Rapidly progressive dementia—associated N-type voltage-gated calcium channel antibody encephalopathy

Smathorn Thakolwiboon, MD , Amputch Karukote, MD , Gyeongmo Sohn, MD, Walter R. Duarte-Celada, MD, and Parunyou Julayanont, MD

Department of Neurology, Texas Tech University Health Sciences Center, Lubbock, Texas

ABSTRACT

Autoimmune encephalopathy is one of the treatable causes of rapidly progressive dementia; however, it is often underdiagnosed. Autoantibodies against voltage-gated calcium channel (VGCC) have been linked to several neurological disorders, including Lambert-Eaton syndrome, but VGCC antibody-associated encephalopathy is uncommon. Herein, we present a case of a 74-year-old woman with prominent neuropsychiatric symptoms followed by rapid cognitive decline. Extensive initial studies were nondiagnostic. Subsequently, serum N-type VGCC antibody was positive. After treatment with intravenous immunoglobulin, the patient's cognition and neuropsychiatric symptoms significantly improved.

KEYWORDS Autoimmune encephalopathy; N-type voltage-gated calcium channel; rapidly progressive dementia; VGCC encephalitis

Rapidly progressive dementias (RPDs) are generally defined as dementias that develop in <1 to 2 years after symptom onset.¹ Prion diseases, which are untreatable and associated with poor prognosis, are the prototypical etiology of RPDs. RPD secondary to autoimmune encephalopathies are treatable.² Moreover, voltage-gated calcium channel (VGCC) antibody is not a common autoantibody causing autoimmune encephalopathy. Herein, we present a case of RPD with positive serum N-type VGCC antibody, which presented with prominent psychiatric symptoms followed by rapidly progressive cognitive decline and significantly improved after immunotherapy.

CASE REPORT

A previously healthy 74-year-old, right-handed black woman presented with a 6-month history of progressive cognitive decline and behavioral changes. She had 12 years of education and was a retired farmer who had moved from Nigeria to the United States 5 years earlier. The patient lived independently without cognitive difficulty prior to the illness. Her family reported that she started having bizarre visual hallucinations and persecutory delusions 6 months prior to this presentation. Three months after the onset of psychosis, she developed progressive cognitive impairments characterized by

short-term memory problem and inattention. She was brought to the emergency department by a police officer after she was found wandering around a street. She had no history of psychiatric illness or substance abuse and no known family history of dementia. Neurological examination showed no focal neurological deficits. There were no abnormal movements, extrapyramidal dysfunction, akinetic mutism, or visual impairment on the exam. During the bedside examination, she was verbally aggressive. She scored 16/30 on the Mini-Mental State Examination (*Table 1*). Apart from her low body mass index (17 kg/m²), her general physical examination was normal.

Laboratory investigations, including complete blood count, metabolic panel, urine drug screen, serum alcohol, HIV and syphilis screening, thiamin, vitamin B12, folate, thyroid-stimulating hormone, ammonia, erythrocyte sedimentation rate, C-reactive protein, C3, and C4, were within normal limits. Antinuclear antibody, rheumatoid factor, antineutrophil cytoplasmic antibodies, anti-SSA, anti-SSB, anti-thyroid peroxidase, and antithyroglobulin antibodies were negative.

Magnetic resonance imaging of the brain showed mild microangiopathic changes in subcortical white matter without significant cerebral atrophy or an abnormal enhancing lesion. Her electroencephalogram was normal. Cerebrospinal

Corresponding author: Smathorn Thakolwiboon, MD, Department of Neurology, Texas Tech University Health Sciences Center, 3601 4th Street Stop 8321, Lubbock, TX, 79430 (e-mail: smathorn.thakolwiboon@ttuhsc.edu)

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Table 1. Mini-Mental State Examination results before and after intravenous immunoglobulin treatment

Variable	Pretreatment (Oct. 17, 2018)	Posttreatment (Nov. 22, 2018)
Orientation to time and place	5/10	5/10
Registration	3/3	3/3
Attention	1/5	4/5
Delayed recall	0/3	1/3
Naming	2/2	2/2
Repetition	1/1	1/1
Comprehension	3/3	3/3
Reading	1/1	1/1
Sentence writing	0/1	0/1
Pentagon copying	0/1	0/1
Total	16	20

fluid test results were unremarkable (*Table 2*). A serum autoimmune encephalopathy panel was positive for N-type VGCC antibody at 0.08 nmol/L (normal ≤ 0.03 nmol/L) (*Table 3*). Cancer screening by computed tomography of chest, abdomen, and pelvis was negative.

