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【 CASE REPORT 】

Anti-LGI1 Encephalitis Developing Immunoglobulin Responsive Orthostatic Hypotension after Remission

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Abstract:
Anti-leucine-rich glioma-inactivated 1 (LGI1) antibody is associated with limbic encephalitis. We herein report a patient with anti-LGI1 encephalitis who developed severe orthostatic hypotension (OH) responsive to immunoglobulin therapy five years after developing symptoms of encephalitis. A 71-year-old man presented with amnesia caused by limbic encephalitis. The symptoms of encephalitis improved partially without any immunotherapy. Five years later, he developed severe OH, and anti-LGI1 antibody was positive. The catecholamine dynamics indicated that the central autonomic nervous system was the lesion of his OH. Intravenous immunoglobulin therapy improved the OH. This case suggests that anti-LGI1 antibody can be associated with severe OH.

Key words: voltage-gated potassium channel (VGKC), leucine-rich glioma-inactivated 1 (LGI1), limbic encephalitis, autonomic dysfunction, orthostatic hypotension (OH), tilt test

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Introduction

Anti-voltage-gated potassium channel (VGKC) complex antibody-associated syndrome contains a wide spectrum of neurological diseases, such as limbic encephalitis, Morvan's syndrome, and neuromyotonia (1). The antibodies include mainly anti-contactin-associated protein-like 2 (CASPR2) antibody and anti-leucine-rich glioma-inactivated 1 (LGI1) antibody, and the clinical manifestations differ depending on the antibody. Anti-LGI1 antibody is commonly associated with limbic encephalitis, which usually causes subacute memory deficit, behavioral and spatial disorientation, seizure, and hyponatremia (1). However, orthostatic hypotension (OH) has not been reported as a symptom.

We herein report a patient with anti-LGI1 encephalitis who developed severe OH responsive to immunoglobulin therapy about five years later.

Case Report

A 71-year-old man was admitted to our department because of memory disturbance. He had previously been healthy but developed amnesia three months before admission. Upon admission, he exhibited a severe impairment of his recent memory and an irritable mood. His intelligence was preserved, and he did not show any other neurological symptoms or seizure. His Mini-Mental State Examination (MMSE) score was 25/30, and delayed recall was impaired (1/3). His delayed recall score on the Wechsler Memory Scale-Revised (WMS-R) was 56.

Brain magnetic resonance imaging (MRI) showed left-dominant medial temporal lobe signal hyperintensity on fluid-attenuated inversion recovery (FLAIR) without gadolinium enhancement (Fig. 1a). These areas exhibited increased blood flow on N-isopropyl-p-[^{123}I] iodoamphetamine single-photon emission computed tomography (^{123}IMP-SPECT) (Fig. 1b). An electroencephalogram (EEG) showed

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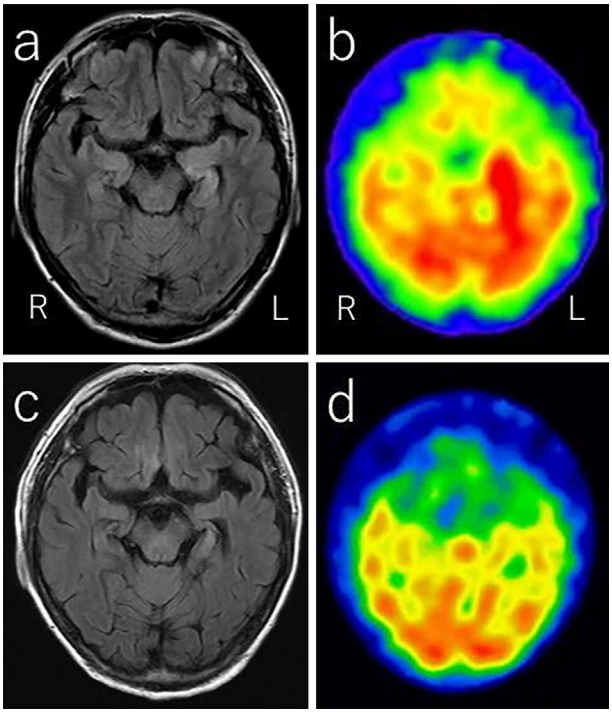

