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Case Report

Stiff Person Syndrome and Brittle Type 1 Diabetes: Report of 2 Cases

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ABSTRACT

Background/Objective: Stiff person syndrome (SPS) and type 1 diabetes (T1D) are heterogeneous disorders characterized by antibodies (Abs) against glutamic acid decarboxylase (GAD).
Case Report: We describe 2 patients with T1D and autoimmune thyroid disease who presented with muscle rigidity and intermittent spasms that affected gait and with elevated circulating anti-GAD titers. Classic SPS and stiff limb syndrome were diagnosed, respectively. Muscle spasms resolved with immunotherapy and muscle relaxants in both patients, and the ability to ambulate without an assistive device was restored in 1 patient. Patients also had brittle diabetes with high glycemic variability, requiring the use of flash glucose monitoring with an insulin pump and a second-generation basal insulin analog, respectively.
Discussion: GAD Ab–associated syndromes include SPS, T1D, and other endocrinopathies. The clinical heterogeneity implies variable susceptibility of γ-aminobutyric acid-ergic neurons and pancreatic beta cells to anti-GAD or other autoantibodies.
Conclusion: Our case series represent the heterogeneity in natural history, clinical course, and response to therapy in patients with Abs against GAD-spectrum disorders.

Introduction

Stiff person syndrome (SPS) is an uncommon immune-mediated condition characterized by progressive truncal and limb rigidity, painful muscle spasms, and generalized anxiety disorder producing gait difficulties, falls, and deterioration in quality of life. SPS is related to serum anti–glutamic acid decarboxylase (GAD) antibodies (Abs). GAD is an enzyme that catalyzes the production of γ-aminobutyric acid (GABA), an important neurotransmitter of the central nervous system, and present in pancreatic beta cells.[1] These autoantibodies are also linked with type 1 diabetes (T1D). We report 2 cases of middle-aged women with a known history of T1D and autoimmune thyroid disease, presenting with muscle rigidity and intermittent spasms that affected gait and with elevated circulating anti-GAD titers. A classic presentation of SPS and stiff limb syndrome were diagnosed, respectively.

Case Report

Patient 1

A 50-year-old woman with medical history of hypothyroidism after radioactive iodine therapy for Graves disease, generalized anxiety disorder, and T1D since the age of 35 years presented with a 1-year history of progressive stiffness and tender spasms of her back and both legs, causing difficulty in standing up, leaving her wheelchair bound. On presentation, the lower limbs were rigid with flexed hips and knees, and movements were severely limited and painful. Her muscle tone was significantly increased in both lower limbs. Deep tendon reflexes were mildly brisk. Needle electromyography showed continuous motor unit activity in the anterior tibialis bilaterally and both biceps. Anti-GAD 65 titers were found to be 144 U/mL (normal, <0.9 U/mL). Fludeoxyglucose F18 positron emission tomography revealed normal results. SPS of

Abbreviations: Ab, antibody; CGM, continuous glucose monitoring; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase; HbA1c, glycosylated hemoglobin; SPS, stiff person syndrome; T1D, type 1 diabetes.

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classic presentation was diagnosed. Treatment with oral diazepam marginally reduced the frequency of lower limb spasm and pain episodes. Intravenous immunoglobulin (2 g/kg over 5 days) followed by administration of oral baclofen and prednisone resulted in a marked reduction in hypertonicity. At 6 months after treatment, she could walk without support (Table and Fig. 1).

The patient had trouble achieving glycemic control goals. At presentation, the glycosylated hemoglobin (HbA1c) level was 8.5%, 69 mmol/mol. Continuous glucose monitoring (CGM) revealed a time in range of 56% and coefficient of variation of 60.5%. After ineffective efforts to adjust her insulin injections based on carbohydrate counting and preprandial glucose readings, brittle diabetes was diagnosed. She was placed on continuous subcutaneous insulin infusion along with CGM. After 4 weeks of hybrid closed-loop system, the CGM showed no hypoglycemic events and improvement in glycemic control.

