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Stiff Person syndrome and Graves' disease: A rare autoimmune overlap with therapeutic insights

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Abstract

Stiff Person Syndrome (SPS) is a rare autoimmune neurologic disorder characterized by progressive muscle rigidity and frequently associated with anti-GAD65 antibodies. While SPS has established links with autoimmune conditions such as type 1 diabetes and celiac disease, its association with hyperthyroidism, particularly Graves' disease, is exceptionally rare. We report a case of a 34-year-old woman who presented with acute paranoia, hallucinations, and altered mental status. She was found to have thyrotoxicosis and was diagnosed with Graves' disease based on suppressed TSH, elevated free T4, and positive Thyroid-Stimulating Immunoglobulin (TSI) and Thyrotropin Receptor Antibody (TRAb) antibodies. Despite antithyroid therapy, her neuropsychiatric symptoms worsened, prompting neurologic evaluation. Brain Magnetic Resonance Imaging (MRI) and Electroencephalogram (EEG) were unremarkable, but lumbar puncture revealed elevated oligoclonal bands and high-titer Glutamic Acid Decarboxylase 65 (GAD-65) antibodies in cerebrospinal fluid, consistent with autoimmune encephalitis within the SPS spectrum. The patient showed marked clinical improvement following treatment with therapeutic plasma exchange and rituximab. At one-month follow-up, she remained clinically stable off antithyroid medications, with negative TSI and TRAb titers, suggesting that treatment of the underlying autoimmune neurologic disorder effectively resolved her concurrent Graves' disease. This case illustrates the rare coexistence of SPS and Graves' disease and highlights plasma exchange as a potentially novel and effective approach to treating both conditions when conventional therapies fail.

Background

Stiff Person Syndrome (SPS) is a rare autoimmune neurological disorder first described in 1956, characterized by a spectrum of motor symptoms and varying degrees of functional impairment [1]. It predominantly affects women (approximately 70% of cases) and typically presents between the ages of

20 and 60, with a median age of 40 years, although pediatric and elderly cases have been documented [2]. The clinical presentation typically includes episodic or persistent muscle stiffness, exaggerated lumbar lordosis, impaired gait, and frequent falls. Muscle spasms are often precipitated by sudden sensory stimuli, emotional stress, or voluntary movements [3]. Despite growing recognition, limited awareness of the diverse presentations often leads to delayed or incorrect diagnoses during the early course of the disease.

SPS is caused by impaired Gamma-Aminobutyric Acid (GABA)-mediated inhibition due to autoantibodies against Glutamic Acid Decarboxylase 65 (GAD65) and is strongly associated with high-titer anti-GAD65 antibodies in both serum and cerebrospinal fluid. Beyond the nervous system, SPS frequently coexists with other autoimmune conditions, with up to 70% of patients with GAD65 antibodies having at least one additional autoimmune disorder, most commonly type 1 diabetes mellitus and autoimmune thyroiditis [4]. While autoimmune thyroid disease, especially Hashimoto's thyroiditis, is relatively well-documented in SPS [5,6], the association between SPS and hyperthyroidism, particularly Graves' disease, is exceedingly rare and limited to case reports [7-10].

We describe a patient with both SPS and Graves' disease, confirmed by positive Thyroid-Stimulating Immunoglobulin (TSI) and Thyrotropin Receptor Antibodies (TRAb) positive, who showed marked improvement following plasma exchange. This case highlights the diagnostic challenges that arise from the wide-ranging clinical presentations of SPS, a rare autoimmune disorder, and its uncommon coexistence with other autoimmune endocrinopathies.

Case Presentation

A 34-year-old woman with a history of depression, cannabis use disorder and potential cyclic vomiting syndrome was transferred from a psychiatric facility to our emergency department for evaluation of persistent tachycardia, agitation, and profound fatigue. Three weeks prior, she had been admitted for new-onset paranoia, auditory hallucinations, and behavioral disturbances, including fear of contamination and covering windows. Her family reported a 15-pound weight loss during this period. She was started on aripiprazole 10 mg daily at the psychiatric facility. On arrival to the ED, the patient appeared confused and reported visual hallucinations. Vitals revealed tachycardia (heart rate 100–120 bpm), and otherwise stable measurements. She was tremulous and disoriented, with a mild goiter on exam. ECG showed sinus tachycardia without ST/T wave abnormalities. Laboratory evaluation revealed thyrotoxicosis with TSH <0.008 μIU/mL (reference range (RR): 0.4–4.0), free T4 4.13 ng/dL (RR, 0.8–1.8), and total T3 4.98 ng/mL (RR: 0.8–2.0). A TSH result one year prior had been normal. Mild transaminitis was noted (ALT 62 U/L[RR 7–56 U/L], AST 43 U/L[10–40 U/L]). She had no personal or family history of autoimmune disease.

