CLINICAL PRACTICE
*Clinical Vignettes*

# Stiff Person Syndrome and Type 1 Diabetes Mellitus: a Case of the Chicken or the Egg?

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Anti-glutamic acid decarboxylase (anti-GAD) antibodies are linked with both autoimmune diabetes and the rare neurological disorder stiff person syndrome (SPS). SPS is an uncommon autoimmune-mediated condition characterized by painful episodic spasms and progressive muscle rigidity. We present the case of a 23-year-old non-diabetic, insulin-naïve woman with known SPS who was hospitalized for SPS-related symptomatology. The patient quickly developed type 1 diabetes mellitus (T1DM) with unexpectedly large insulin requirements. To our knowledge, there are no other reports describing rapid T1DM development during an acute hospitalization for SPS and fewer than 5 case reports describing the association of SPS with extreme insulin resistance. Our case highlights the key clinical features, pathology, and pathogenesis of both SPS and T1DM and explores the relationship between the two disease processes.

*KEY WORDS:* stiff person syndrome; type 1 diabetes mellitus; anti-glutamic acid decarboxylase (anti-GAD) antibodies.

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## INTRODUCTION

Stiff person syndrome (SPS) is a rare immune-mediated disorder characterized by rigidity and episodic spasms that can be progressive and fatal.[1–3] Circulating anti-glutamic acid decarboxylase (anti-GAD) antibodies are thought to create a γ-aminobutyric acid (GABA)-scarce environment within the body.[2] These autoantibodies, although orders of magnitude greater in SPS,[4] are also associated with type 1 diabetes mellitus (T1DM).[5] We describe the case of a 23-year-old woman with a known history of SPS, presenting with high circulating anti-GAD titers and SPS symptomatology, who promptly developed T1DM with unexpectedly large insulin requirements. It is currently unknown if anti-GAD titers at SPS levels hasten the development of T1DM in undiagnosed, at risk individuals.

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## CASE PRESENTATION

A 23-year-old Hispanic woman with a past medical history of autoimmune atrophic gastritis and pernicious anemia, depression, anxiety, and SPS was transferred to our facility from an outside hospital with intractable seizure-like episodes. The onset of her illness was at age 18, 5 years prior to presentation. Tightening in her ankles slowly progressed to whole-body stiffness leaving her wheelchair bound. anti-GAD titers were found to be high in both serum (448 nmol/L, normal $\leq 0.02$) and CSF (21.9 nmol/L, normal $\leq 0.02$), and SPS was clinically diagnosed at age 19.

The seizure-like episodes consisted of stiffness, rhythmic activity, and eye fluttering. EEG was not consistent with epileptic features. Some episodes resulted in major oxygen desaturation events requiring intubation. anti-GAD titers before attempted apheresis were 2141 nmol/L. Six apheresis treatments were performed without significant clinical response. Prednisone was introduced with the goal of lowering antibody titers. Mycophenolate mofetil and azathioprine were attempted, but not tolerated. Levetiracetam and prednisone were eventually down-titrated and discontinued, while diazepam was slowly up-titrated. Diazepam administration, combined with biweekly IVIG infusions, eventually resulted in substantial clinical improvement.

The patient's 4-month hospital course was complicated by hospital-acquired pneumonia, pulmonary embolism, and prolonged ventilator dependence resulting in tracheostomy and PEG tube placement. Anxiety surrounding tracheostomy capping trials frequently induced spasms, which caused additional oxygen desaturation events.

The patient also experienced difficult-to-control hyperglycemia. Family history was significant for a grandfather with type 2 diabetes and mother with type 1 diabetes. At presentation, HbA1c was 5.9% and the patient was insulin naive. During her hospitalization, she had relatively high insulin requirements, peaking at 140 IU daily, initially attributed to steroid administration and new tube feedings. Her HbA1c increased to 6.2% and then to 6.6%. The C-peptide level was 1.3 ng/mL (normal 0.9–6.9 ng/mL). As the patient's SPS became more clinically controlled, there were mildly reduced insulin requirements. Steroids had been discontinued for more than 7 weeks at time of discharge and more than 60 IU of insulin daily were still required. At 1-month and 4-month outpatient follow-up, the patient continued to require 60 IU of insulin daily.

