR: N-methyl-D-aspartate receptor, CSF: cerebrospinal fluid**

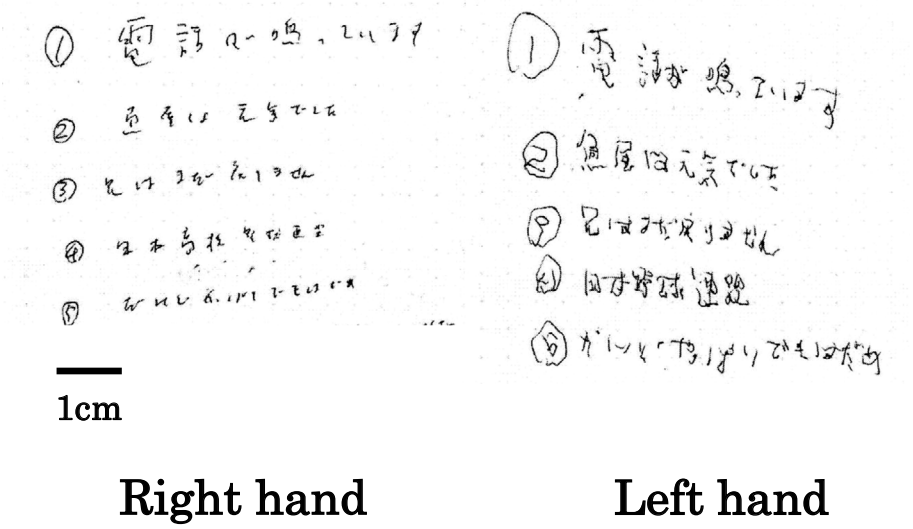

Figure 3. **Handwriting using both hands 11 months after onset. Micrographia was observed with both hands, but more obviously with the right hand. The handwritten characters showed a progressive reduction in size along the same line.**

characterized by persisting parkinsonism. MRI revealed causal lesions in the basal ganglia, which is detected in only 5% of the patients with anti-NMDAR encephalitis (1). Immunotherapy including IVIG and steroids improved all neurological symptoms except micrographia, which endured for a long period. Although encephalitis relapsed 7 months after onset, it improved again following steroid therapy. The anti-NMDAR antibody titer in the CSF gradually decreased as the patient recovered. Thus, the anti-NMDAR antibody is most likely to be associated with the neurological symptoms observed in this case.

One-third of the patients with anti-NMDAR encephalitis present with parkinsonism and rigidity (4). Inactivation of GABAergic neurons due to a decrease in the NMDAR levels may cause movement disorders through disinhibition of the excitatory pathways (2). Our case was unique in that his parkinsonism had been prominent since disorder onset. In general, typical cases of NMDAR encephalitis sequentially develop prodromal symptoms, psychosis, hypoventilation, orofacial dyskinesias and bizarre involuntary movements (5). To the best of our knowledge, no case of anti-NMDAR encephalitis showing parkinsonism as a predominant clinical feature has been reported so far. We should investigate the presence of anti-NMDAR antibodies in patients with acute