Endocrinology was consulted, and the diagnosis of Graves' disease was made based on elevated TSI (3.0 IU/L; reference range: <0.55 IU/L), TRAb (4.05 IU/L; reference range: 0–0.9 IU/L), and anti-TPO antibody (300.2 IU/mL; reference range: <35 IU/mL). Thyroid ultrasound revealed a diffusely enlarged, heterogeneous, and hypervascular gland. The patient was diagnosed with Graves' disease and started on methimazole 20 mg daily and propranolol 25 mg twice daily.

Broad laboratory testing (Complete blood count, comprehensive metabolic panel, vitamin B12, folate, β-hCG, erythrocyte sedimentation rate, and intact parathyroid hormone) were unrevealing, except for an elevated creatinine kinase (561 U/L, RR, 20–200 U/L). Computed Tomography (CT) of the head, Electroencephalogram (EEG), Magnetic Resonance Imaging (MRI) brain and CT abdomen/pelvis were normal. The inpatient Neurology team was consulted, and they performed a Cerebrospinal fluid (CSF) analysis which showed mild lymphocytic pleocytosis (9 white blood cells/μL [RR, 0-5 cells/uL]), normal glucose (67 mg/dL, RR 50-80 mg/dL), and protein (23 mg/dL, RR 15–45 mg/dL). CSF autoimmune antibody testing was sent, including Glutamic Acid Decarboxylase 65 (GAD65) antibody, N-Methyl-D-Aspartate Receptor (NMDA-R) antibody, Gamma-Aminobutyric Acid B Receptor (GABA-B-R) antibody, as well as a panel of paraneoplastic markers.

Despite resolution of tachycardia within three days, her neuropsychiatric symptoms persisted. Due to limited improvement, aripiprazole was replaced with risperidone. Ten days after admission, the patient was discharged to psychiatry for ongoing care. However, the following day, she was found slumped in her seat with drooling, unresponsiveness, and extremity tremors, prompting immediate readmission.

Diagnostic assessment

On readmission, neurological exam revealed non-rhythmic left-predominant tremors, bilateral upper extremity stiffness, and hyperreflexia. EEG showed mild diffuse encephalopathy; MRI remained normal. Repeat thyroid testing showed partial improvement (free T4: 2.27 ng/dL, total T3: 2.71 ng/mL). Pending CSF returned positive for 13 oligoclonal bands in CSF (absent in serum), suggestive of intrathecal antibody production. CSF GAD65 antibodies were markedly elevated at 183 IU/mL (ref: <5), and serum GAD65 was 1600 IU/mL, confirming GAD65 antibody-mediated autoimmune encephalitis. All other autoimmune CSF antibodies returned negative.

Given the association between autoimmune encephalitis and thymoma, chest CT was obtained and showed a 5.0×6.8 cm anterior mediastinal soft tissue mass with signal dropout on opposed-phase imaging, consistent with benign thymic hyperplasia. Positron Emission Tomography imaging showed no tracer-avid malignancy.

Treatment

Upon readmission, patient was treated with IV methylprednisolone 1 g daily empirically for suspected autoimmune encephalitis. Once the diagnosis was confirmed, she received five sessions of therapeutic plasma exchange and was started on baclofen 5 mg three times daily for rigidity. She improved steadily, becoming interactive, alert, and following commands, with mental clarity improving with every session of plasma exchange, and rigidity, myoclonus, and hyperreflexia diminished. Methimazole was tapered in response to improving thyroid labs: free T4 and total T3 normalized (0.87 and 0.46 ng/dL). Atenolol 25 mg daily replaced propranolol due to hypotension. Methimazole was reduced to 10 mg, then 5 mg, and discontinued after stabilization of thyroid hormones (TSH 0.010 μIU/mL, free T4 of 0.64 ng/dL and total T3 0.28 ng/mL. In addition, she received a single 1000 mg dose of rituximab prior to discharge.