## DISCUSSION

SPS is frequently associated with other autoimmune diseases, with up to 80% of patients having at least one other endocrinopathy.[3,6] Pernicious anemia, autoimmune thyroid disease, and insulin-dependent diabetes mellitus have comorbid frequencies of 5%, 10%, and 35–60% respectively at time of SPS diagnosis.[2,7,8] When treating a patient with SPS, clinicians should maintain a high level of suspicion for the coexistence of associated undiagnosed autoimmune diseases.

SPS remains a clinical diagnosis (Fig. 1), primarily characterized by simultaneous contracture of agonist and antagonist muscles, resulting in rigidity.[2,3] Superimposed sudden painful episodic spasms are common[2,3,8] and can be forceful enough to bend surgical pins, dislocate joints, and cause femoral fractures.[10–13]

Spasms are triggered by heightened sensitivities to external stimuli such as unexpected auditory, tactile, or visual stimuli, and to psychological stimuli such as emotional upset, anxiety, or task-specific phobias.[2,3,8,13,14] A subset of spasms involving the respiratory or thoracic musculature can result in life-threatening restrictive respiratory failure.[2,15] The spasms in our patient were linked to the task-specific phobia of tracheostomy capping trials, resulting in repeated bouts of acute hypoxic respiratory failure. Episodes seemed less frequent when family was at bedside providing comfort.

The pathophysiology of SPS involves the impairment of GABAergic neurotransmission. While 6 separate autoantigens have been identified,[9] the presence of anti-GAD antibodies has been reported in 43%[9] to 85%[2,4] of patients. The inhibition of GAD, the rate-limiting enzyme in the synthesis of GABA, leads to systemic deficiency. As the body's predominant inhibitory neurotransmitter, clinical stiffness is attributed to the lack of reciprocal inhibition in GABA-mediated neuromuscular pathways, while reduced cerebral GABA may contribute to psychiatric comorbidities.[16]

anti-GAD is not unique to SPS and has also been associated with cerebellar ataxia, palatal myoclonus, Batten's disease, temporal lobe epilepsy, thymomas, lung and breast carcinomas, autoimmune polyendocrine syndromes, and T1DM.[2]

SPS and T1DM share pathophysiologic characteristics (Fig. 2). anti-GAD is present in up to 80% of patients with T1DM at time of diagnosis,[18,19] although titers are typically orders of magnitude less than present in SPS.[3,4,17] anti-GAD in SPS has been shown to inhibit GAD enzymatic activity[20,21] and reduced cerebral GABA has been objectively demonstrated.[22] anti-GAD in T1DM has not been shown to play a direct

