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Stiff Person with Anti-GAD Antibodies

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Abstract

Stiff Person Syndrome (SPS) is a rare autoimmune disease related to the lack of inhibition of excitatory neurons in the central nervous system leading to multiple motor dysfunction and symptoms due to uncontrolled motor neuron firing. The pathophysiology of the disease is not completely understood; however, high titers of Glutamic acid decarboxylase antibodies (anti-GAD Ab) have been found in such patients, which leads to its high association with the disease. We present a case of a 52-year-old female with a 20-year history of ongoing gait and balance issues. She is diagnosed with multiple conditions, including stiff person syndrome (GAD+), spinocerebellar ataxia with epilepsy, systemic lupus erythematosus, type 1 diabetes mellitus, IgA deficiency, hypothyroidism, and pernicious anemia. She presented in our institution with a history of a recent fall from a wheelchair. We review the case presentation and association of anti-GAD antibodies with stiff person syndrome and its treatment.

Keywords

Stiff Person, Autoimmune, GAD, Plasmapheresis, GABA, GAD+

1. Introduction

Stiff Person Syndrome (SPS) is a rare autoimmune disease with an estimated prevalence of 1 - 2 cases per million people [1]. It is caused by a lack of inhibition of excitatory neurotransmitters in the CNS, leading to continuous involuntary muscle excitation [1]. It has various presentations, including incomplete localized stiffness in only one limb (stiff limb syndrome, SLS) to fulminant stiff-

ness with encephalomyelitis, brainstem dysfunction, and dysautonomia (progressive encephalomyelitis with rigidity and myoclonus, PERM) [2]. SPS has a variable course. Some patients have a slowly progressive disease, others have acute exacerbations, and others may switch from one phenotype to another [3]. This adds to the diagnostic challenge. Many patients are initially suspected of psychogenic stiffness or malingering. It is important to consider SPS in a patient with stiffness and apparent resistance to passive range of motion on the exam. SPS is an autoimmune-mediated illness that is treatable if diagnosed [3]. Given the rarity of the disease and varied presentations, our report aims to plug gaps in understanding the presentation of patients with SPS and how certain treatments fare in patients with SPS. We report a case of a patient who had a history of difficulty walking with reported gait and balance issues for over 20 years with multiple autoimmune diseases. She was diagnosed with SPS and spinocerebellar ataxia with epilepsy simultaneously after having progressive lower extremity weakness, difficulty maintaining balance, and epileptic episodes.

2. Case Presentation

The patient is a 52-year-old African American female with a past medical history of type1 diabetes mellitus, hypothyroidism, SLE, IgA deficiency, a seizure disorder that had required left anterior temporal lobectomy in 2005, and a diagnosis of stiff person syndrome (GAD+). Her symptoms began in 2008, at the age of 27, when she developed chronic lower back pain and bilateral knee pains, which progressed to involve right leg stiffness and frequent falls. She had a negative workup by her primary care physician and specialists at an outside hospital; however, her symptoms continued to progress until she was diagnosed with stiff person syndrome and spinocerebellar ataxia with epilepsy associated with anti-GAD antibodies after extensive immunological and radiological workup. She has been wheelchair-bound since then.

She presented to the ED with acute RUE and RLE weakness with a fall 48 hours before the presentation when she got up from a sitting position. She denies dizziness, recent seizures, or loss of consciousness.

On exam, the patient was afebrile with no aphasia or dysarthria. Heart, lung, and abdomen exams were benign. The musculoskeletal exam did not show any synovitis, effusions, or tenderness to palpation of joints. Motor weakness; RUE: 4/5 strength LUE: 5/5 RLE: 3/5 LLE: 5/5. Plantar reflex was absent on right side, present left side.

MRI brain was negative for acute stroke. Bilateral temporal lobe hyperintense signals, left temporal encephalomalacia, and lobectomy changes were noted (**Figure 1**). An extensive laboratory workup was significant for GAD-65 > 30.0 units/ml (normal < 5 units/ml, ANA 1:1280; pattern speckled, IgA < 8, TSH 0.46, Thyroid peroxidase Ab 796, HbA1c 8.1. The remaining laboratory results were negative or within normal limits.