Patient 2

A 52-year-old woman with a past medical history of Hashimoto thyroiditis, generalized anxiety disorder, and T1D since the age of 30 years presented with episodic stiffening of her right leg every month for 1 year. The sudden stiffness was exacerbated by stressful events, with the need to walk with a support device and resulted in multiple falls 6 months before admission. Physical examination revealed muscle stiffness, and deep tendon reflexes were mildly brisk in her right leg. Anti-GAD 65 titers were 105 U/mL (normal, <0.9 U/mL), and the results of studies to search for neoplasia were negative. Partial SPS (stiff limb syndrome) was diagnosed. Treatment with 10 mg of baclofen daily for 1 year followed by administration of pregabalin and carbamazepine resulted in significant reduction in hypertonicity, and the patient could walk with the minimal use of the assistive device (Table and Fig. 2). The patient also had trouble controlling hyperglycemia; at presentation, the HbA1c level was 7.9%, 63 mmol/mol, despite multiple daily insulin injections (glargine U100 before breakfast and lispro before each meal). CGM revealed a time in range of 66%, time below range of 7% predominantly due to nocturnal hypoglycemia, and coefficient of variation of 41.4%. She was instructed to perform carbohydrate counting and preprandial glucose readings and to switch from insulin glargine U100 to glargine U300. After 4 months, the HbA1c level was 6.8%, and nocturnal hypoglycemia was resolved.

Table
Demographic Characteristic, Laboratory Results, Diagnosis, and Treatment of the 2 Patients

Characteristics	Patient 1	Patient 2
Age, y	50	52
Sex	Female	Female
Body mass index, kg/m^2	28	25
Medical history	Graves disease, T1D	Hashimoto thyroiditis, T1D
Onset of symptoms	1 y	1 y
Symptoms	Progressive stiffness and painful spasms of her back and both legs	Episodic stiffening of her right leg
Anti-GAD Ab titers, U/mL	144	105
HbA1c, %	8.5	7.9
Time in range on CGM, %	56	66
Coefficient of variation on CGM, %	60.5	41.5
Diagnosis	Classic SPS	Stiff limb syndrome
Treatment	Diazepam, IVIg, baclofen, and prednisone	Baclofen, pregabalin, and carbamazepine
Outcome	Walk without assistance	Walk with the minimal use of an assistive device

Abbreviations: anti-GAD Ab = antibodies against glutamic acid decarboxylase; CGM = continuous glucose monitoring; HbA1c = glycosylated hemoglobin; IVIg = intravenous immunoglobulin; SPS = stiff person syndrome; T1D = type 1 diabetes.

Highlights

- Stiff person syndrome is characterized by muscle rigidity and anti-GAD antibodies
- Type 1 diabetes (T1D), also present anti-GAD Ab, can coexist with SPS
- We present 2 cases with SPS and brittle T1D successfully managed

Clinical Relevance

Stiff person syndrome is a rare condition; however, it should be suspected when muscle rigidity is present along with high titers of anti–glutamic decarboxylase antibodies. It may coexist with other autoimmune diseases.

Discussion

The original description of SPS reported a series of 14 patients with progressive fluctuating muscle rigidity, intermittent painful spasms, phobias, and postural unsteadiness and recurrent falls.[2] Women are found to be affected in 70% of cases, in an age range between 20 and 50 years.[3] In this case series, we report 2 women in the sixth decade who were diagnosed with SPS in its classic presentation and as a stiff limb syndrome with favorable outcomes.