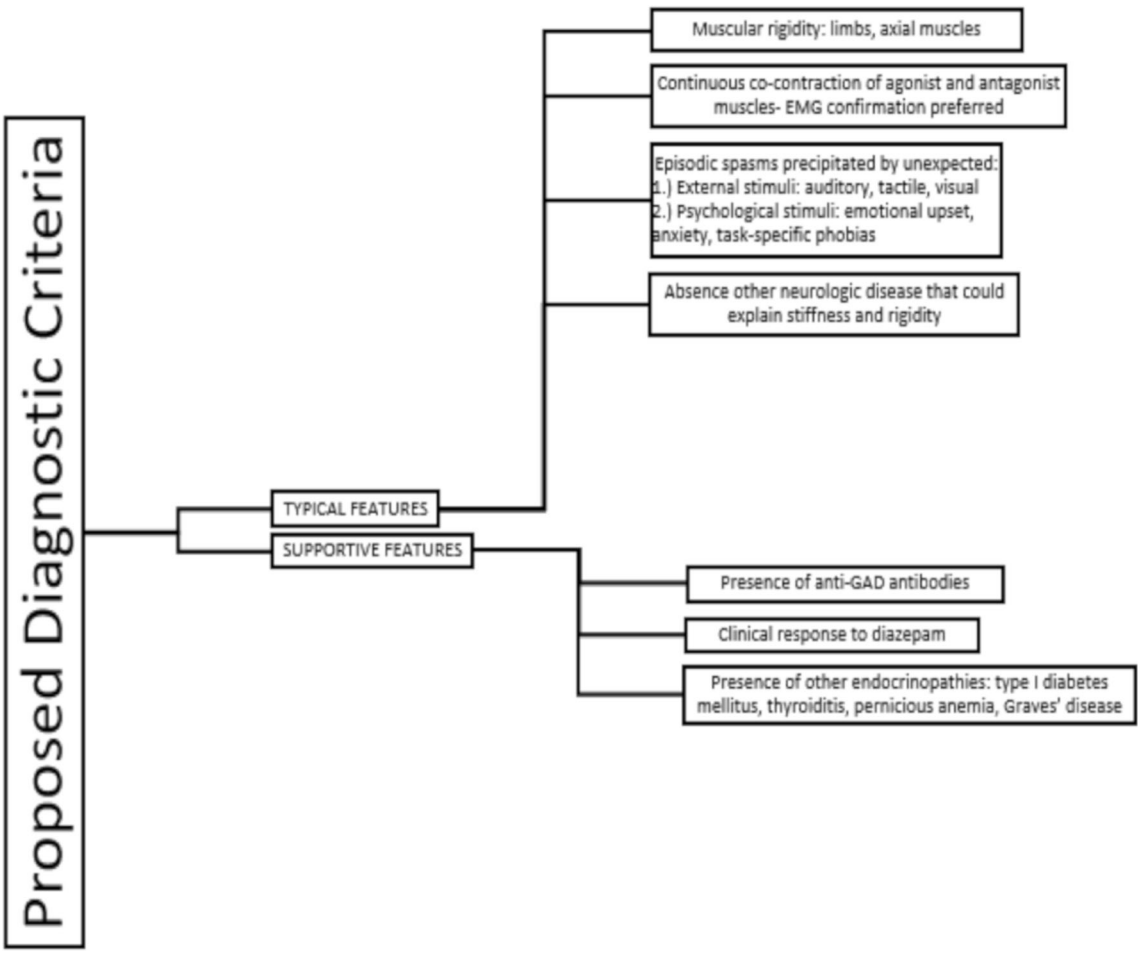


**Figure 1 No unified diagnostic criteria for SPS exists; however, the above clinical diagnostic criteria[2, 3, 9] for SPS have been generally accepted in practice and in research characterization of the disease.**

