

# Rare Association of Autoimmune Limbic Encephalitis and Stiff Person Syndrome

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## ABSTRACT

Antibodies to Glutamic Acid Decarboxylase (GAD) have been implicated in the pathogenesis of both autoimmune Limbic Encephalitis (LE) and Stiff Person Syndrome (SPS). However, their association is quite rare. We present a case of a 48-year-old Caucasian female who presented with symptoms of recurrent severe headaches, behavioral and cognitive dysfunction, and an episode of seizure. She was found to have high titers of anti-GAD65 antibodies in both cerebrospinal fluid and serum. She was diagnosed with LE and SPS, and was started on immunosuppressive therapy with steroids and intravenous immunoglobulins (IVIG). The patient responded well to treatment with improvement in her symptoms.

**KEYWORDS:** Stiff person syndrome, SPS, Limbic encephalitis, LE, GAD 65

## INTRODUCTION

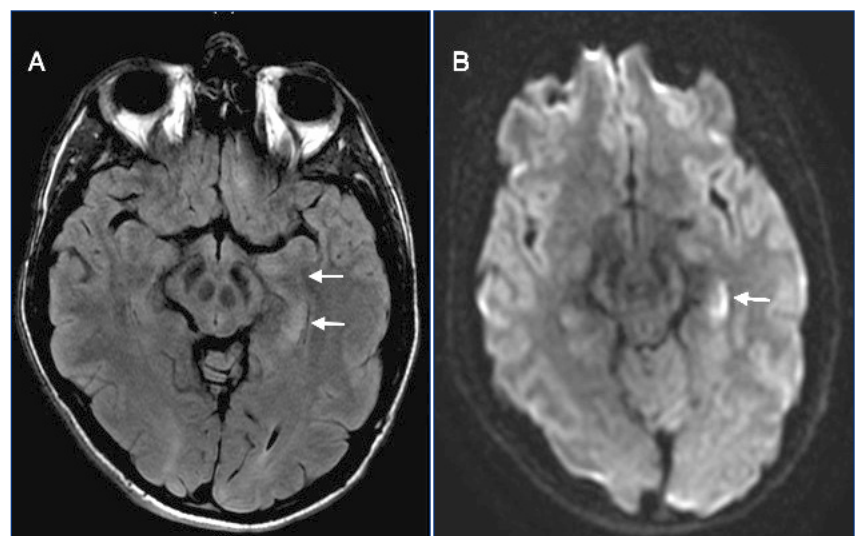
Stiff-person syndrome (SPS) is a rare neurological disorder, characterized by progressive muscle rigidity, stiffness, and painful muscle spasms.<sup>1,2</sup> It predominantly affects the trunk and proximal extremity muscles, leading to difficulty with ambulation and recurrent falls.<sup>3</sup> The likely pathogenesis of SPS is autoimmune, and most patients are found to have antibodies to glutamic acid decarboxylase (GAD).<sup>4,5</sup> GAD antibodies are also associated with other neurological conditions, such as cerebellar ataxia, epilepsy, palatal tremor, and autoimmune limbic encephalitis (LE).<sup>6</sup> Autoimmune LE is increasingly being identified as an underlying cause in individuals presenting with neurocognitive and psychiatric symptoms. Although antibodies to GAD are implicated in the pathogenesis of both SPS and autoimmune LE their association is quite rare. Here we present a rare case of concurrent LE and SPS, which was successfully treated with immunosuppressive therapy.

## CASE DESCRIPTION

A 48-year-old right-handed woman presented to the hospital after having an episode of generalized tonic-clonic seizure. She had been complaining of recurrent severe headaches, along with episodes of confusion, agitation, and hallucinations for the past two weeks. She also complained of stiffness and rigidity involving neck and back muscles, with muscle spasms, and difficulty ambulating with frequent falls. She did not have any known history of seizure disorder.

Physical exam demonstrated a heart rate of 76 beats per minute, blood pressure of 133/79, respiratory rate of 15 breaths per minute, and oxygen saturation of 99% on room air. The patient was alert but confused, and only oriented to person. Neurological examination showed grossly intact cranial nerves; motor evaluation demonstrated generalized rigidity, and muscle strength was 5/5 in all four limbs. Deep tendon reflexes were normal, Babinski reflexes were negative bilaterally, and her sensory evaluation was unremarkable. However, an evaluation of her gait was not performed. Laboratory evaluation was unremarkable, including a normal complete blood count, basic metabolic profile, liver function test, uric acid level, thyroid stimulating hormone, and hemoglobin A1c. Magnetic resonance imaging (MRI) of the brain showed signal hyperintensity involving the left

**Figure 1.** Magnetic resonance imaging of brain showing hyperintensity involving left temporal lobe on FLAIR sequence (A) with evidence of diffusion restriction on DWI (B).



temporal lobe on FLAIR sequences, with evidence of diffusion restriction on diffusion-weighted imaging (**Figure 1**). Electroencephalography (EEG) showed increased epileptogenicity in the left frontotemporal lobe. Lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis showed a white cell count of 5 cells/mm<sup>3</sup> with 24% lymphocytes and 2% segmented neutrophils, protein of 42 mg/dL, and glucose of 67 mg/dL. Gram stain and cultures for bacteria, fungus, and mycobacteria were negative; PCR for HSV 1 and 2, HHV-6, West-Nile virus and JC virus were negative. Antibodies in the paraneoplastic panel (ANNA 1&2, AGNA 1, PCA 1&2, CRMP – 5, P/Q and N type calcium channel, anti-AChR, anti-amphiphysin) were also negative. However, the autoimmune evaluation of CSF demonstrated elevated anti-GAD65 antibodies, with titers of 148 IU/mL, and normal or undetectable titers for other autoantibodies, such as anti-NMDAR, anti-VGKC complex, anti-LGI, anti-Caspr 2, and anti-GABA<sub>B</sub>R. In addition to CSF, serum anti-GAD65 antibodies were checked and were found to be elevated as well. Electromyography (EMG) showed continuous motor unit activity in agonist and antagonist muscles. Given the patient's clinical presentation and resulting investigational workup, a diagnosis of autoimmune LE and SPS was considered.

