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A 47-Year Old Female with Muscular Rigidity, New-Onset Diabetes and Hypothyroidism

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Background

This case highlights a rare but devastating neurologic condition, Stiff Person Syndrome (SPS). While symptoms of muscular rigidity and spasms are associated with numerous neuromuscular conditions, the association between SPS, autoimmune diabetes, and other autoimmune disorders such as thyroiditis, pernicious anemia, and vitiligo, could aid in the early diagnosis of this debilitating condition.

Case Presentation

A 47-year-old African American female presented with six months of progressively worsening rigidity and spasticity of her axial muscles and extremities. The patient was in good health until one and a half years prior to admission when she lost consciousness while driving and was subsequently diagnosed with epilepsy. Her daughter was a passenger in the car and suffered a brief coma. Over the next year, the patient started having anxiety with increasingly more frequent and severe panic attacks. Six months prior to admission, she developed muscle stiffness and painful spasms that were so severe, she had difficulty ambulating and eventually became bed-bound. Magnetic Resonance Imaging (MRI) of the brain and spine did not reveal any pathology. Additionally, during the past year she was diagnosed with diabetes, which was unusual given her thin body habitus (Body-Mass Index of 20.9).

Investigations

The patient was admitted to the hospital for further work-up of her neuromuscular symptoms. On physical exam, her abdomen was tightly flexed and rigid, almost "board-like." Musculoskeletal exam revealed significant spinal lordosis with tight contraction of the abdominal and paraspinal muscles. She also had several muscle contractures including bilateral externally rotated and adducted shoulders, bilateral elbow flexion, left wrist flexion, bilateral knee extension, bilateral ankle plantar flexion, and flexion of the left fingers (Figure 1a-b). There was no joint effusion or erythema. Neurologic exam revealed cranial nerves II-XII to be grossly intact. She had hypertonicity of the upper and lower extremities, abdominal, and paraspinal muscles, as well as intermittent myoclonic jerks of the limbs and neck that could be elicited by auditory or tactile stimuli. She had normal reflexes and no motor, sensory or cognitive deficits. In addition, telemetry monitoring revealed wide fluctuations in blood pressure (109/63 - 181/109 mmHg) and heart rate (104-140 beats per minute). Admission labs were significant for an elevated erythrocyte sedimentation rate, C-reactive protein and thyroid stimulating hormone (Table 1).