The patient was initially treated with gabapentin and baclofen; however, there

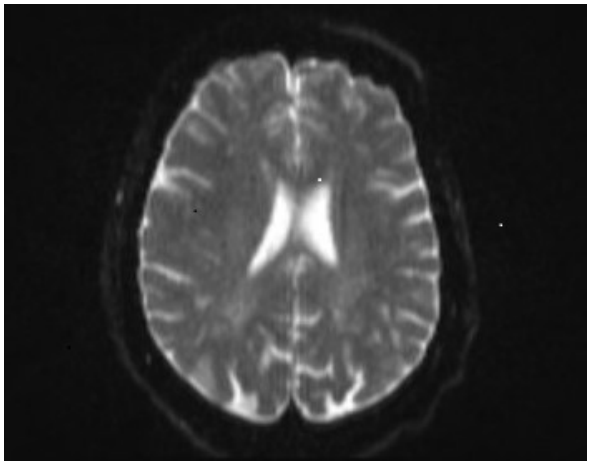

Figure 1. Brain MRI.

was no significant improvement in her stiffness. Baclofen was discontinued, and diazepam was started along with inpatient physical therapy with some initial improvement in spasticity. She completed 4 sessions of plasmapheresis and was transferred to a tertiary hospital for further evaluation and management. Her neurological symptoms did not improve despite the sessions.

3. Discussion

SPS is a rare disease with an estimated prevalence of 1 - 2 cases per million [1] [2]. The pathophysiology is incompletely understood; however, high titers of anti-GAD Ab are strongly associated with this disease. Different immunosuppressive therapies help minimize neurological symptoms [3] [4]. The underlying pathophysiology involves central inhibition of inhibitory signals, which leads to the inability of opposing skeletal muscles to relax when the contralateral muscles contract, causing characteristic rigidity and painful spasm [4]. SPS has various presentations, including classic SPS, partial SPS, and paraneoplastic SPS, all of which share the characteristic symptom of muscle stiffness. Classic SPS, first described in 1956 [5], is described as diffuse stiffness, truncal rigidity, and muscle spasms, exaggerated with symptoms precipitated by sudden stimuli. Partial SPS only affects part of the body, commonly known as "stiff limb syndrome," mainly involving the legs. It may present with more spasticity in one leg than the other and causes difficulty in ambulation. In approximately 5% of cases, paraneoplastic SPS is usually associated with lung cancers. It looks identical to classic SPS but is usually anti-GAD Ab negative, has positive amphiphysin antibodies, and is resistant to immunomodulatory treatment [4].

As assessed by Tsiortou *et al.* and colleagues in a retrospective cohort of 57 patients, the initial presenting symptoms were slowly progressive proximal leg stiffness which then progressed to muscle spasms, stiffness in the thoracolumbar spine, muscle rigidity, and hyperreflexia [4]. Many patients were noted to have comorbid anxiety due to fear of falling and the unpredictable nature of the muscle spasms, leading to an erroneous diagnosis of a psychogenic disorder [4]. Di-

agnosis of SPS is difficult and includes CSF analysis, brain imaging to exclude structural abnormalities, and antibody and electrophysiological testing. Most patients will have stiffness of axial muscles, high anti-GAD Ab, symptoms of anxiety, and electromyographic (EMG) findings of continuous motor unit firing in the absence of any other physiologic cause after extensive investigation. Anti-GAD Ab is pathognomonic; another commonly associated autoantibody is glycine-a1 receptor Ab (anti-GlyR), also found in progressive encephalomyelitis [1].

Treatment for SPS is a combination of symptomatic treatment and immunosuppression. Gamma-aminobutyric acid (GABA) agonists such as benzodiazepines, gabapentin, baclofen, and pregabalin provide immediate relief and help mobilize the patient quickly. Immunomodulators address the underlying autoimmune defect and provide lasting benefits; however, therapy is dictated by symptom severity. Treatment initially involves Gamma-Amino-ButyricAcidergic (GABAergic) therapy, usually with benzodiazepines, since the pathogenesis involves the destruction of the GAD enzyme, which is essential in manufacturing GABA [6]. Diazepam and clonazepam are the drugs of choice, with patients showing great responses. The dosage of these drugs can be up to 60 mg daily, and although patients have relief of symptoms, they risk dependence and withdrawal [6]. This has also prompted further use of other muscle relaxants like the alpha-one blocker tizanidine, often combined with a benzodiazepine. Tizanidine, however, prevents the release of glutamate, and thus, patients with SPS are at risk of developing convulsions [7]. The second line of therapy for SPS is with the muscle relaxant baclofen, which is given orally but sometimes intrathecally; however, no significant data support one method over the other [6]. Other medications that can be used initially before more aggressive strategies include but are not limited to levetiracetam, pregabalin, and propofol, all of which increase GABAergic activity [6].

