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【 CASE REPORT 】

Gerstmann's Syndrome in a Patient Double-positive for Antibodies against the N-methyl-D-aspartate Receptor and NH_2-terminal of α-enolase

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Abstract:

We herein report a case of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis concurrent with NH_2-terminal of α-enolase (NAE) antibodies. A 36-year-old Japanese woman presented with Gerstmann's syndrome followed by jerky involuntary movements, seizure, autonomic instability, and consciousness disturbance. NAE antibodies were detected in the serum; however, NMDAR antibodies were identified in the cerebrospinal fluid with a cell-based assay, confirming the diagnosis of anti-NMDAR encephalitis. This case highlights the fact that Gerstmann's syndrome can be a manifestation of anti-NMDAR encephalitis and that NAE may be identified concurrently with NMDAR antibodies, suggesting that the diagnosis of Hashimoto encephalopathy requires the reasonable exclusion of alternative diagnoses, including anti-NMDAR encephalitis.

Key words: anti-N-methyl-D-aspartate receptor encephalitis, Hashimoto's encephalitis, Gerstmann syndrome, single-photon emission computed tomography

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis caused by autoantibodies against the GluN1 subunits of the NMDARs. Patients with anti-NMDAR encephalitis usually present with the acute onset of psychobehavioral or memory alterations that evolve into decreased levels of consciousness accompanied by seizures, movement disorders, hypoventilation, and autonomic instability (1, 2). Atypical symptoms, such as cerebellar ataxia, parkinsonism, hemiparesis, hemichorea, or hemidystonia, have also been reported (2-4). However, Gerstmann's syndrome has rarely been reported in anti-NMDAR encephalitis (5).

In autoimmune encephalitis associated with autoantibodies, the target antigens usually define the range of symptoms, syndrome specificity, or characteristics of tumor association. However, a patient may harbor multiple autoantibodies. A small number of patients with anti-NMDAR encephalitis have been reported to have concurrent glial or neuronal surface antibodies, and it is suggested that coexisting autoantibodies may contribute to additional clinical features, such as demyelinating syndrome (6, 7).

Although NH_2-terminal of α-enolase (NAE) antibodies were originally reported as a disease-specific marker of Hashimoto encephalopathy (8), the antibodies can be identified in anti-leucine-rich glioma inactivated 1 (LGI1) encephalitis (9), and the clinical significance of the NAE antibodies remains controversial. No case of anti-NMDAR encephalitis concurrent with NAE antibodies has been reported previously.

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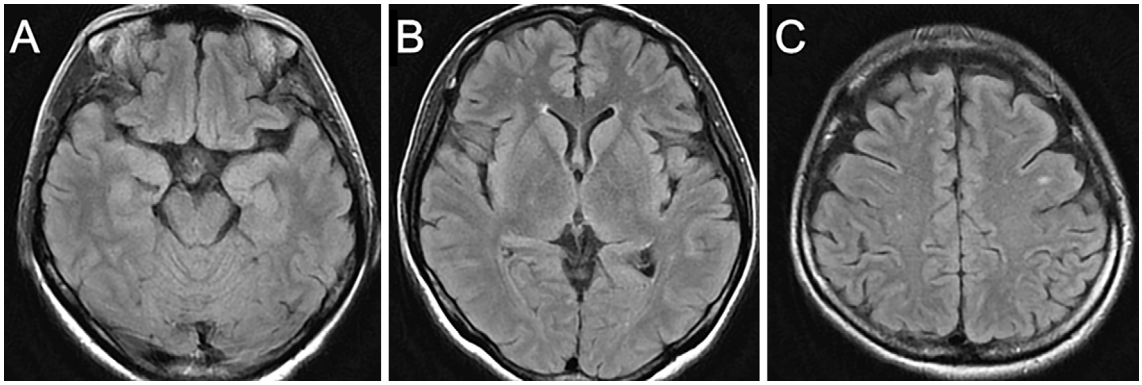

Figure 1. Brain magnetic resonance imaging (MRI) findings on admission. There were no increased fluid-attenuated inversion recovery (FLAIR) signals in the medial temporal lobes (A, B), but nonspecific small increased signals were seen in the subcortical white matter (B, C).

We herein report a patient with anti-NMDAR encephalitis with NAE antibodies who presented with Gerstmann's syndrome and describe the usefulness of N-isopropyl-p-(^{123}I)-iodoamphetamine (IMP) single-photon emission computed tomography (SPECT) for monitoring the functional alterations due to NMDAR antibodies.