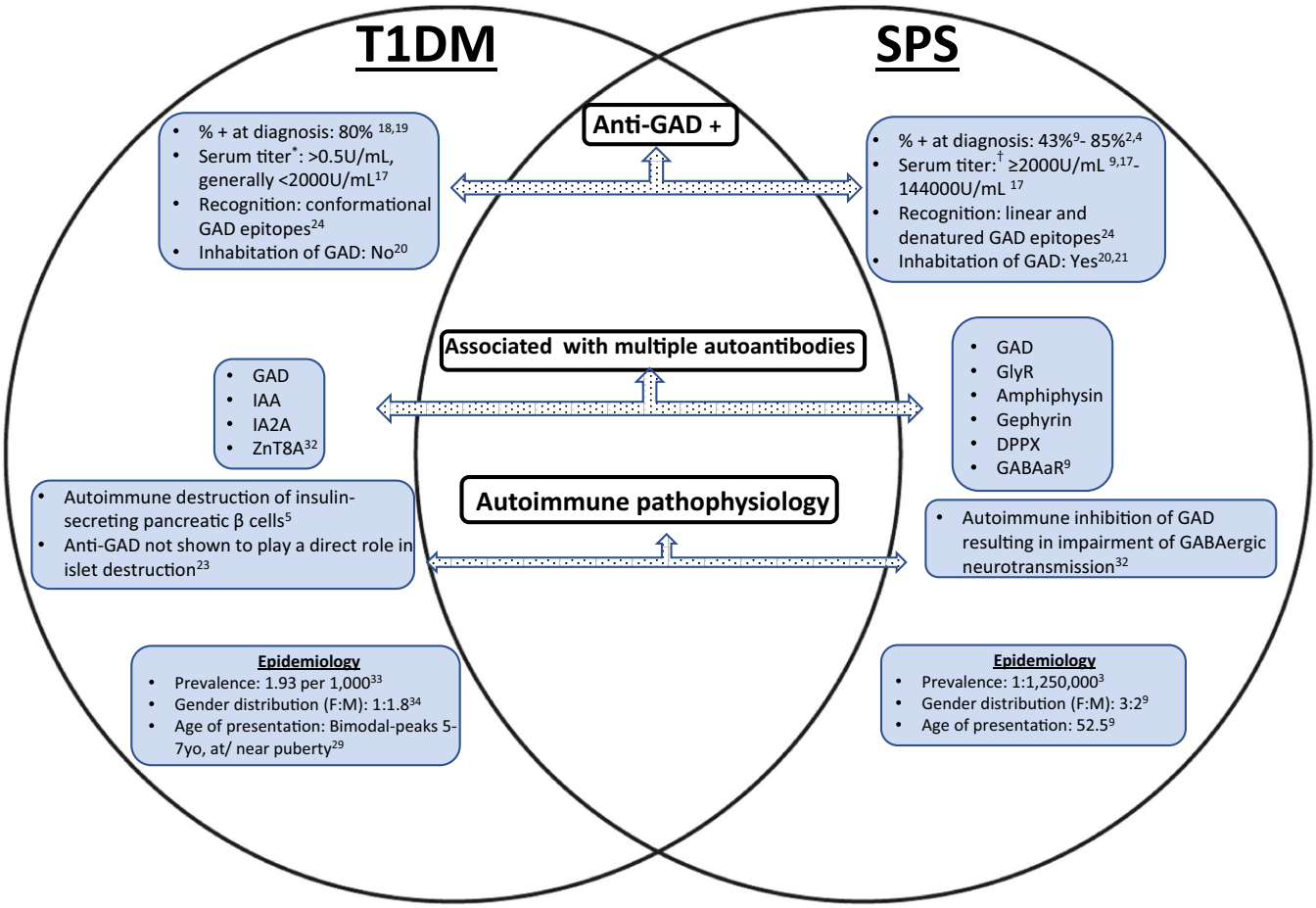


**Figure 2 Comparison of stiff person syndrome (SPS) and type 1 diabetes mellitus (T1DM). GAD, glutamic acid decarboxylase; IAA, insulin autoantibodies; IA2A, insulinoma-associated antigen 2; ZnT8A, zinc transporter 8 antibodies; GlyR, glycine receptor antibodies; DPPX, dipeptidyl peptidase-like protein 6; GABAaR, γ-aminobutyric acid-A receptor antibodies. Asterisk symbol indicates anti-GAD titers are generally < 2000 U/mL in isolated T1DM; however, rare reports of titers > 2000 U/mL exist.[17] Dagger sign indicates SPS anti-GAD titers start at ≥ 2000 U/mL[9, 17] with reports of titers up to 144,000 U/mL.[17]**

role in islet destruction[23] and, converse to SPS, has not been shown to inhibit GAD enzymatic activity.[20] In general, anti-GAD antibodies in SPS and T1DM are thought to recognize two different epitopes: a linear denatured NH2-terminal GAD epitope and a conformational GAD epitope respectively.[24] Interestingly, up to 5% of anti-GAD associated with T1DM will recognize the SPS-type epitope.[25] Consequently, most assays do not differentiate anti-GAD in patients with T1DM and SPS.[17] It remains to be determined if this pathophysiological overlap correlates with concurrent SPS and T1DM development.

