CASE REPORT

Stiff-Person Syndrome Associated with Anti-Glutamic Acid Decarboxylase Autoimmune Encephalitis in a Young Woman: A Case Report

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Abstract A 34-year-old female with stiff-person syndrome (SPS) is reported in this paper. She experienced short-term memory impairment and was diagnosed with anti-glutamic acid decarboxylase (GAD) autoimmune encephalitis (AE) at the local hospital. However, after the treatment with intravenous immunoglobulin and high-dose glucocorticoids, her symptoms unchanged. Two months later, she was admitted to our hospital due to an unstable gait and persistent leg stiffness, at which point she was diagnosed as anti-GAD AE concomitant with SPS. Her clinical symptoms improved with an increased dose of γ -aminobutyric acid (GABA)-enhancing drug and plasma exchange. Anti-GAD antibody-associated AE combined with SPS is extremely rare. Treatment with GABA-enhancing drugs and appropriate immunotherapy can improve the neurological function of patients suffering from the combination of SPS and limbic encephalitis.

AUTOIMMUNE encephalitis (AE) is a group of encephalitic conditions mediated by various autoimmune disorders. Anti-glutamic acid decarboxylase (GAD) antibody-associated AE is an extremely rare condition which is characterized by the acute or subacute onset of seizures, memory deficits, cognitive impairment and psychiatric symptoms.^[1] Meanwhile, the association between anti-GAD and Stiff-Person Syndrome (SPS) is well known. SPS is characterized by progressive rigidity and muscle spasms affecting the axial and limb muscles, predominantly in females.^[2] Here, we report a rare case of anti-

GAD AE concomitant with SPS in a young woman.

CASE DESCRIPTION

A 34-year-old female was referred to our office due to an unstable gait and leg stiffness lasting two months. She had previously presented to the local hospital for short-term memory impairment for twenty months prior to visiting us and was diagnosed as anti-GAD AE based on the detection of anti-GAD antibodies in her cerebrospinal fluid. She received therapy of intravenous immunoglobulin combined with high-dose glucocorticoids, but her memory defects remained unimproved. On admission, the patient complained of stiffness and pain in both her legs, lumbago and

cognitive impairment, and she was demonstrated lumbar lordosis and could barely walk. Physical examination revealed horizontal nystagmus, a rigid trunk, high muscle tension and weakness in both lower limbs. Hyperactivity of tendon reflexes and Babinski signs were observed in both her lower limbs.

Magnetic resonance imaging (MRI) of the head showed bilateral abnormal signals in the hippocampus (**Figure 1, A–C**), while 18F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) scan demonstrated increased flake-like radioactive uptake in bilateral medial temporal lobes, with a greater signal change in the left than the right and the bilateral putamen (**Figure 1, D–F**). An electroencephalogram (EEG) showed single high-ultra-high potential 2-3 c/s sharp slow wave emitted at different steps in bilateral temporal regions in sleep stage, which was more obvious on the left side. Anti-GAD antibody was double positive in serum (anti-GAD titer: >2000 IU/mL; normal range: 1–10 IU/mL) and cerebrospinal fluid (CSF) (anti-GAD titer: 1:3.2; normal: 1:1). Electromyography (EMG) showed normal action potential when the right extensor muscle completely relaxed. Therefore, the patient was diagnosed as anti-GAD AE concomitant with SPS.

Clonazepam (1 mg, bid) and baclofen (10 mg,

tid) were given orally, and 5 sessions of plasma exchange (1700 mL/day) were performed. The muscle stiffness alleviated significantly so that she could walk without assistance. Thirty days later, as detected by the Mini-Mental State Examination (MMSE) and the Montreal scale (MoCA), her impaired short-term memory had partially improved. MRI showed bilateral abnormal signals in the insular cortex, medial temporal lobe and hippocampus. EMG revealed that the motor and sensory nerve conduction velocity and amplitude were within the normal range. A recheck of serum anti-GAD showed a titer of >2000 IU/mL.