Case Report

A 36-year-old Japanese woman was admitted to our hospital in November 2018 with relapse of psychobehavioral alterations. The patient had been in her usual state of health until 14 months before admission in September 2017 (at 35 years of age), when she had a vague feeling of anxiety, memory loss, and dysgeusia. She had been evaluated at another hospital and undergone brain magnetic resonance imaging (MRI), but the findings were unremarkable. A psychiatric disorder was suspected, and she was treated with antidepressants for two months, resulting in the resolution of her symptoms. However, two months before admission, she began to have difficulty writing and calculating. Four weeks before admission, she started to complain of feeling that "there is someone in the room" and became irritable and hypersensitive to noise, ultimately leading to admission to our hospital with possible encephalitis. She had a history of scrub typhus seven years earlier but no prodromal viral illness, such as a fever or headache, before admission.

On an examination, her body temperature was 37.1°C, blood pressure was 133/89 mm Hg, and pulse rate was 86 beats per minute with a regular rhythm. On a neurologic examination, the patient was mildly agitated, and she had dysgraphia, dyscalculia, right-left disorientation, and finger agnosia, which were compatible with Gerstmann's syndrome. She also had ideomotor and ideational apraxia. Neither abnormal posture nor involuntary movement was seen. Her motor and sensory systems were normal. The Mini Mental State Examination (MMSE) score was 17/30, with decreased scores on orientation to time (2/5), orientation to place (3/5), attention and calculation (0/5), repetition (0/1), complex command (write a sentence) (0/1), and complex command (copy pentagons) (0/1).

The blood test results at admission (day 1), including the thyroid function, were unremarkable except for the presence of leukopenia (2,900/μL). Additional tests for ANA, glutamic acid decarboxylase antibody (GADA), and thyroid peroxidase (TPO) antibodies (37 IU/mL, normal <16 IU/mL) were unremarkable; however, thyroglobulin (Tg) antibodies were markedly elevated (263 IU/mL, normal <28.0 IU/mL). Her cerebrospinal fluid (CSF) contained 13 white blood cells/mm^3 (100% were mononuclear cells), 30 mg/dL protein, and 55 mg/dL glucose (blood glucose, 92 mg/dL). CSF-specific oligoclonal bands and immunoglobulin G (IgG) index were not examined.

Brain MRI showed scattered small increased T2/fluid-attenuated inversion recovery (FLAIR) signals in the subcortical white matter of the frontal lobes but not in the medial temporal lobes (Fig. 1). IMP-SPECT revealed focal hyperperfusion in the right temporal cortex and left cerebellum and hypoperfusion in the left frontal, parietal, and occipital cortices (Fig. 2). Hypoperfusion and hyperperfusion images were created using a three-dimensional stereotactic surface projection analysis, as previously reported (Fig. 2) (10). Electroencephalography on admission showed diffuse delta slowing without epileptiform discharges.

After admission, the patient was empirically treated with intravenous acyclovir (1,500 mg/day) for possible herpes simplex encephalitis until day 12, when a negative result of a CSF herpes simplex virus polymerase chain reaction test was obtained, and was also given intravenous high-dose methylprednisolone (IVMP, 1 g/day, 5 days) from day 1 for suspected Hashimoto encephalopathy or anti-NMDAR encephalitis.

On day 2, a fever, tachycardia, and excessive sweating developed. On day 3, bladder retention also developed, requiring the insertion of an indwelling catheter. Despite treatment with IVMP, she became drowsy (Glasgow Coma Scale E3V4M6) on day 4. On day 8, she received an additional cycle of IVMP, followed by oral prednisolone starting at 100 mg every other day.