Patients with the acute and more aggressive disease at initial presentation may benefit from immunosuppression with interventions like high-dose steroids, plasmapheresis, various steroid-sparing immunosuppressants, and rituximab, all have been tried with varying degrees of efficacy [1]. Novel treatments for SPS include rituximab, high-dose intravenous immunoglobulin (IVIG), and plasma exchange. B cells in our body are the major producers of antibodies. Since SPS is, for the most part, an antibody-mediated disease, it is within reason to try to stop the production of B cells altogether, which then decreases the levels of the antibodies, in this case, anti-GAD antibodies [6]. Rituximab achieves this by blocking CD-20, thus reaching a constant state of B-cell depletion. Rituximab has also proven to be useful in other autoimmune neurologic conditions as well [8]. Not much data exists to support the use of this, however. The largest trial performed by Dalkas *et al.* in 2017 (NEJM) showed no statistically significant difference in the 24 patients randomized to receive biweekly infusions of 1g rituximab vs. placebo [6] [9]. Patients also who are refractory to initial treatments usually re-

quire immunomodulators [6]. Given the rarity of the disease, not much data exists to evaluate the effectiveness of IVIG, but one double-blind placebo-controlled study performed by Dalaks *et al.* evaluated 16 patients where the treatment group (6 patients) received 2 g/kg of IVIG. The study lasted 3 months, and at the end of the time period, patients who got the IVIG were found to have significant clinical improvements, which was the primary endpoint [10]. Other smaller studies have been performed, but due to the lack of power, the significance of these studies cannot be determined.

Our patient showed temporary relief of symptoms with baclofen, diazepam, and gabapentin initially. The more aggressive course of the disease led to the choice of treatment with plasmapheresis. Five sessions of plasmapheresis were done but without any significant improvement in the patient's symptoms. The final frontier in the treatment of SPS is plasma exchange therapy, usually conducted in one cycle with five sittings of plasma exchange [6]. The mechanism by which this works is still in the gray, but it is hypothesized that removing cytokines during this process leads to the relief of symptoms [11]. The data that exists to support this method is mixed. Casa-Fages *et al.* found only two patients that responded to exchange therapy with elevated levels of anti-GAD Ab afterward. In another trial with ten patients, six patients were treated with plasma exchange chronically in an outpatient setting, but only 50% had symptom relief [6] [11] [12].

The mainstay of treatment in patients with SPS is symptom relief. While no one particular method is significantly superior, monotherapy or combination therapy of any of the above therapies mentioned above may be used to achieve relief of symptoms.

4. Conclusions

SPS is a rare disease with multiple presentations and treatment options. SPS remains an important differential diagnosis in cases of unexplained muscle stiffness since early intervention slows disease progression and prevents some of the disabilities. Considering unusual presentations of rare diseases before diagnosing psychogenic diseases is vital.

In conclusion, diagnosing Stiff Person Syndrome (SPS) can be challenging due to its rarity and similarity to other neurological disorders. However, an elevated level of anti-GAD antibodies in the blood can significantly indicate the condition. As a result, clinicians should consider SPS a potential diagnosis when evaluating patients with stiff muscles and other neurological symptoms, especially when accompanied by high levels of anti-GAD antibodies. Therefore, healthcare providers should remain vigilant and consider SPS when assessing patients with these symptoms. Appropriate diagnostic tests, including anti-GAD antibody testing, should be conducted to confirm or rule out the diagnosis. Early recognition and diagnosis of SPS are crucial for prompt treatment, symptom management, and improved quality of life for affected individuals.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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