The diagnosis of classic SPS included the Dalakas criteria and was confirmed by the presence of anti-GAD 65 (or amphiphysin) autoantibodies, measured by western blot, immunocytochemistry, or radioimmunoassay.[4]

Three subcategories of cryptogenic SPS have been described: (1) classic SPS, (2) stiff limb syndrome, and (3) progressive encephalomyelitis with rigidity.[5] The reasons for heterogeneity probably imply variable susceptibility of GABAergic neurons and pancreatic beta cells to anti-GAD. The paraneoplastic SPS involves 5% of patients and is linked with cancers of the breast, small cell lung, colon, and Hodgkin lymphoma.[6]

Pathophysiology of classic SPS has not been totally explained. It is widely accepted that the etiology of SPS is autoimmune and involves autoantibodies that impair GABAergic neurotransmission including anti-GAD, antiamphiphysin, antigephyrin, antidipeptidyl peptidase-like protein, and antiglycine receptor. In 43% to 85% of cases, the occurrence of anti-GAD Abs is described. In this case series, the anti-GAD 65 titers were >100 U/mL. The inhibition of this enzyme limiting GABA synthesis leads to systemic deficit,[7] due to which patients present with clinical stiffness and psychiatric manifestations.[8]

SPS is strongly linked with other autoimmune diseases; more than 80% of cases have at least 1 endocrinopathy; therefore, screening for other autoimmune diseases should be performed. Thyroid disease and autoimmune diabetes are found in 10% and 35% to 60%, respectively, at SPS diagnosis.[9] The appearance of these diseases can coincide or present after SPS. Genetic predisposition associated with certain human leukocyte antigen alleles, particularly those implicated in T1D and thyroid disease, may be

Fig. 1. The patient with classic stiff person syndrome 6 months after therapy.

Fig. 2. The patient with stiff limb syndrome 6 months after therapy.

associated with an increased risk of developing SPS. The 2 SPS cases described had T1D and autoimmune thyroid disease (Graves disease and Hashimoto thyroiditis, respectively).

In 1988, Solimena and Folli[10] proposed that autoantibodies against GAD, an enzyme found in the pancreatic Langerhans islets and central nervous system, were relevant in both diseases. Anti-GAD is detected in 80% of individuals with T1D at diagnosis and 60% to 80% of patients with SPS; titers in T1D are lower than in SPS.[11,12] GAD has 2 isoforms: (1) active 67-kd isoform (GAD 67) in the cytoplasmic and (2) an isoform of 65 kd (GAD 65) associated with synaptic membranes. The first provides a continuous GABA basal production, and the second acts to supply pulses of GABA. GAD 65 is a typical autoantigen in T1D and SPS, and the activated immune response affects insulin secretion and impairs neurotransmission. Anti-GAD 67 Abs are reported in 10% of patients with T1D and 60% of patients with SPS. The anti-GAD Abs in SPS and T1D recognize 2 different epitopes: (1) a linear denatured NH2-terminal GAD epitope and (2) a conformational GAD epitope, respectively.[13,14] GAD 65 is the major target antigen in both syndromes, and because of the cross reactivity between GAD 65 and GAD 67, it was the isoform measured in these cases. Typically, the diagnosis of T1D precedes SPS by a median of 5 years.[15] Our patients were diagnosed with SPS at the sixth decade of life, 2 decades earlier T1D was diagnosed.

Our cases were diagnosed with brittle diabetes due to high glycemic variability; they required the use of flash CGM with an insulin pump and a second-generation basal insulin analog, respectively.[16] Although it is known that the presence of 2 Abs and higher anti-GAD titers in T1D are associated with an earlier age of disease onset,[17] it is unknown whether T1D in the context of SPS is associated with brittle diabetes, a greater need for insulin, or an early appearance of microvascular or macrovascular complications.

Conclusions

SPS is an uncommon autoimmune neurologic condition that presents with endocrinopathies, the most prevalent is T1D. Their coexistence is illustrated by high titers of anti-GAD Abs compared with T1D alone. In the description of the cases, diabetes appeared 15 years preceding the diagnosis of SPS, and there was heterogeneity in the natural history, clinical course, and response to treatment. This warrants further investigation for an understanding of the pathophysiologic mechanisms of the anti-GAD Abs on both disorders.

Disclosure

The authors have no conflicts of interest to disclose.

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Patient's consent was obtained. We thank them for their support.

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