Based on the clinical features and the positive test results

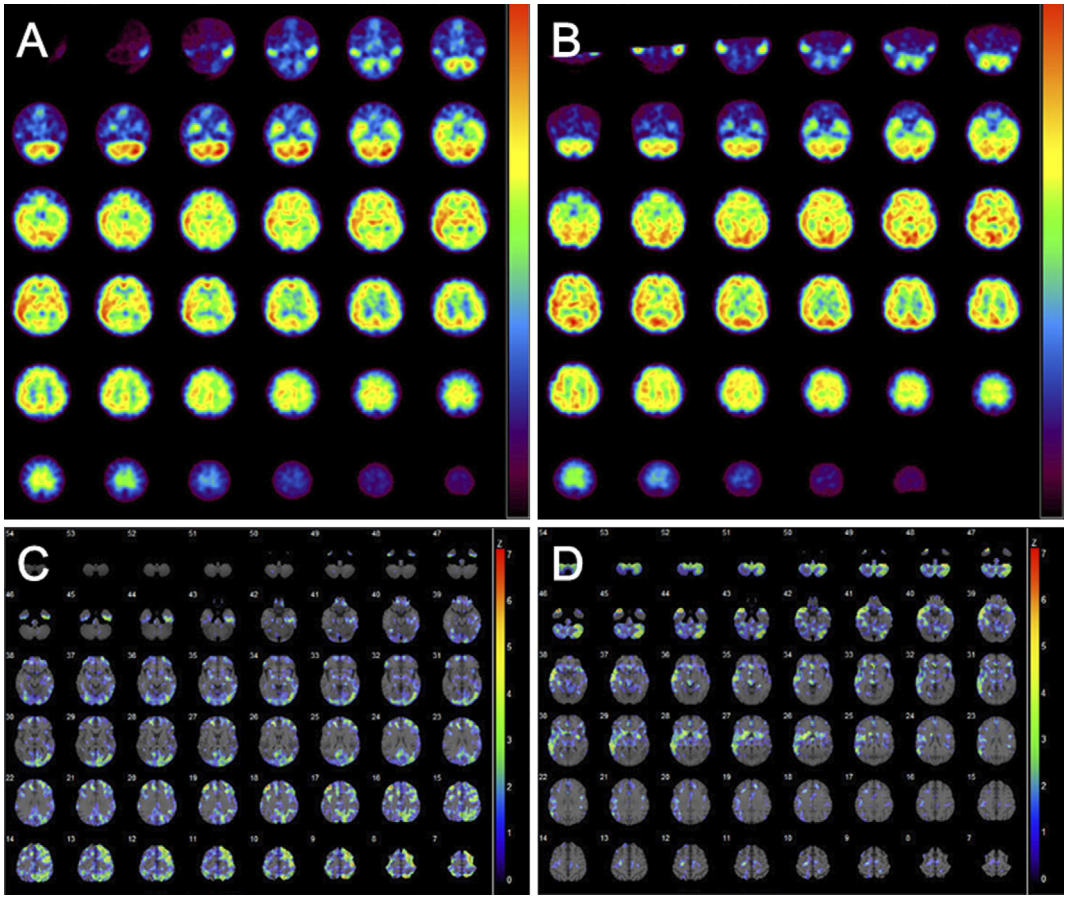

Figure 2. **Brain IMP-SPECT findings obtained on admission and after the recovery of symptoms. IMP-SPECT obtained on admission (A) shows hypoperfusion in the left frontal, parietal, and occipital cortices and hyperperfusion in the right temporal cortex, whereas follow-up IMP-SPECT obtained four months after admission (B) shows resolution of the abnormal perfusion pattern. The areas of hypoperfusion and hyperperfusion on admission are also shown on 3D-SSP hypoperfusion (C) and hyperperfusion (D) maps. A, C, and D were obtained on admission. B was obtained four months after admission. IMP-SPECT: N-isopropyl-p-(^{123}I)-iodoamphetamine single-photon emission computed tomography, 3D-SSP: three-dimensional surface projection**

for NMDAR antibodies in the CSF determined by a cell-based assay, the patient was diagnosed with anti-NMDAR encephalitis and started on two cycles of immunoadsorption plasmapheresis on day 14, followed by two cycles of plasma exchange. However, her level of consciousness deteriorated further (Glasgow Coma Scale E1V1M4), accompanied by jerky involuntary movements in the bilateral upper extremities and paroxysmal conjugate eye deviation to the right. Levetiracetam (3,000 mg/day) and carbamazepine (200 mg/day) were administered. A gynecological examination, whole-body computed tomography, and transvaginal ultrasound did not reveal presence of a tumor. However, considering the severe clinical symptoms that had worsened despite combined immunotherapies and the possibility of the presence of an occult teratoma, she underwent bilateral salpingo-oophorectomy on day 29. No teratoma was pathologically confirmed.

On day 40, the patient received intravenous cyclophosphamide 500 mg/m^2. Following these combined immunotherapies, her level of consciousness began to improve gradually. The MMSE score improved to 30/30 on day 70. On day 86, she returned home without residual symptoms. Follow-up IMP-SPECT obtained six months after the onset of relapse showed resolution of cerebral blood flow abnormalities (Fig. 2). Steroid treatment was gradually tapered off 13 months after the onset of relapse (Fig. 3). At the last follow-up (21 months after the onset of relapse), she was able to drive and take care of her children without any difficulties.

