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CASE REPORT

Coexistence of Anti-GAD and Anti-GABAAR Antibodies in an Autoimmune Encephalitis Patient: A Case Report

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Background: Coexistence of autoimmune encephalitis (AE) with multiple autoantibodies is of particular concern because overlying antibodies may cause variation of clinical manifestations. Coexistence of anti-glutamic acid decarboxylase (GAD) and anti-Gamma-aminobutyric acid-α-receptor (GABAAR) antibodies in AE was rare.

Case Presentation: A 44-year-old female patient presented to our hospital due to cognitive decline for 4 years, seizures, slowed speech and depression for 2 months. Based on her clinical manifestations and laboratory assessment results (positive anti-GAD and anti-GABAAR antibodies), she was diagnosed as AE with coexisting anti-GAD and anti-GABAAR antibodies. After treatment with intravenous methylprednisolone (at dose of 1000mg/d, 500mg/d, 250mg/d, 120mg/d, 80mg/d for 3 days respectively) and intravenous immunoglobulin (400 mg/kg/d for 5 days), her symptoms gradually improved with exception for the slowed speech. Oral prednisone acetate was continued after discharge, her symptoms of slowed speech improved at 6-month follow-up.

Conclusion: We report a case of AE co-existing with anti-GAD and anti-GABAAR antibodies, which has different characteristics from previous cases. Coexistence of neural auto-antibodies should be considered when patients suspected with autoimmune encephalitis.

Keywords: autoimmune encephalitis, anti-GAD antibody, anti-GABAAR antibody

Introduction

Autoimmune encephalitis (AE) is an intricate neurological disease caused by abnormal immune responses.[1] The exact etiology of autoimmune encephalitis remains unknown. In clinical practice, the diagnosis of autoimmune encephalitis is a challenge. On the one hand, the disease manifests with diverse symptoms, including memory deficits, seizures, psychiatric symptoms, making it susceptible to misdiagnosis and hard to distinguish from other diseases, like viral encephalitis.[2–4] On the other hand, the auxiliary examinations with MRI and EEG cannot provide a definitive diagnosis of the disease which may be helpful for excluding other causes, indicating that AE lacks specific imaging and electrophysiological diagnostic criteria.[5] Therefore, diagnosing AE is based on the combination of a clinical history consistent with pediatric or adult AE, and supportive diagnostic testing, including antibody testing.[1,6,7] Immunotherapy plays a pivotal role in the treatment of autoimmune encephalitis and early intervention is beneficial for patients.[8]

In recent years, specific antibodies were found in the serum and/ or cerebrospinal fluid of AE patients, such as anti-N-methyl D-aspartate Receptor (NMDAR), anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), anti-Gamma-aminobutyric acid-α-receptor (GABAAR), anti-Gamma-aminobutyric acid-β-receptor (GABABR), anti-Leucine-rich glioma inactivated 1 (LGI1), anti-glutamic acid decarboxylase (GAD) and so on.[1] These antibodies serve as specific biomarkers, helping neurologists distinguish AE from other neurological diseases with similar clinical symptoms. Furthermore, different autoantibodies are correlated with distinct clinical phenotypes and outcomes. For example, AE with anti-NMDAR antibodies is associated with psychiatric symptoms,[9] whereas anti-LGI1

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antibodies are linked to limbic encephalitis.[10] Therefore, detection of specific autoantibodies has emerged as a crucial tool for diagnosing AE and guiding targeted therapeutic interventions.[11] Herein, we reported a case of anti-GAD and anti-GABAAR antibodies occurring in a middle-aged woman with autoimmune encephalitis.

Case Report

A 44-year-old female patient was admitted to our hospital due to "Cognitive decline for 4 years and paroxysmal loss of consciousness with convulsion for 2 months". Four years before admission, the patient had developed cognitive decline without obvious inducement, easily forgotten the names of her relatives and forgot what to do without headache and dizziness. Two months before admission, she had a temperature of 39.5 ˚C, and developed paroxysmal loss of consciousness with convulsion, mainly manifesting as her eyes turned up, foaming at the mouth, clenched teeth, limb twitching and unconsciousness, lasting approximately 15 minutes. She was unable to recall after the attack. This situation occurred three times. After that, she was easily distracted and could not concentrate on work. She felt depressed easily and her speech slowed, and was found incompetent for her job. Cranial magnetic resonance imaging (MRI) (plain scan) at a local hospital showed no abnormalities. She came to our clinic for further diagnosis and treatment. She had a history of Hashimoto's thyroiditis and hypothyroidism.

On admission, her neurological examination revealed decreased verbal fluency. Cranial nerve examination was unremarkable. Her muscle strength was normal, and no other remarkable physical findings of nervous system were observed. The Glasgow coma score was normal. Physical examinations of the heart, lungs, and abdomen were unremarkable. She scored 25/30 on the Mini-Mental State Examination (MMSE), 24/30 on the Montreal Cognitive Assessment (MoCA), showing that the patient had mild cognitive impairment. Mild depression (51 points) was found after evaluation with Self-rating Depression Scale (SDS). No anxiety was found after evaluation using the Self-rating Anxiety Scale (SAS).

