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【 CASE REPORT 】

A Patient with Limbic Encephalitis Associated with Anti-leucine-rich Glioma-inactivated 1 (LGI1) Antibody Presenting with Slowly Progressive Cognitive Impairment and Fluctuating Striatal Lesions

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Abstract:
We herein report the case of a 59-year-old man with anti-leucine-rich glioma-inactivated 1 (LGI1) antibody encephalitis who presented with slowly progressive cognitive impairment mimicking dementia for over 3 years and then developed seizures. Unique brain magnetic resonance imaging (MRI) findings of fluctuating striatal lesions were observed during the disease course. He was treated with intravenous methylprednisolone pulse therapy followed by oral prednisolone, which dramatically improved his neurological function. Taken together, these findings indicate that anti-LGI1 encephalitis may present as slowly progressive cognitive impairment mimicking dementia and that fluctuating MRI striatal lesions may be a characteristic radiological finding of this disorder.

Key words: anti-voltage-gated potassium channel (VGKC) complex antibody, anti-leucine-rich glioma-inactivated 1 (LGI1) antibody, anti-contactin-associated protein-like 2 (CASPR2) antibody, encephalitis, magnetic resonance imaging (MRI)

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Introduction

Voltage-gated potassium channel (VGKC) complex antibodies cause a broad spectrum of neurological syndromes, including neuromyotonia, Morvan's syndrome, epilepsy, and limbic encephalitis (1). Recent investigations have demonstrated that most of the antibodies that were previously thought to be directed towards the VGKC instead bind to other proteins, such as leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), and contactin-2 (2, 3). Among the syndromes associated with these antibodies, anti-LGI1 encephalitis typically presents as limbic encephalitis with amnesia, seizures, psychiatric disturbances, and occasionally faciobrachial dystonic seizures (FBDSs) (3, 4). Patients with anti-LGI1 encephalitis usually demonstrate an acute or subacute progressive clinical course (5) unless they are precisely diagnosed and properly treated. Radiologically, patients with anti-LGI1 encephalitis frequently present with high signal changes in the hippocampal region on T2-weighted magnetic resonance imaging (MRI) (3-6). An abnormally high T2 signal in the striatum has also been reported in several patients (6).

We herein report the case of a Japanese patient with anti-LGI1 encephalitis who showed slowly progressive cognitive impairment over the course of 3 years. We also observed unique brain MRI findings of fluctuating striatal lesions during the natural course of the disease in this patient.

Case Report

The patient was a 59-year-old Japanese man who worked in the manufacturing industry and had no remarkable medical history. He had been relatively healthy until 56 years of age; however, he then he began making frequent mistakes at work (Fig. 1). At 57 years of age, he developed forgetful-

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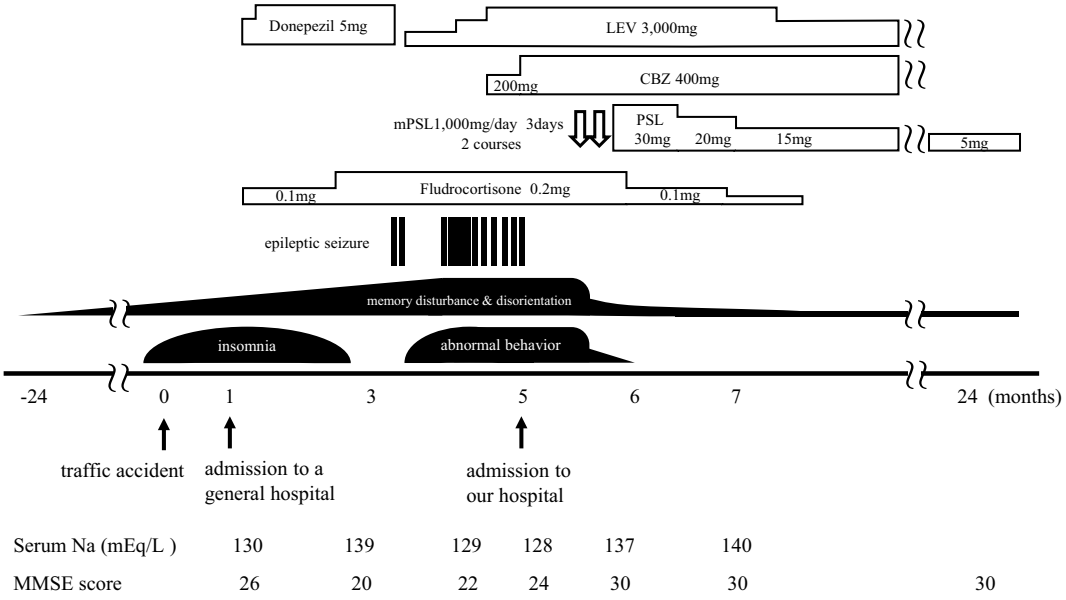