Figure 1. Brain imaging. Radiological findings of encephalitis (a, b) and five years after remission (c, d). During encephalitis, MRI showed FLAIR hyperintensity at the bilateral medial temporal lobes (a), and ^{123}IMP-SPECT showed an increase in blood flow at the left medial temporal lobe (b). MRI five years after remission showed diminished signal abnormality and slight atrophy of the affected area (c). No increased blood flow was observed on ^{123}IMP-SPECT (d). FLAIR: fluid-attenuated inversion recovery, ^{123}IMP-SPECT: N-isopropyl-p-[^{123}I] iodoamphetamine single photon emission computed tomography, MRI: magnetic resonance imaging

transient theta bursts at the bilateral frontal lobes. Serum sodium was 135 mEq/L (136.0-145.0 mEq/L). A cerebrospinal fluid analysis showed that protein (37.1 mg/dL) and cell counts (2/μL) were within the normal ranges. Through the examination, prostate cancer was found. Radiation and hormone therapies were initiated for prostate cancer, and the serum level of prostate specific antigen (PSA) decreased from 11.5 ng/mL to below 1.0 ng/mL (normal range 0.0-4.0 ng/mL). We prescribed 400 mg of carbamazepine for the abnormal EEG. His mood was stabilized, and the memory disturbance remained without further deterioration. Although his serum turned out to be positive for the anti-LGI1 antibody, we did not perform any immunotherapies.

At 76 years old, 5 years later, the patient complained of dizziness when standing up and developed hypertension (systolic blood pressure: about 200 mmHg). He was prescribed 2.5 mg of amlodipine and visited our hospital when he became unable to stand up by himself a week later. Upon admission, he had mild amnesia, which had not changed in five years. He did not show any other neurological symptoms. His MMSE score was 26/30, with a delayed recall score of 3/3. His delayed recall score on the WMS-R was still 56. The Schellong test showed severe OH; his systolic blood pressure was over 140 mmHg in the supine position. However, his radial artery pulsation became impalpable in the upright position, accompanied by a feeling of fainting.

We ceased the administration of amlodipine, but his OH did not improve. He had diarrhea and constipation. Routine laboratory examinations showed no apparent abnormalities. A cerebrospinal fluid analysis showed a slightly elevated protein level (51.6 mg/dL), normal cell count (2/μL), and a negative oligoclonal band. The serum anti-LGI1 antibody was positive, whereas the anti-CASPR2 antibody was negative. Antibodies for the following were negative: serum anti-ganglionic acetylcholine (ACh) receptor, anti-neural antibodies (amphiphysin, CV-2, PNMA2, Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, Tr), and cerebrospinal fluid anti-N-methyl-D-aspartate receptor (NMDAR). The serum PSA level was 0.8 ng/mL. The patient was still on carbamazepine, and epileptic discharge was not observed on an EEG. An electrocardiogram showed a heart rate of 70 bpm with a normal sinus rhythm. The coefficient of variation of the R-R interval (CVR-R) was slightly decreased (1.6%). On brain MRI, the bilateral medial temporal lobes had shrunk and the hyperintensity lesions diminished (Fig. 1c). The blood flow decreased in the same area on ^{123}IMP-SPECT (Fig. 1d). ^{123}I-ioflupane SPECT showed a normal uptake in both striata. ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy was normal (early and delayed H/M ratios of 2.73 and 2.75, respectively, and washout rate of 30.5%). ^{18}F-fluorodeoxyglucose positron emission tomography showed no abnormal uptake in the whole body, including the prostate.

His OH was not improved by midodrine (6 mg/day), droxidopa (900 mg/day), pyridostigmine (120 mg/day), or fludrocortisone (0.2 mg/day). Three courses of methylprednisolone therapy (1,000 mg/day, three days) did not relieve his symptoms. Three weeks after the last methylprednisolone therapy, we administered intravenous immunoglobulin (IVIg) (400 mg/kg/day, 5 days). His blood pressure gradually stabilized, and he became able to walk without any assistance two weeks after the IVIg administration. However, eight weeks after the infusion of IVIg, he developed dizziness and became unable to stand by himself. His OH relapsed, so he was re-admitted to our hospital. Immunoglobulin therapy improved his symptoms two weeks after the second IVIg administration.