Auxiliary examinations were performed. Lung computed tomography (CT) revealed chronic inflammation in both lungs. Cranial magnetic resonance imaging (MRI) (plain scan + enhanced) showed no abnormalities. No obvious abnormality was found in cerebral CT vascular enhancement. 24-hours ambulatory electroencephalogram was normal. The result of gynecological and abdominal ultrasound was normal.

Her intracranial pressure was 80 mmH2O. CSF analysis showed normal cell count (total cell 2×10^6/ L, nucleated cells 1×10^6 /L), protein, glucose, chloride, lactate, and adenosine deaminase were within the normal range. Gram staining, fungal smear, acid-fast staining, ink staining, and pathogen culture of CSF were all negative. Cerebrospinal fluid oligoclonal band was negative. CSF and serum samples were collected for examination of AE antibodies, including anti-NMDAR, anti-AMPAR1, anti-AMPAR2, anti-LGI1, anti-CASPR2, anti-GABABR, anti-DPPX, anti-IgLON5, anti-GlyRα1, anti-GABAARα1, anti-GABAARβ3, anti-mGluR5, anti-D2R, anti-Neurexin-3α, anti-GAD65, anti-GABAARγ2 antibody IgG (cell-based assay). The significant findings included a positive anti-GAD65 antibody (titer of 1:32) and positive anti-GABAARγ2 antibody (titer of 1:32) in the CSF, and both were negative in serum (Figure 1). In addition, high levels of homocysteine (16.9μmol/L; normal range:<15μmol/L), total cholesterol (5.57mmol/L; normal range: <5.18mmol/L), high-density lipoprotein (HDL) (1.8 mmol/L; normal range:1.29–1.55mmol/L), low-density lipoprotein (LDL) (3.68mmol/L; normal range: <3.37mmol/L) were presented. High level of thyroid peroxidase antibody (TPO-Ab) (228 IU/mL; normal range: <34 IU/mL) and low level of Vitamin B12 (119.4 pg/mL; normal range: 189–883 pg/mL) were presented. The results of other examinations were unremarkable.

After being diagnosed with AE with coexisting anti-GAD and anti-GABAAR antibodies, the patient was treated with intravenous immunoglobulin (400 mg/kg/d for 5 days), intravenous methylprednisolone (at dose of 1000mg/d, 500mg/d, 250mg/d, 120mg/d, 80mg/d for 3 days respectively) and levetiracetam (0.5g PO bid). Twenty days later, her symptoms, such as cognitive decline, gradually improved during the treatment and no seizures occurred. After treatment for 20 days, she scored 26/30 on the Montreal Cognitive Assessment at discharge. Oral prednisone acetate tablets at dose of 1mg/kg/d, reduced by 5 mg every two weeks, were continued. At her 6-month follow-up, her epileptic seizures disappeared, cognitive function was normal, and speed improved.

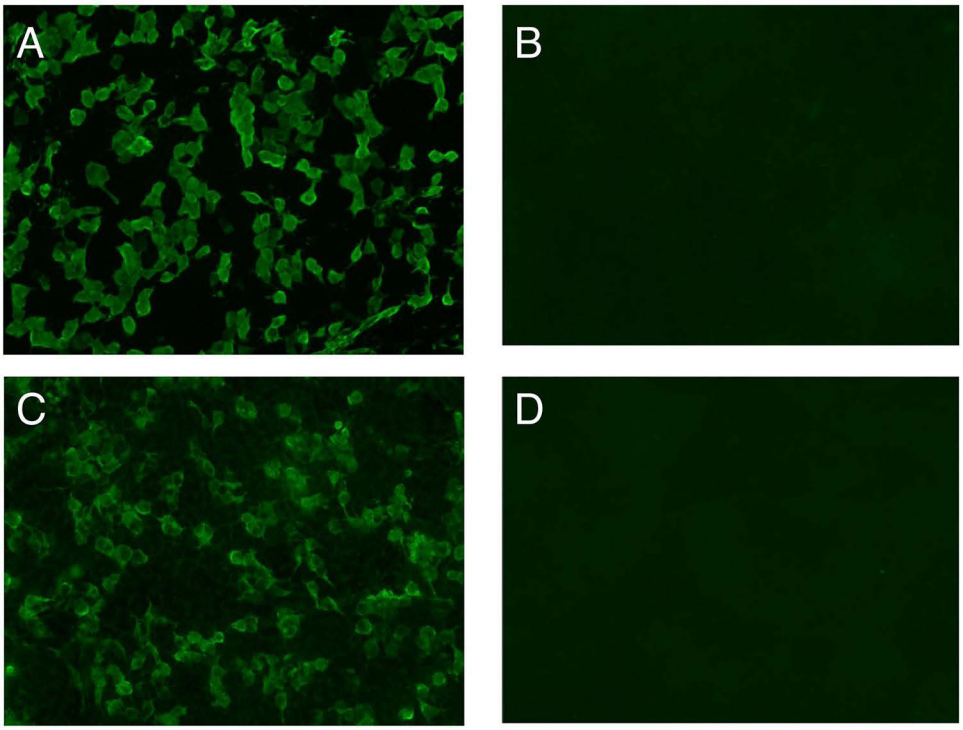

Figure 1 (**A**) Anti-GAD antibody in CSF (titer 1:32); (**B**) Anti-GAD antibody in serum (negative); (**C**) Anti-GABAAR antibody in CSF (titer 1:32); (**D**) Anti-GABAAR antibody in serum (negative).