Antibody Assays

We also measured additional antibodies against neuronal surface or synaptic proteins, including NMDAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropinic acid receptor (AMPAR), GABAB receptor (GABAbR), GABAA receptor (GABAaR), metabotropic glutamate receptor 5 (mGluR5), dipeptidyl peptidase-like protein 6 (DPPX), contactin-associated protein-like 2 (Caspr2), LGI1, and neurexin 3. These neuronal surface antibodies were measured in the laboratory of Josep Dalmau (University of Barcelona) using

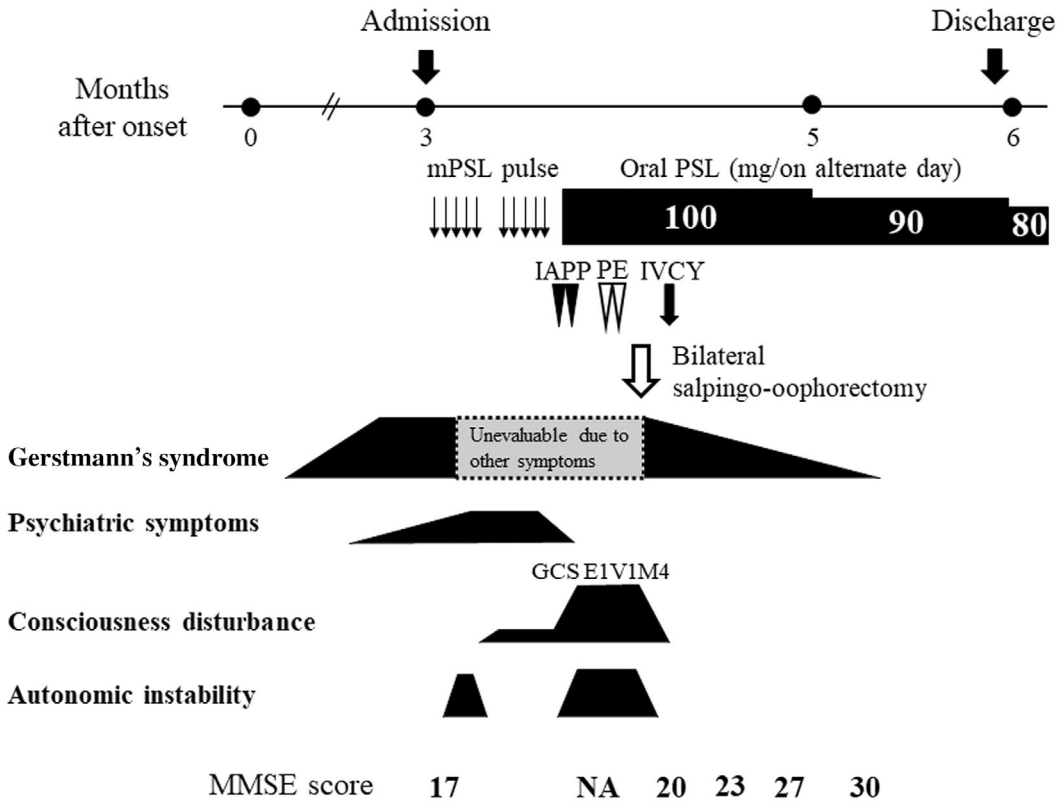

Figure 3. Clinical course of anti-NMDAR encephalitis. Note that Gerstmann's syndrome was the first manifestation of anti-NMDAR encephalitis. mPSL: methylprednisolone, PSL: prednisolone, IAPP: immunoadsorption plasmapheresis, PE: plasma exchange, IVCY: intravenous cyclophosphamide, GCS: Glasgow Coma Scale, MMSE: Mini-Mental State Examination

a rat brain immunohistochemistry and cell-based assay in both serum and the CSF (except NMDAR, which was determined in the CSF).

In addition to these neuronal surface antibodies, we measured NAE antibodies in the serum with an immunoblotting analysis, as previously reported (11), as high titers of Tg antibodies were detected in the serum. Among these neuronal surface antibodies, only GluN1 antibodies were identified in the CSF, whereas NAE antibodies were also identified in the serum.

Discussion

This study showed that 1) Gerstmann's syndrome can be the presenting manifestation of anti-NMDAR encephalitis, 2) IMP-SPECT may detect functional alterations in brain regions appearing normal on MRI corresponding to the focal signs before the development of diffuse encephalopathy, and 3) NAE antibodies may be detected concurrently with NMDAR antibodies in cases of encephalitis with high titers of Tg antibodies.