Outcome and follow-up

At her 6-week outpatient Endocrinology follow-up, she reported having complete resolution of symptoms of rigidity, and tremors. She remained psychiatrically stable and was able to resume her usual activities. She also remained euthyroid off of antithyroid medications, and her atenolol 25 mg dose was discontinued due to resolution of tachycardia. Repeat TRAb and TSI during this visit were negative. She is maintained on rituximab infusions every six months for disease stabilization.

Discussion

This case describes a rare overlap of GAD65 antibody–positive SPS and Graves' disease, presenting initially with prominent neuropsychiatric symptoms and thyrotoxicosis. The patient's acute onset of hallucinations, paranoia, tremors, and weight loss, in the absence of prior autoimmune or psychiatric history, created a complex diagnostic challenge. While methimazole treatment partially improved thyroid function, her neurological and psychiatric symptoms persisted, with eventual identification of intrathecal GAD65 antibodies and oligoclonal bands confirming autoimmune encephalitis within the SPS spectrum.

Once the diagnosis of SPS was made, therapeutic plasma exchange was initiated, and her response was both rapid and profound, with resolution of psychiatric and motor symptoms and normalization of thyroid function. Notably, she was able to discontinue methimazole entirely within weeks of treatment, and at 6-week follow-up, her TRAb and TSI titers had become negative, indicating complete resolution of the underlying Graves' autoimmune process rather than the transient biochemical control seen when plasma exchange is used as a temporizing measure in thyrotoxicosis [11]. This remarkable outcome suggests that treatment of the GAD65-mediated autoimmunity effectively addressed both the neurological manifestations and the concurrent thyroid autoimmunity, supporting the hypothesis of a shared autoimmune process.

The pathogenesis of SPS involves impaired Gamma-Aminobutyric Acid (GABA)-mediated inhibition, primarily due to autoantibodies against Glutamic Acid Decarboxylase 65 (GAD65), the enzyme responsible for GABA synthesis in the central nervous system. High-titer serum GAD65 antibodies (>10,000 IU/mL) strongly suggest intrathecal synthesis and, in some cases, may eliminate the need for CSF testing [12]. When titers are lower, CSF analysis may reveal oligoclonal bands indicative of CNS autoimmune activity.

While classically considered a neurological disorder, SPS frequently presents with features that transcend motor dysfunction. Autonomic involvement is common and may manifest as episodic tachycardia, diaphoresis, hypertension, pupillary abnormalities, hyperpyrexia or autonomic crises, that can culminate in sudden death [13]. Neuropsychiatric symptoms are very common in SPS but are frequently underrecognized. Anxiety disorders, particularly task-specific phobias such as fear of open spaces or falling have been reported to be present in 50-56% of patients [14]. These fears are often tightly linked to physical symptoms, as spasms may be triggered by emotional stimuli. Depression has been reported in 40-45% of patients. Other less common psychiatric conditions associated with SPS include eating disorders, and alcohol abuse [15]. GABAergic deficiency due to autoantibody-mediated inhibition is thought to underlie these psychiatric manifestations [14]. In some cases, psychiatric symptoms such as hallucinations, paranoia, or

confusion predominate, leading to misdiagnoses as primary psychiatric illnesses and delaying appropriate evaluation. This diagnostic pitfall was evident in our patient, whose initial presentation was dominated by acute psychiatric symptoms.

Co-occurrence of autoimmune conditions is a recognized phenomenon in SPS, with approximately 70% of patients with GAD65 antibodies having at least one additional autoimmune condition [16]. Some of these include vitiligo, celiac disease, pernicious anemia, Type 1 diabetes and Hashimoto's thyroiditis. These conditions may precede or follow the neurological manifestations of SPS and reflect a shared underlying autoimmune mechanism. Among thyroid autoimmunity, Hashimoto's thyroiditis is the most commonly reported association, with several large case series supporting its co-occurrence with SPS [2,6]. A retrospective study of 205 patients by found that 30% of individuals with SPS were positive for thyroperoxidase (TPO) antibodies [17].