We conducted a head-up tilt test before and after IVIg treatment (Fig. 2). In the resting position, the blood pressure, noradrenaline (NA), and arginine vasopressin (AVP) values were within normal limits. However, when raising his head, his blood pressure dropped remarkably, and he felt nauseous and nearly fainted. His NA and AVP levels increased as the blood pressure dropped. When we moved him back to the flat position, rebound hypertension was observed. After the treatment, his systolic BP did not decrease below 80 mmHg, and he did not feel nauseous. The amount of increase in the NA and AVP levels was larger than that

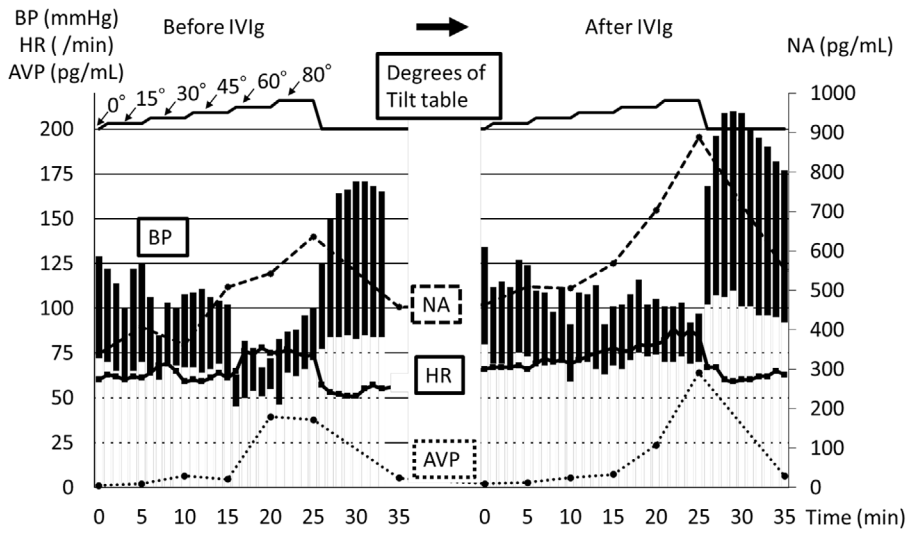

Figure 2. **The tilt test before and after intravenous immunoglobulin (IVIg) therapy. The patient was placed in the supine position for 15 min before the tilt test. The head side of the table was raised every 5 min to 15°, 30°, 45°, 60°, and 80°, and then restored to the horizontal position. To analyze NA and AVP, blood samples were obtained every 5 min just before changing positions and 10 min after restoring the flat position. In the resting position, the BP, NA, and AVP values were within normal limits. However, before treatment and while raising the head, his BP dropped remarkably, and he felt nauseous and nearly fainted; the NA and AVP levels increased as the BP decreased. When he returned to the flat position, rebound hypertension was observed. After treatment, his systolic BP did not decrease below 80 mmHg, and he did not feel nauseous. The increases in the NA and AVP levels were larger than those before treatment. AVP: arginine vasopressin, BP: blood pressure, HR: heart rate, IVIg: intravenous immunoglobulin, NA: noradrenaline**

before the treatment.

Discussion

We described a case of anti-LGI1 encephalitis which developed severe OH responsive to IVIg five years after the symptoms of encephalitis.

Anti-LGI1 encephalitis can manifest with subacute memory deficit, behavioral and spatial disorientation, seizures, and hyponatremia. Patients develop combinations of these symptoms (1). Our patient developed subacute memory deficit and an irritable mood. Although he did not manifest with seizure or hyponatremia, his clinical course was compatible with anti-LGI1 encephalitis. We conducted treatment for the prostate cancer, considering the encephalitis to be a paraneoplastic manifestation of the prostate cancer. After chemotherapy for the prostate cancer was initiated, his mood stabilized, and his cognitive dysfunction stopped deteriorating without any immunotherapy. The increased blood flow on ^{123}IMP-SPECT had also disappeared. However, spontaneous recovery of anti-LGI1 encephalitis has been reported (2). Furthermore, there is only one report of the concurrence of prostate cancer and anti-LGI1 encephalitis (3). Accordingly, the encephalitis might have improved as part of its natural course.