Discussion

Autoimmune encephalitis, an immunity-associated encephalitis, often involves antibodies against NMDAR and LGI1, rarely involves antibodies against AMPAR, GAD, DPPX, GABABR and GABAAR.[12] The anti-GAD antibody inhibits the activity of the GAD enzyme, which is essential for the formation of an inhibitory neurotransmitter named gamma aminobutyric acid (GABA) in the brain.[13] Anti-GAD antibody has been reported to be involved in the pathogenesis of autoimmune neurological disorders such as epilepsy, stiff-person syndrome, cerebellar ataxia and limbic encephalitis.[14] Anti-GAD encephalitis has diverse clinical manifestations, like seizures,[15] severe dysautonomia,[16] behavioral disorder,[17] difficulty walking and dizziness.[18] Tumors can be found in anti-GAD encephalitis, like thymoma and small cell lung carcinoma.[19] GABAA receptors (GABAAR) mediate GABA actions either at the synapses or at extra-synaptic sites responding to ambient GABA to provide a basal tonic inhibitory state, modulating most of the fast inhibitory synaptic transmission in the brain.[20] Anti-GABAAR encephalitis usually presented with status epilepticus, altered behavior, cognitive decline and a decreased level of consciousness.[21] Typical brain MRI findings of anti-GABAAR encephalitis include extensive multifocal abnormalities on FLAIR and T2WI, which involve both the cortex and subcortical white matter, usually without contrast enhancement.[22] Tumors can be found in GABAAR encephalitis, such as thymoma.[23]

In recent years, increasing cases with multiple co-existing neural auto-antibodies in AE have been reported, which deserve special attention because overlapping neuronal auto-antibodies may cause variation of clinical syndromes. Besides, it is hard to verify which antibodies are mainly pathogenic, and researchers may get a tendentious result based on the clinical manifestations. Autoimmune encephalitis associated with anti-GAD and anti-GABAAR antibodies is rare. To the best of our knowledge, only two cases have been reported to date. Gagnon et al reported a case of encephalitis associated with GAD65 and GABAAR antibodies in a 38-year-old woman who presented with dysgueusia, dysosmia, episodes of hyperventilation that evolved into refractory status epilepticus, and multifocal lesions (the right temporal lobe, both frontal lobes, and parasagittal area) on T2-weighted images.[24] Another case associated with GAD, LGI1 and GABAAR antibodies reported by Nakano et al was a 62-year-old man, who showed cognitive impairment and epileptic seizures. Brain magnetic resonance imaging revealed multifocal lesions (bilateral frontal lobes and right parietal lobe) on T2-weighted images.[25] No malignancy

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was found in either patient and they achieved a favorable clinical outcome after treatment with corticosteroids, IVIg, plasma exchange, and anti-epileptic drugs (AED). Our patient was a 44-year-old woman who presented with cognitive impairment, seizures, emotional change and slowed speech, and she recovered after treatment with corticosteroids, IVIg, and AED. Furthermore, these cases highlight that seizures and cognitive impairment are prominent clinical manifestations of anti-GAD and anti-GABAAR antibody-associated autoimmune encephalitis. Both anti-GAD and anti-GABAAR antibodies related with the function of GABA, may lead to dysfunction in neurotransmission and neuronal activity, contributing to seizures and cognitive dysfunction.

Currently, immunotherapy plays a crucial role in the treatment of autoimmune encephalitis, demonstrating notable efficacy in palliating symptoms and improving clinical outcomes.[8] The first-line treatment of AE is the combination use of corticosteroids, intravenous immunoglobulin, and/or plasma exchange. If failed, second-line treatment, such as rituximab and cyclophosphamide can be used. In the present case report, this patient received high-dose methylprednisolone pulse therapy combined with IVIG. The pateint's clinical symptoms largely disappeared after discharge. Considering her age, financial situation and the side effects of drugs, the patient was unwilling to start the second-line treatment. She completed regular outpatient follow-up and the symptoms did not recur.

In cases of autoimmune encephalitis such like this, multiple autoantibodies may be present simultaneously. Therefore, it is necessary to screen patients for various autoantibodies to achieve an accurate diagnosis.[26] Although auxiliary tests showed no tumor in this case, long-term follow-up is necessary. The limitation of our study was that we were unable to conduct foundational research related to coexistence of anti-GAD and anti-GABAAR antibodies at animal or cellular level, which may provide further information on the pathology.

Conclusion

Herein, we describe a case of AE with co-existing anti-GAD and anti-GABAAR antibodies, which has different characteristics from previous cases. Coexistence of neural autoantibodies should be considered when patients suspected with autoimmune encephalitis.

Consent for Publication

This case report obtained written informed patient consent.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

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