The patient was given one dose of intravenous methylprednisolone 1000 mg and was started on an IVIG infusion of 60 gm once daily for five days. Levetiracetam 1000mg two times per day and diazepam 5mg four times per day orally were also initiated, and the patient showed significant improvement in cognitive and behavioral symptoms. No further seizure activity was reported, and there was improvement in her muscle stiffness. The patient was transitioned to oral prednisone 60mg daily maintenance dose and discharged to an acute care rehabilitation facility.

## DISCUSSION

SPS is a rare neurological disorder, with an increased incidence in females over males (ratio of 2:1). It commonly occurs in the third to sixth decades of life.<sup>1,7</sup> SPS is clinically characterized by muscle stiffness and rigidity, predominantly affecting the axial and proximal limb muscles.<sup>1,2</sup> Stiffness and rigidity cause difficulty with posturing, gait imbalance, muscle spasms, leading to frequent falls.<sup>2,3</sup> Muscle spasms are often precipitated by external stimuli (tactile or auditory) and emotional stress.<sup>3</sup> SPS is a progressive disease, with muscle stiffness and rigidity becoming more fixed with time, and spasms becoming more frequent, leading to functional impairment and progressive disability.<sup>1</sup> Psychiatric disorders, such as depression, generalized anxiety disorder, panic attacks, and phobias, are also commonly associated with SPS.<sup>8,9</sup>

Autoantibodies to GAD have been implicated in pathogenesis of SPS, and these antibodies are found in high titers

in both serum and CSF of these patients.<sup>5</sup> GAD is a crucial enzyme involved in synthesis of gamma aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the central nervous system. The enzyme GAD is present in two isoforms, namely GAD65 and GAD67.<sup>10</sup> GAD65 is a membrane-bound enzyme found in GABAergic neurons in the CNS, and pancreatic beta cells in the gastrointestinal tract. GAD67 is a soluble form and is found only in the CNS. Anti-GAD65 antibodies are present in the serum and CSF of 80% and 75% of SPS patients, respectively.<sup>2,11,12</sup> Anti-GAD67 antibodies are found in 50% of patients with SPS, but in much lower titers when compared to anti-GAD65.<sup>12</sup> These antibodies are present in one percent of the normal population and five percent of patients with other neurological disorders, such as cerebellar ataxia, epilepsy, palatal tremor, and autoimmune limbic encephalitis (LE).<sup>6,13</sup> Diagnosis of SPS is made on clinical findings with supportive evidence from serology and EMG. Demonstration of continuous, involuntary simultaneous firing of motor units on EMG is characteristic of SPS in agonist and antagonistic muscles.<sup>2</sup> Immunosuppressive/immunomodulation therapy with steroids, rituximab, IVIG, and plasmapheresis has been utilized in the treatment of SPS.<sup>14</sup> Medications that increase GABA activity, such as diazepam and baclofen, also help to alleviate symptoms.<sup>14</sup>

The hallmark of autoimmune LE is the rapid development of confusion, cognitive dysfunction, behavioral symptoms, and seizures.<sup>15,16</sup> Furthermore, the subacute development of short-term memory deficits is a well-recognized characteristic of this disorder.<sup>15</sup> LE was initially described as paraneoplastic, and was found in association with certain malignancies, such as lung cancer and testicular tumors.

Onconeural (intracellular) antibodies, such as anti-Hu and anti-Ma, are elevated in paraneoplastic LE, whereas antibodies against neuronal cell surface (extracellular) proteins, such as LGI 1, Caspr 2, NMDAR, AMPAR, GABA<sub>B</sub>R and glycine receptor, are commonly associated with autoimmune LE.<sup>16,17</sup> GAD is distinct to these as it is an intracellular antigen but not an onconeural antigen, and yet has also been associated with the pathogenesis of autoimmune LE.<sup>18</sup> CSF analysis typically shows lymphocytic pleocytosis in 60–80% of LE patients, with approximately 50% of patients having oligoclonal bands and an elevated IgG index.<sup>16</sup> Imaging with MRI or positron emission topography (PET) scan classically shows hyperintense signals in bilateral medial temporal lobes, but unilateral abnormalities or normal scans can also be found in LE patients.<sup>15</sup> It is important to exclude infections and metabolic etiologies that can present with a similar clinical picture before establishing the diagnosis of autoimmune LE. Treatment of autoimmune LE is by immunosuppression, with pulsed steroids, followed by high dose oral prednisone and IVIG, with or without plasmapheresis.<sup>19</sup>

Although cases of both SPS and autoimmune LE are described in literature, their association is very rare. Both

these disorders have been described in association with GAD antibodies, but the exact mechanism of how these antibodies interact with neural antigens is not fully known. It has been hypothesized that these antibodies interfere with synthesis of GABA in the CNS, leading to its reduced levels. This relative deficiency of GABA can lead to malfunction of major inhibitory pathways.<sup>3,5</sup> Therefore, it is important to highlight the role of anti-GAD antibodies as a marker for these neurological disorders, rather than the actual cause of dysfunction. Lastly, Sharma et al in 2016 described a case of SPS with autoimmune LE in a patient with type 1 diabetes mellitus (DM) associated with anti-GAD65 antibodies.<sup>20</sup> Our patient did not carry a diagnosis of DM at the time of her presentation. To our knowledge this is the second reported case of a of SPS with concurrent autoimmune LE.

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