Based on the clinical assessments, we concluded that the OH of our patient was due to immune-mediated central autonomic dysfunction. MIBG scintigraphy showed a normal uptake, suggesting that the OH had not been caused by peripheral autonomic dysfunction. The NA and AVP values at rest were within normal limits and increased when we raised the patient's head (Fig. 2). These results suggest that his OH was caused by a disturbance of the central efferent pathway of the autonomic nervous system, including the hypothalamus and medulla oblongata (Table) (5). Before presenting with severe OH, the patient developed hypertension, possibly as a result of sympathetic overactivity syndrome. The improvement in his OH by the administration of IVIg suggested an autoimmune mechanism underlay his OH.

OH can be caused by several conditions, such as drug use, Parkinson's disease, multiple system atrophy, polyneuropathy, and autonomic autoimmune ganglionopathy (AAG) (5). The adverse effects of drugs, neurodegenerative disorders, or neuropathy were excluded by the clinical assessment. Although AAG is an autoimmune disorder that causes autonomic dysfunction responsive to IVIg, it was considered unlikely because it causes postganglionic autonomic failure, and nearly half of AAG cases are positive for anti-ganglionic ACh receptor antibody (6). In some types of encephalitis, such as anti-NMDAR encephalitis and anti-GAD encephalitis, autonomic dysfunction can be induced by the impairment of the subthalamus or brainstem (7-9). However, these antibodies were negative.

Since the above-mentioned known causes of OH were excluded, we suspected that the OH was associated with anti-LGI1 antibody. Anti-LGI1 antibody binds to the magnocel-

Table. Relation between Cathecolamine Dynamics during the Tilt Test and the Lesions of Orthostatic Hypotension.

	Resting AVP	ΔAVP	Resting NA	ΔNA
Peripheral afferent	normal	low	normal-high	low
Peripheral efferent	normal-high	preserved	low	low
Central afferent	normal	low	normal	preserved
Central efferent	normal-high	preserved	various value	preserved

AVP: arginine vasopressin, NA: noradrenaline

Modified from Zerbe RL, et al. Am JMed 1983; 74: 265-271

lular neurons of the paraventricular nucleus (PVN) of the subthalamus and causes dysregulated ADH secretion, which is considered the cause of hyponatremia in anti-LGI1 encephalitis (10). The PVN also includes the parvocellular neurons, which project to autonomic preganglionic neurons in the spinal cord (11). When anti-LGI1 antibody binds to the parvocellular neurons of the PVN, dysregulation of the blood pressure is expected to occur. Anti-LGI1 antibody inhibits the ligand-receptor interaction between LGI1 and ADAM22/23, resulting in a reduction in synaptic AMPA receptors (12). Some studies have shown that AMPA receptors in the PVN play an important role in central blood pressure regulation (13, 14). Furthermore, the PVN is involved in the central efferent pathway of the autonomic system, which corresponded to the supposed lesion of the OH in our patient. Our patient likely lacked accompanying seizure because he was taking carbamazepine, which had been prescribed for his irritable mood. The patient did not experience any worsening of his recent memory in the interim, possibly because he had already developed memory disturbance and no further disturbance was evident at that time.

We cannot exclude the possibility that unknown neuronal surface antibodies, such as the other isotype of anti-VGKC antibody, were involved in the OH in the present patient. The association between anti-LGI1 antibody and OH is unclear for several reasons. First, we were unable to investigate the correlation between the antibody titer and the clinical course. Second, there was a temporal dissociation between OH and the symptoms of encephalitis. Third, there have been no other reports describing the concurrence of anti-LGI1 antibody and OH.

The present findings suggest that anti-LGI1 antibody may be associated with severe OH. However, unknown antibodies may have caused the OH in our patient. The further accumulation of similar patients is thus warranted to elucidate the pathophysiology of immunotherapy-responsive OH.

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

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