Figure 1. **Clinical course of the patient. CBZ: carbamazepine, LEV: levetiracetam, mPSL: methylprednisolone, PSL: prednisolone**

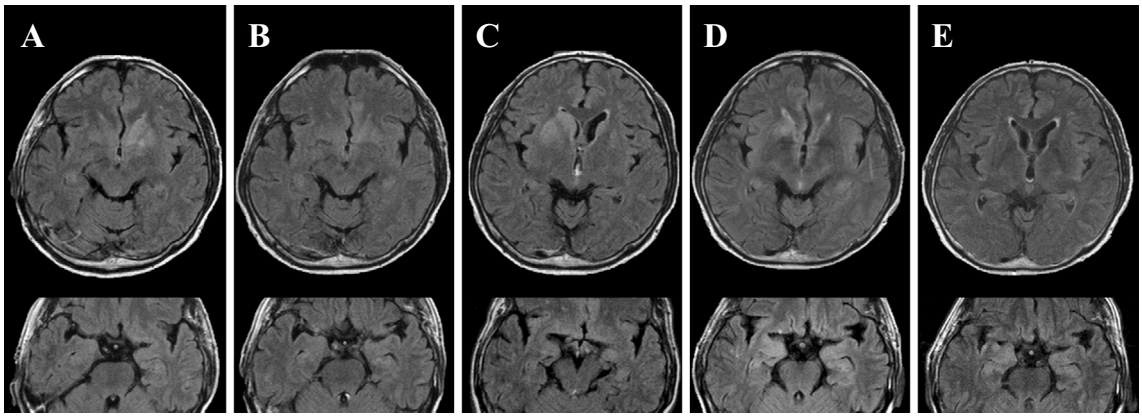

Figure 2. **Brain magnetic resonance (MR) images of the patient (fluid-attenuated inversion recovery images, axial view). (A) MR image acquired five months before admission to our hospital (at the time of the traffic accident). A high signal intensity and mild swelling are visible in the left striatum. (B) MR image acquired four months before admission to our hospital (one month after the traffic accident). The size of the left striatal lesion has decreased, and the lesion is less visible. (C) MR image acquired three months before admission to our hospital (two months after the traffic accident). A high signal intensity and considerable swelling are visible in the right striatum, while the left striatal lesion has resolved. (D) Brain MR image acquired upon admission to our hospital (five months after the traffic accident). A high signal intensity with swelling can be observed in the bilateral medial temporal lobes, while the size of the right striatal lesion has decreased. (E) Brain MR image acquired one month after admission to our hospital (six months after the traffic accident). No abnormal signal intensities and brain atrophy are observed.**

ness and insomnia. The amnesia and disorientation worsened at 58 years of age. At 59 years of age, the patient was involved in a traffic accident and was transferred to an emergency hospital.

Brain MRI showed an abnormal hyperintense lesion in the left striatum on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 2A), and he was diagnosed with an obsolete cerebral infarction. One month after the traffic accident, the patient visited the neurology department of a general hospital seeking a detailed neurological examination owing to his concerns regarding cognitive impairment. The results of his physical and neurological examinations upon admission were normal, but he showed mild cognitive impairment [Mini-Mental State Examination (MMSE) score 26/30].