Intravenous immunoglobulin 0.4 g/kg/day was given for 5 days. Subsequently, the patient's behavior and cognition significantly improved. Psychiatric symptoms were controlled with low-dose haloperidol. Seven days after receiving intravenous immunoglobulin, she scored 20/30 on the Mini-Mental State Examination (*Table 1*). After discharge, the patient went back to her home country. According to family members, she continued improving and could perform basic activities of daily living independently 1 year after discharge.

DISCUSSION

Although prion diseases are the prototypical etiology of RPD, recent studies showed that a large proportion of RPDs are treatable, especially immune-mediated etiologies.^{2–5} In autoimmune dementia, patients with seropositivity of a cation channel complex autoantibody including VGCC are more likely to respond to immunotherapy than seronegative patients with an odds ratio of 8.0 (95% confidence interval 1.6–39.2).⁶ Therefore, it is important to carefully investigate any treatable causes, including autoimmune encephalopathy, in patients with RPDs.⁵

In our patient, the VGCC antibody test must be carefully interpreted because the test can be positive in 1.7% of healthy controls and 4% of neurological asymptomatic lung cancer patients.⁷ In patients with a low VGCC antibody concentration (0.03–0.09 nmol/L), the positive predictive value is only 19%.⁷ Although the serum VGCC antibody

Table 2. Cerebrospinal fluid examination

Variable	Value
Open pressure (cm H ₂ O)	12
Red blood cell count (/μL)	74
White blood cell count (/μL)	2
Neutrophils (%)	2
Lymphocytes (%)	46
Monocytes (%)	52
Protein (mg/dL)	40
Glucose (mg/dL)	59
HSV-1,2, HHV-6, CMV, and VZV PCR	Negative
West Nile virus antibodies	Negative
Bacterial and fungal cultures	Negative
Protein 14-3-3 (ng/mL)	<2.0

CMV indicates cytomegalovirus; HHV-6, human herpesvirus 6; HSV-1,2, herpes simplex virus 1 and 2; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

Table 3. Serum autoimmune encephalopathy panel

Autoantibody	Result	Reference value
N-methyl-D-aspartate receptor	Negative	
Neuronal voltage-gated potassium channel (nmol/L)	0.01	≤ 0.02
Leucine-rich glioma inactivated 1 (LGI-1)	Negative	
Contactin-associated protein 2 (CASPR2)	Negative	
Glutamate decarboxylase 65 (GAD 65) (nmol/L)	0.02	≤ 0.02
Gamma-aminobutyric acid-B receptor	Negative	
Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R)	Negative	
Type 1 anti-neuronal nuclear antibody (anti-Hu)	Negative	<1:240
Type 2 anti-neuronal nuclear antibody (anti-Ri)	Negative	<1:240
Type 3 anti-neuronal nuclear antibody	Negative	<1:240
Anti-glial nuclear antibody 1	Negative	<1:240
Type 1 Purkinje cell cytoplasmic antibody (anti-Yo)	Negative	<1:240
Type 2 Purkinje cell cytoplasmic antibody	Negative	<1:240
Type Tr Purkinje cell cytoplasmic antibody (anti-Tr)	Negative	<1:240
Amphiphysin	Negative	<1:240
P/Q-type voltage-gated calcium channel (nmol/L)	0.00	≤ 0.02
N-type voltage-gated calcium channel (nmol/L)	0.08	≤ 0.03

level in our case was considered low, other alternative diagnoses were excluded. Moreover, significant clinical improvement after treatment with intravenous immunoglobulin

supported the role of N-type VGCC antibodies in mediating central nervous system inflammation in this patient.

The N-type calcium channels are found in dendritic spines on hippocampal pyramidal neurons.⁸ This may explain the role of N-type VGCC antibody in causing limbic encephalopathy in our case. In addition to an association with Lambert-Eaton syndrome, a recent study showed a wide spectrum of VGCC antibody-associated disorders such as autoimmune encephalopathy, movement disorders, seizures, and dysautonomia.⁷ Moreover, VGCC antibody-associated encephalopathy can mimic several neurological disorders including chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) syndrome, multiple sclerosis, and frontotemporal dementia.^{9–11} Because of its low positive predictive value, clinical correlation and exclusion of alternative diagnoses are mandatory before diagnosing VGCC antibody-associated encephalopathy.

In summary, we report a case of RPD secondary to non-paraneoplastic N-type VGCC antibody-associated encephalopathy. Furthermore, our case demonstrates the benefit of intravenous immunoglobulin in this condition.

ORCID

Smathorn Thakolwiboon <http://orcid.org/0000-0003-0607-904X>

Amputch Karukote <http://orcid.org/0000-0002-7234-4625>

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