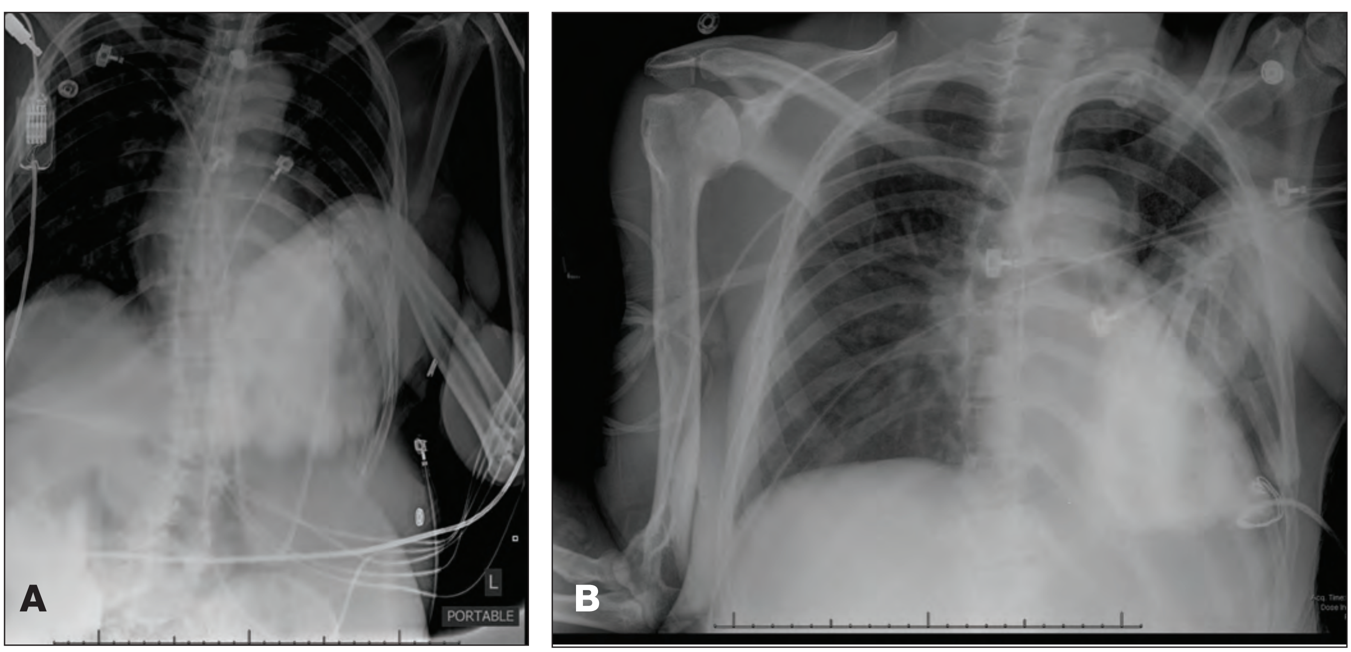

Figure 1A, B. Representative X-rays showing upper extremity contractures

Table 1. Pertinent lab values		
Lab	**Patient's Lab Value**	**Reference Range**
CRP	4.20	0.0-0.8 mg/dL
ESR	56	0-20 mm/hr
Hemoglobin A1C	6.3	<5.7%
TSH	7.06	0.3-5.0 mIU/mL
Free T4	1.0	0.7-1.7 ng/dL
Free T43	1.5	2.0-4.4 pg/mL
Vitamin B12	729	210-950 pg/mL
Anti-Amphiphysin Ab	Negative	Negative
Anti-GAD65 Ab	>30.0	<1.0 units
Anti-Islet Cell Ab	1:64	<1:4
Anti-Thyroglobulin Ab	0.1	<0.6 units
Anti-Thyroid Peroxidase (TPO) Ab	>1000	0.0-100.0 units
TSH Receptor Ab	<0.90	<1.75 units
Paraneoplastic Ab Panel (anti-Hu, anti-Ri, anti-Yo, cancer-associated retinopathy (CAR) Ab, Lambert-Eaton myasthenic syndrome (LEMS) Ab)	Negative	Negative

Differential Diagnosis

Neurology was consulted to evaluate the patient's undiagnosed neuromuscular disorder. The differential diagnosis included Stiff Person Syndrome (SPS), neuromyotonia (Isaac's syndrome), and chronic inflammatory demyelinating polyneuropathy (CIDP). However, there was also a suspicion of a psychological etiology to her symptoms. She had blood tests sent for anti- glutamic acid decarboxylase (GAD) 65, anti-voltage gated potassium channel, and anti-GM1 ganglioside antibodies to evaluate for SPS, neuromyotonia, and CIDP, respectively. Her anti-GAD65 antibody level was above the upper limit of detection. She was also found to have markedly elevated anti-islet cell and anti-thyroid peroxidase antibodies. Her elevated anti-GAD65 antibody level, clinical presentation, and concurrent autoimmune diabetes and thyroiditis led to the diagnosis of SPS. She was evaluated for the paraneoplastic variant of SPS with anti-amphiphysin antibody, a paraneoplastic antibody panel, and Computed Tomography (CT) of the abdomen and pelvis, which were all negative.

Treatment

She was started on a regimen of GABA-ergic and anti-spasticity medications including high-dose diazepam, tizanidine, baclofen, and dantrolene. She was then initiated on a five-day course of intravenous immunoglobulin (IVIG) with no relief in her symptoms. Joint manipulation under anesthesia was unsuccessful. Botulinum toxin injections mildly improved her range of motion.

Outcome & Follow-up

Her hospital course was complicated by esophageal dysmotility causing aspiration pneumonia, Pseudomonas bacteremia, and ventilator-dependent respiratory failure. She was weaned from the ventilator and discharged to rehabilitation with plans of implanting a baclofen pump.

Discussion

Stiff person syndrome is a rare central nervous system (CNS) disorder characterized by progressive rigidity of the axial and proximal musculature with intermittent superimposed spasms. The age of onset of SPS is typically the fifth decade, and the disorder affects twice as many females as males.[1] Two symptoms are key to the characterization of SPS: (1) stiffness of axial and proximal limb muscles due to continuous contraction and co-contraction of agonist and antagonist muscles and (2) superimposed intermittent painful spasms.[2] In the classic form of this disorder, patients will experience aching and tightness in the neck and axial musculature and will develop hyperlordosis due to simultaneous contraction of abdominal and paraspinal muscles. The rigidity will spread to involve the proximal muscles of the lower extremities and is often asymmetric at onset.[3]