Routine blood tests revealed that his serum sodium level

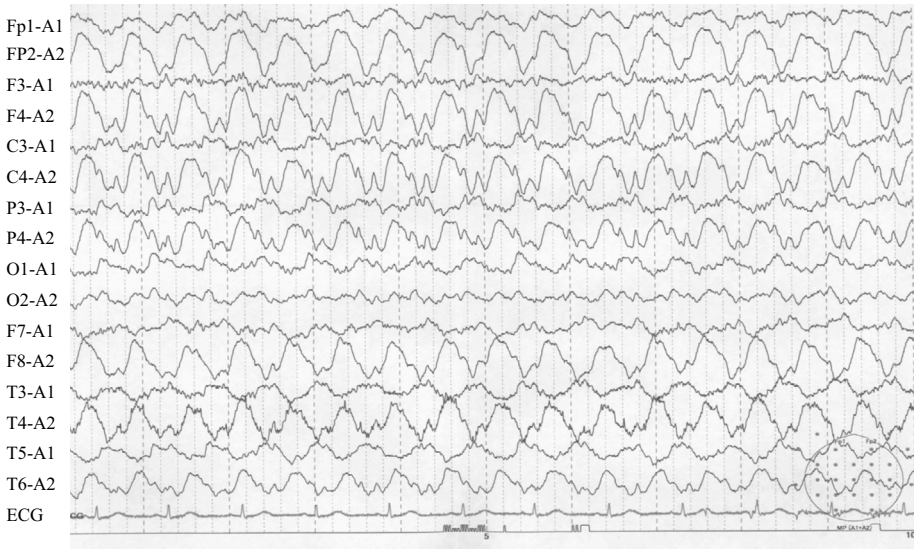

Figure 3. Electroencephalogram of the patient. Bursts of sharp-and-slow wave complexes can be observed in the right hemisphere.

was low at 130 mEq/L (normal range, 135-145 mEq/L). Brain MRI showed the previously identified hyperintense lesion in the left striatum on T2-weighted and FLAIR images (Fig. 2B), although the lesion was smaller than it had been in the images obtained 1 month earlier (Fig. 2A). The patient was diagnosed with early-onset dementia and treated with donepezil; however, his cognitive impairment worsened. One month later, he developed generalized clonic seizures and was transferred to a general hospital (Fig. 1). Electroencephalography showed bursts of sharp-and-slow wave complexes in the right hemisphere (Fig. 3). Brain MRI showed an abnormal hyperintense lesion with swelling in the right striatum on T2-weighted and FLAIR images, but the abnormal lesion in the left striatum was no longer visible (Fig. 2C). The patient was treated with levetiracetam (3,000 mg/day) and carbamazepine (200 mg/day), but sufficient seizure control was not achieved. In addition, he developed hallucinations and abnormal behaviors, such as mimicking sewing, ironing, sucking, and closing caps. His MMSE score also deteriorated to 20/30 (Fig. 1).

Five months after the abovementioned traffic accident, the patient was transferred to our hospital. Upon admission, he had mild consciousness disturbance (Glasgow coma scale, E 4V4M6) and disorientation. His cognitive function test scores were as follows: MMSE, 24/30 (orientation, attention, and calculation impairment); Raven's Colored Progressive Matrices, 28; and Frontal Assessment Battery at bedside, 13/18. Routine blood examinations showed that he had hyponatremia (128 mEq/L), despite having received fludrocortisone (0.2 mg/day). The results of the cerebrospinal fluid analysis showed that the fluid was acellular (1 mononuclear cell/μL), with normal protein (34 mg/dL), immunoglobulin G (2.4 mg/dL), and glucose (63 mg/dL) levels. Brain T2-weighted and FLAIR MRI revealed areas of high signal intensity with swelling in the bilateral medial temporal lobes. Furthermore, the size of the right striatal lesion had decreased (Fig. 2D). The serum titer of anti-VGKC complex antibody was 507.1 pM (normal, <72 pM). His serum was positive for anti-LGI1 antibody and negative for anti-CASPR2 antibody. Based on the clinical findings and positivity for the anti-VGKC complex and anti-LGI1 antibodies, we diagnosed the patient with anti-LGI1 encephalitis.

He was treated with intravenous methylprednisolone pulse therapy at a dose of 1 g for 3 days. One week later, the steroid treatment dramatically improved his neurological function, and he no longer experienced epileptic seizures (Fig. 1). He was treated with a second course of intravenous methylprednisolone pulse therapy followed by the oral administration of prednisolone (30 mg/day). One month after treatment, his serum sodium had normalized, and his MMSE score increased to 30/30, although mild attentional dysfunction persisted. Brain MRI demonstrated attenuation of the high signal intensity and swelling in the bilateral medial temporal lobes (Fig. 2E). He was transferred to a rehabilitation hospital after 52 days of hospitalization. His neurological condition continued to improve after the transfer.

Two months later, he was discharged from the rehabilitation hospital and began staying in an assisted living facility. The dose of oral prednisolone was decreased gradually and maintained at 5 mg/day. While some impairment of his executive functions remained, he managed his daily life and returned to work as a part-time employee two years after hospital discharge (Fig. 1).