While most with T1DM do not go on to develop SPS, the majority of those with anti-GAD-positive SPS will develop T1DM.[3,6,17] In 54–65% of these cases, the diagnosis of T1DM predates SPS by a median of 5 years.[6,17] The remainder of T1DM develops after the onset of SPS, a median of 3.5–4.5 years later.[6,17] anti-GAD-negative SPS cases are not strongly associated with T1DM.[6]

Here, we report an insulin-naïve patient with known SPS who was hospitalized for related symptomatology and quickly developed large insulin requirements. Early steroid treatments and new tube feedings initially muddied the clinical picture, making distinguishing between T1DM and T2DM with insulin resistance challenging. Etiological diabetes classification systems utilizing both autoantibodies and an estimated insulin sensitivity score (euglycemic clamp—a validated equation encompassing waist circumference, HbA1C, and triglyceride levels)[26] define T1DM as having at least one positive antibody, regardless of insulin sensitivity.[27] The euglycemic clamp equation objectively defined insulin resistance as an insulin sensitivity score < 8.15, less than the 25th percentile of a control population.[27] With positive anti-GAD titers and an insulin sensitivity score of 7.19, our patient can be categorized as having T1DM with concomitant insulin resistance, a pattern typical for obese patients with T1DM.[27] Further supporting a T1DM diagnosis, the patient's C-peptide level was found to be at an inappropriately low-normal range for the level of hyperglycemia noted. Low to low-normal and high-normal to high serum C-peptide levels have been shown to correlate with autoimmune diabetes and T2DM with insulin resistance respectively.[28] Due to rising levels of obesity, it has been noted that up to 20% of young diabetics may have both autoimmunity and insulin resistance.[27]

Our patient was diagnosed with SPS at 19 years old, decades earlier than the median diagnosis age of 52 years old.[9] When considered independently of SPS, T1DM has bimodal median ages of diagnosis, with peaks at 5–7 years old and at or near puberty.[29] Our patient was diagnosed with T1DM 4 years after initial SPS diagnosis, the timing of which correlates well with previously reported patient series.[6,17] Despite the common association of SPS with T1DM, there is insufficient data on factors in SPS patients that may precipitate the progression to clinical diabetes.

Our patient had anti-GAD titers that were fivefold higher at presentation than at SPS diagnosis. Historically, anti-GAD titers have not been shown to correlate with SPS disease severity or duration;[6] however, recent studies have reported that SPS patients with worsening disability at follow-up have higher anti-GAD titers.[30] Although it is known that higher anti-GAD titers in T1DM predict an earlier age of disease onset and future insulin requirements as compared to patients with lower titers,[5] it is currently unknown if anti-GAD titers at SPS levels hasten the development of T1DM in undiagnosed at risk individuals. In this respect, anti-GAD levels have only been studied in SPS patients who were already affected by T1DM.[21,31] Here, we report SPS level anti-GAD titers that may have hastened the development of T1DM during an acute hospitalization. While further research is needed, to date, investigations have been limited by the rarity of the disorder.

## CONCLUSION

SPS is a rare neurologic disorder characterized by rigidity and episodic spasms. anti-GAD is thought to create a GABA-scarce environment within the body. These antibodies are also independently associated with T1DM, the most prevalent comorbid endocrinopathy associated with SPS. Higher anti-GAD titers may be associated with worsening SPS and independent of SPS are associated with an earlier presentation of T1DM. The effect of SPS level anti-GAD titers on T1DM development has not yet fully been described and warrants further investigation.

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