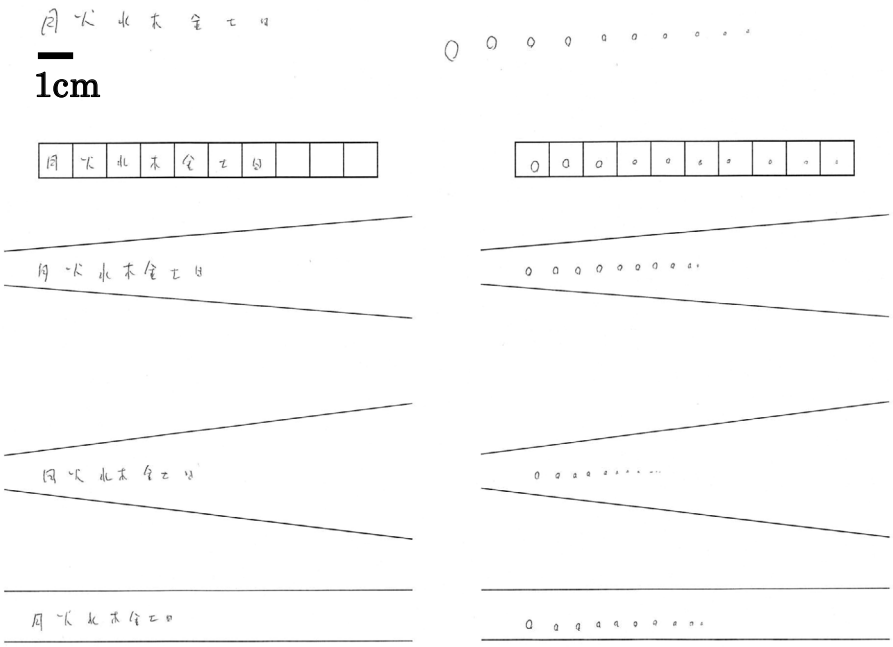

Figure 4. **Handwriting in Kanji and the drawing of a figure (circle) using the right hand at relapse. The handwritten characters showed an initial marked reduction in size. Micrographia was not improved by visual cues, such as writing in cells or on a progressively expanding ruled line.**

or subacute encephalitis of unknown etiology, even if the clinical course is atypical, as reported previously (6).

We considered basal ganglia lesions as the probable cause of parkinsonism in our case, and the severity of parkinsonism seemed to correlate with the degree of abnormal radiological findings in the basal ganglia. We did not use levodopa in our patient, and it is unclear whether the administration of levodopa is effective for parkinsonism in cases with anti-NMDAR encephalitis.

Our case is also unique in that micrographia persisted for a longer duration than that reported in other parkinsonism cases. Micrographia is a form of movement disorder classified into two categories based on the accompanying extrapyramidal symptoms. One category consists chiefly of Parkinson's disease and parkinsonian syndrome (7-9). In a recent cohort study, micrographia was identified in as many as 63.2% of patients with Parkinson's disease and was thought to be caused by a hypometric output driven by the motor-premotor cortex with defects in execution of handwriting (9). The second category of micrographia occurs without other accompanying parkinsonism symptoms and has been described in patients with cerebral infarction, cerebral deep venous thrombosis, brain tumors, multiple sclerosis, and systemic lupus erythematosus (10-18). Only handwriting was impaired in these patients, and micrographia was observed in the right hand with lesions in the left hemisphere in most cases (10-12, 15, 17). Causal lesions were commonly detected in the thalamus, basal ganglia and corona radiata. However, the mechanism of this type of micrographia is still unclear. Although it is undeniable that micrographia emerged as a part of the parkinsonian freezing phenomenon, we speculate that dysfunction in the left basal ganglia due to hypoperfusion was possibly associated with the continuing micrographia, independent of any other parkinsonism symptoms, in this case. In addition, right handedness may contribute to the fact that the micrographia was more apparent in the right hand.

Relapse has been found to occur in 12-24% of patients with anti-NMDAR encephalitis (1, 3, 4, 19), and relapses are usually less severe than the first episode, as in our case (3, 19). Generally, the anti-NMDAR antibody titer in the CSF correlates with the clinical course (4). However, a repeated increase in the antibody titer was not found in our case as the symptoms worsened again, which was diagnosed as relapsed anti-NMDAR encephalitis based on clinical symptoms and radiological findings. In a 2-year follow-up, patients with anti-NMDAR encephalitis without tumors were found to relapse more frequently than were those with tumors (3), and relapse may occur many years after the initial episode (19). Therefore, the performance of yearly tumor surveillance for at least 2 years and careful attention to relapse are required in such patients, regardless of the anti-NMDAR antibody titer.

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

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