Graves' disease, on the other hand, is a much less well-documented but clinically significant endocrine manifestation of SPS. In a 2012 systematic review of 121 patients with GAD antibody–associated syndromes, Martinez-Hernandez et al. assessed thyroid autoimmunity using anti-thyroglobulin and anti–TPO antibodies, but did not evaluate TSI or TRAb [18]. Only a handful of cases exist in the literature, and few confirm the presence of thyroid antibodies. The first reported case was in 1961, when Werk et al. described a 44-year-old man with progressive stiffness, spasms, gait disturbance, and dysphagia, alongside hyperthyroid symptoms such as weight loss, palpitations, and pretibial myxedema [10]. He was diagnosed with Graves' disease based on elevated TRAb and radioactive iodine uptake. Despite antithyroid therapy, his neuromuscular symptoms persisted. In 1990, Solimena et al. reported Graves' disease in 4 of 20 GAD65-positive SPS patients, with none among the GAD65-negative group. Although TPO and thyroglobulin antibodies were tested, TRAb and TSI were not, and diagnostic criteria for Graves' disease were not specified [19]. In 2005, Orija et al. described a 52-year-old woman with SPS and antibody-positive Graves' disease, initially attributed to a strong family history of thyroid autoimmunity. She showed significant improvement in both neurologic and thyroid symptoms following immunosuppressive therapy, suggesting a possible autoimmune link [8]. In 2007, Chia et al. reported a middle-aged woman initially treated for Graves' disease with limited response who later developed stroke-like symptoms and was diagnosed with SPS [20]. Although TRAb was not tested, positive TSI and TPO antibodies supported autoimmunity. Immunotherapy improved both neurological and thyroid symptoms, and her thyroid function remained stable on low dose carbimazole, though TSI levels remained elevated. In 2016, Medeiros et al. reported a 9-year-old girl with falls, gait abnormalities, weight loss, and a tonic-clonic seizure. She was diagnosed with Graves' disease and elevated GAD65 antibodies. Intravenous Immunoglobulin treatment led to marked improvement in ambulation, seizure control, and thyroid function [9].

In our case, the patient's clinical course followed a trajectory that is unfortunately common in SPS. She was first admitted to a psychiatric facility with acute behavioral disturbances, including paranoia and hallucinations. After transfer to our hospital, she was found to have thyrotoxicosis and was diagnosed with Graves' disease and treated appropriately. Although this was a step in the right direction, her diagnosis of Graves' disease did not account for the breadth and severity of the larger clinical picture contributing to her

neuropsychiatric and motor symptoms. This misattribution illustrates a frequent diagnostic pitfall in SPS, where the condition's rarity and its overlap with more common psychiatric and endocrine disorders often lead to delays in appropriate diagnosis. This case reinforces the need to recognize the broad clinical spectrum of GAD65-associated autoimmunity and highlights the importance of early diagnosis and multidisciplinary evaluation in patients with coexisting autoimmune, psychiatric, and neurologic symptoms. Although SPS is rare, it often presents with symptoms that mimic common conditions such as anxiety, depression, and thyroid or pancreatic autoimmunity. Clinicians should therefore maintain a high index of suspicion, as early recognition can lead to targeted therapy with potentially broad therapeutic benefits beyond the primary neurological disorder.

Conclusion

- SPS is a rare autoimmune neurologic disorder caused by impaired GABA-mediated inhibition due to autoantibodies against GAD65 and is strongly associated with high-titer anti-GAD65 antibodies in both serum and cerebrospinal fluid.

- Symptoms associated with SPS include progressive muscle stiffness and spasms, frequently exacerbated by sensory stimuli, or emotional stress. Neuropsychiatric symptoms can be present including anxiety, task-specific phobias, and depression. Autonomic symptoms such as hyperpyrexia, tachycardia and autonomic crisis also occur.

- A large number of patients with SPS have at least one other autoimmune condition, the most common one being type 1 diabetes. Others include vitiligo, pernicious anemia, Hashimoto's thyroiditis, and Graves' disease. Autoimmune conditions are more common in the presence of GAD65 positive SPS.

- In patients with SPS and concurrent Graves' disease, thyrotoxicosis may initially be seen as the sole cause of neuropsychiatric symptoms, masking the broader autoimmune process and contributing to delays in definitive diagnosis, particularly when subtle or early motor findings, such as stiffness or tremors, are underrecognized or misattributed to other causes.

- Multidisciplinary collaboration between neurology, endocrinology, and psychiatry is essential for optimal management of patients with complex autoimmune presentations to achieve accurate and timely diagnosis and treatment.

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