DISCUSSION

The GAD antibody is a known biomarker of non-neurological autoimmune diseases. Type 1 diabetes, autoimmune thyroid disease and pernicious anemia are the most common GAD-related autoimmune conditions. However, GAD antibodies also accompany with many autoimmune central nervous system disorders. Positive anti-GAD serology occurs in about 60% – 80% of SPS patients.^[2] Mainly reported in women, SPS is characterized by the presence of progressive and painful spasms, along with stiffness and

Figure 1. Representative patient images of the 34-year-old female patient with stiff-person syndrome.

(A) Axial DWI, (B) T2WI, and (C) FLAIR MRI images show bilateral abnormal signals in the hippocampus; (D) axial 18F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) scan, (E) PET-CT fusion image, and (F) coronal PET-CT image demonstrate increased flake-like radioactive uptake in the bilateral medial temporal lobes, with a greater signal change observed in the left than in the right.

rigidity of the axial and proximal muscles. EMG studies show evidence of continuous normal action potential in resting state. The pathogenesis is still unclear; it is possibly because anti-GAD antibodies block the production of γ -aminobutyric acid (GABA). The loss of GABAergic inputs to the motor neurons results in tonic firing at rest and excessive excitation in response to sensory stimuli.^[3] In this case, the patient was a young female with stiffnesses of persistent trunk muscle and bilateral lower limbs. The EMG test result, along with positive anti-GAD antibodies in serum and cerebrospinal fluid, were consistent with the diagnosis of SPS.

Due to the ability to detect autoantibodies against the surface of neurons or synaptic proteins, the recognition of AE has gradually increased. Anti-GAD antibody associated AE is a rare type of inflammatory encephalopathy that includes limbic and extra-limbic encephalitis. Limbic encephalitis (LE) is characterized by subacute memory loss, seizures, and psychiatric symptoms. In cases of LE, MRI FLAIR imaging depicts bilateral hyperintensities of mesiotemporal signal, and FDG-PET shows extensive bilateral mesiotemporal hypermetabolism, in addition to hypometabolism.^[4,5] Malter identified high-titer anti-GAD65 in 17% of LE patients.^[1] Thus, LE pathogenesis may be related to the high expression of GAD65 in CA1 and hippocampal dentate gyrus.^[6,7] The clinical symptoms, cranial MRI and FDG-PET manifestations pointed to the diagnosis of LE clearly in this patient. The combination of SPS and LE related to anti-GAD65 antibody is extremely rare. A study by Titulaer *et al.* found that only one out of 52 patients with anti-GAD positive SPS had concurrent LE.^[8] The relevant pathological mechanism remains unconfirmed.

Responses to immunotherapy for anti-GAD-associated neurological disorders vary. Most SPS patients show improvement with GABA-enhancing drugs (e.g., baclofen, gabapentin, levetiracetam, diazepam or other benzodiazepines) and appropriate immunotherapy (e.g., steroids, plasmapheresis, intravenous immunoglobulin, rituximab, cyclophosphamide and mycophenolate). Also, for SPS patients with tumors, complete tumor removal is recommended before initiation of immunotherapy.^[9] Unfortunately, LE is poorly responsive to immunotherapy, and the persistence may cause intractable seizures or memory disorders.^[10] In this case, the short-term memory decline of the patient did not significantly improve after intravenous immunoglobulin and high-dose glucocorticoids. This is not surprising

considering the patient had high-titer anti-GAD and a relatively short course of disease. In addition, the high risk of adverse effects and the uncertain clinical efficacy of other immunotherapy (e.g., rituximab, cyclophosphamide and mycophenolate) are considered.^[9,11] Therefore, we decided to increase the dose of the GABA-enhancing drug and add plasma exchange to her therapeutic regimen, after which SPS symptoms significantly improved and the memory decline partially recovered. This case study indicates that anti-GAD titer is not related to the severity of symptom, so titer monitoring may be unnecessary during treatment.^[11] So far, there has been no clinical consensus on the treatment of this disease.

Anti-GAD antibody-associated AE combined with SPS is extremely rare. Treatment with GABA-enhancing drugs and appropriate immunotherapy can improve the neurological function of the patients suffering from the combination of SPS and LE. By reporting this case, we hope to enrich the understanding of this kind of disease.

Conflict of interests

The authors declared no conflicting interests.

Compliance with ethics

Written informed consent was obtained from the reported patient.

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