Discussion

Anti-LGI1 encephalitis typically shows an acute or subacute clinical course, with a median time from the onset to the nadir of the disease being 22 weeks (5). In contrast, our patient presented with slowly progressive cognitive impairment and insomnia over a three-year period, which is the most intriguing finding of the case.

Table. Clinical Features of Patients with Anti-VGKC/LGI1 Encephalitis That Developed Chronic Progressive Dementia.

Reference	Age(years)/ Sex	Antibody	Symptoms at diagnosis	Diagnostic delay (months)	Brain MRI abnormalities (T2/FLAIR high intensity lesion)	Treatment	MMSE or FAB score Before/after immunotherapy	Prognosis
7	82/Male	VGKC	Changes in personality	6	Medial temporal	PSL	MMSE 27/29 FAB 11/17	Independently
8	75/Female	VGKC/ LGI1	Cognitive impairment	9	Hippocampus	IVMP, PE	MMSE 26/29	Details unknown
9	60/Female	VGKC	Cognitive impairment	6	-	PSL, AZP	MMSE 15/29	Totally independently
Present case	59/Male	VGKC/ LGI1	Cognitive impairment, seizure	>48	Striatum, medial temporal (fluctuating)	IVMP, PSL	MMSE 24/30	Almost independently Work as part-time employee

AZP: azathioprine, IVIg: intravenous immunoglobulin, IVMP: intravenous methylprednisolone, PE: plasma exchange, PSL: oral prednisolone

To date, only four patients with anti-VGKC/LGI1 encephalitis who developed chronic progressive dementia have been described, including the patient reported in the present study (7-9). Table compares the clinical characteristics of these patients. McKeon et al. (7) reported the case of a patient with anti-VGKC encephalopathy mimicking frontotemporal dementia who presented with a six-month history of progressive personality changes characterized by increasing irritability, aggressive outbursts, poor self-care, repetitive facial grimacing, and diminished insight. In contrast, Marquetand et al. (8) reported the case of a patient with anti-LGI1 encephalitis who, over the course of nine months, slowly developed chronic progressive verbal and episodic memory deficits and spatial orientation difficulties, particularly in novel environments, mimicking incipient Alzheimer's disease. None of the previously reported patients developed seizures during the clinical course, which might have delayed the diagnosis. The absence of seizures in cases of anti-LGI1 encephalitis is rare, with approximately 80-90% of patients exhibiting seizures at the diagnosis (3, 5). Our patient did not develop seizures until three years into his disease, which may be a reason why he was misdiagnosed with early-onset dementia. Furthermore, all previously reported patients, as well as our own, showed marked improvements in their cognitive function following the administration of immunotherapies, including steroids, plasma exchange, intravenous immunoglobulin therapy, and azathioprine (7-9).

Another interesting finding in the present case was the fluctuating striatal MRI lesions we observed during the natural course of the disease. With regard to MRI findings, increased T2/FLAIR signal intensity in mesiotemporal and hippocampal lesions is commonly found in patients with anti-LGI1 encephalitis (2-4). Signal changes in the basal ganglia are less common in patients with anti-LGI1 encephalitis, although they may be observed during the FBDS stage (6). In our patient, lesions in the bilateral striatum were identified during the non-FBDS stage. In addition, obvious fluctuations in the striatal lesions were observed prior to immunotherapy. This MRI finding of fluctuations and the slowly progressive cognitive impairment might have created complications and delayed the diagnosis. Several diseases are associated with increased T2/FLAIR signal intensity in the striatum, including hyperammonemia, hypoxic encephalopathy, hypoglycemia, osmotic myelitis, cerebral vein thrombosis, and Creutzfeldt-Jakob disease (10). However, fluctuations in striatal lesions are less likely in these diseases than in anti-LGI1 encephalitis. The case reported herein suggests that fluctuating striatal lesions may be a specific but rare MRI finding of anti-LGI1 encephalitis. Although fluctuations in MRI lesions have not been described previously in the literature, the spontaneous remission of clinical symptoms has been reported in several patients with anti-LGI1 encephalitis (11). The clinical course of anti-LGI1 encephalitis may therefore present as spontaneous fluctuations rather than monophasic worsening of disease activity.

In conclusion, the details from the case reported herein indicate that anti-LGI1 encephalitis may present as a slowly progressive cognitive impairment mimicking dementia and that fluctuating MRI lesions may be a characteristic radiological finding of this disorder.

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

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