Although ovarian teratoma was not pathologically confirmed, we made the diagnosis of anti-NMDAR encephalitis based on the diagnostic criteria proposed in 2016 (12). Our patient had two separate episodes. The first episode manifested as an isolated psychosis (first episode psychosis), and the second episode presented with Gerstmann's syndrome followed by the typical spectrum of anti-NMDAR encephalitis. The first episode of psychosis that occurred 14 months before adminission was presumed to also be due to anti-NMDAR encephalitis. Although a wide range of symptoms may develop in this disorder, including psychobehavioral or memory alterations, speech dysfunction, autonomic symptoms, hypoventilation, dyskinesias, and sleep disturbance (1, 13), isolated focal central nervous system manifestations have also been reported in both children (4) and adults (14). However, Gerstmann's syndrome has been documented in only 1 case report (5), in which a 16-year-old girl presented with seizures followed by a decline in her school performance; on a neurologic examination, Gerstmann's syndrome was found (5). In our patient, Gerstmann's syndrome was a presenting symptom of anti-NMDAR encephalitis. The previous case and our case have little in common, other than a lack of a confirmed ovarian teratoma diagnosis. Furthermore, the results of thyroid antibody and NAE antibody detection were not described in the previous case. To our knowledge, no case of Hashimoto encephalopathy with Gerstmann's syndrome as the presenting manifestation has been reported until now.

Although brain MRI did not reveal any causal lesion, IMP-SPECT showed hypoperfusion in the left cerebral hemisphere corresponding to Gerstmann's syndrome. An-

other study using IMP-SPECT reported frontotemporal hypoperfusion in two patients with severe anti-NMDAR encephalitis. However, IMP-SPECT was performed 7 and 12 months after symptom presentation during the protracted course of the disease, and the authors speculated that antibody-mediated functional disruption of neuron-astrocyte networks and alteration of tissue metabolism, particularly in the frontotemporal lobes, contributed to the hypoperfusion (15). In our patient, IMP-SPECT performed on admission showed hypoperfusion in the left cerebral hemisphere, which may have reflected neuronal dysfunction due to antibody-mediated functional alterations rather than irreversible tissue damage. Although both hyperperfusion and hypoperfusion have been reported in patients with anti-NMDAR encephalitis, IMP-SPECT may provide additional information that will be useful for monitoring the antibody-mediated functional alterations in anti-NMDAR encephalitis, even in brain regions with normal-appearing MRI findings.

In our patient, NAE, Tg, and NMDAR antibodies were simultaneously identified. It is important that both NAE and Tg antibodies were identified in a case initially suspected of being autoimmune encephalitis. Hashimoto encephalopathy is an encephalitis with a presumed autoimmune mechanism characterized by the presence of autoantibodies against thyroid proteins (12). When clinicians encounter a patient with encephalitis of unknown cause with high titers of serum thyroid antibodies (TPO, Tg), Hashimoto encephalopathy is usually considered in the differential diagnosis, as in our case. Furthermore, NAE antibodies, which are found in up to 68% of patients with Hashimoto encephalopathy (11), were also found in our patient, along with high titers of Tg antibodies. In such situations, if pathogenic neuronal surface antibodies are not examined, the patient may be misdiagnosed with Hashimoto encephalopathy. Neuroimaging findings similar to those in the present case, i.e., nonspecific scattered increased signals in the subcortical white matter on brain MRI and focal hypoperfusion in the area corresponding to the patient's clinical symptoms on brain perfusion SPECT, may also be observed in patients with Hashimoto encephalopathy (16, 17).

Although NAE antibodies have been proposed as a specific marker of Hashimoto encephalopathy (8, 11), the target antigen is an intracellular protein, and the causative role of the antibodies has not been fully established (18, 19). These antibodies were also identified in patients with Creutzfeldt-Jakob disease and limbic encephalitis with LGI1 antibodies (9, 18, 20). Therefore, confirmation of the absence of well-characterized neuronal antibodies in the serum and CSF is essential for the diagnosis of Hashimoto encephalopathy (12).

This study is limited by its retrospective evaluation of a single case report, the titers of NAE and NMDAR antibodies not being determined, and the NAE antibodies in the CSF not being measured. However, despite these limitations, it is important that both NAE and Tg antibodies were identified in a case of anti-NMDAR encephalitis. Further studies are needed to determine whether the coexistence of NAE antibodies affects the clinical course of anti-NMDAR encephalitis.

Gerstmann's syndrome can be the presenting symptom in patients with anti-NMDAR encephalitis and can be concurrent with the presence of NAE antibodies. Brain perfusion IMP-SPECT may be useful for detecting functional alterations in anti-NMDAR encephalitis, such as hypoperfusion in brain regions that appear normal on MRI.

Author's disclosure of potential Conflicts of Interest (COI).
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