Along with progressive stiffening of the musculature, patients also experience intermittent, sudden painful spasms which can be triggered by visual, auditory, or tactile stimuli, as well as emotional stress.[4] In some cases, individuals can identify a major stressful life event that preceded the onset of their psychological and neuromuscular symptoms.[5] The association between the exacerbation of the patient's symptoms and emotional stress often leads to psychiatric evaluation. Early in the course of the disease, a patient's neuromuscular symptoms may be non-specific, and the psychological features of anxiety and depression may dominate the clinical picture. This often leads to a diagnosis of a psychogenic movement disorder as their neuromuscular symptoms progress.[5] Frequently, the misdiagnosis of a psychogenic movement disorder can be reinforced by the exacerbation of the patient's symptoms by emotional stress and the improvement of symptoms with benzodiazepines. Finally, patients may suffer paroxysmal autonomic dysfunction, dysphagia from esophageal dysmotility, and seizures.[6,7]

Case reports have demonstrated an association between SPS and diabetes, but a major breakthrough in understanding the pathophysiology of SPS came in 1988 when Solimena et al identified antibodies against glutamic acid decarboxylase (GAD) in the serum and cerebrospinal fluid (CSF) of a patient with SPS and diabetes.8 GAD is the rate-limiting enzyme involved in the synthesis of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS (Figure 2). The hypothesis that the loss of GABA-signaling in the CNS is the cause of SPS was supported by magnetic resonance spectroscopy showing a selective reduction in GABA in the sensorimotor cortex of patients with SPS.[9]

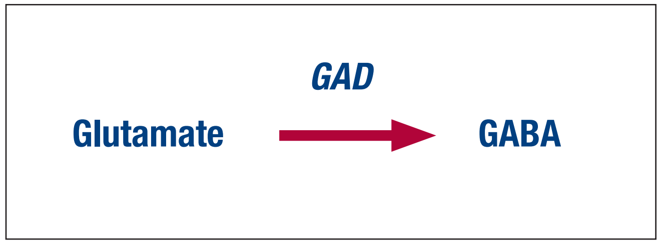

Figure 2.

Beyond anti-GAD antibodies, other autoantibodies targeting GABA synthesis, transport, and signaling have been recognized in patients with SPS (Table 2). More recently, antibodies targeting GABAA receptor-associated protein (GABARAP), have been identified in up to 70% of patients with SPS.[11] A variant of SPS that occurs as a paraneoplastic syndrome has also been identified. This syndrome is most commonly associated with breast cancer but also has been observed in colon, lung, thymus cancers, as well as Hodgkin's lymphoma. Autoantibodies against amphiphysin and gephyrin have been identified in the serum of patients with paraneoplastic SPS.[2, 9, 10]

Clinical criteria for diagnosing SPS were last revised in 20092 as new discoveries regarding the pathophysiology of the disorder were made (Table 3). Beyond these diagnostic criteria, clinical response to diazepam is often included in the clinical criteria for the diagnosis of SPS.

Table 2. Autoantibodies associated with stiff person syndrome

Autoantibody	Function of Target Protein
Anti-GAD65	Rate-limiting enzyme in the synthesis of GABA
Anti-Amphiphysin	Synaptic vesicle protein involved in the recruitment of dynamin to sites of clathrin-mediated endocytosis which is involved in retrieving vesicle membrane from axon terminals after exoctyosis of GABA
Anti-Gephyrin	Tubulin-binding protein involved in the clustering of $GABA_A$ and glycine receptors at the postsynaptic membranes of inhibitory synapses
Anti-GABAA Receptor-Associated Protein (GABARAP)	Linker protein between gephyrin and GABAA receptors which is involved in postsynaptic clustering and stability of $GABA_A$ receptors at the post-synaptic membrane

Table 3. Dalakas diagnostic criteria for stiff person syndrome

Muscular rigidity in the limbs and axial (trunk) muscles, prominent in the abdominal and thoracolumbar paraspinals leading to a fixed deformity (hyperlordosis)
Continuous co-contraction of agonist and antagonist muscles, confirmed clinically and electrophysiologically
Episodic spasms precipitated by unexpected noises, tactile stimuli, or emotional upset
Absence of any other neurologic disease that could explain the stiffness and rigidity
Positive anti–glutamic acid decarboxylase (or amphiphysin) antibodies assessed by immunocytochemistry, Western blot, or radioimmunoassay

Adapted from: Dalakas MC. Stiff person syndrome: advances in pathogenesis and therapeutic interventions. Curr Treat Options Neurol 2009;11:102-10.

Table 4. Treatment options for patients with stiff person syndrome		
GABA-Enhancing Drugs		
Benzodiazepines (e.g. diazepam, clonazepam, alprazolam, lorazepam)	diazepam: 5-100 mg; clonazepam: 2.5-6 mg; alprazolam: 2-4 mg; lorazepam: 6 mg	Central $GABA_A$ agonist
Antiepileptic drugs (e.g. vigabatrin, valproate, gabapentin, levetiracetam, tigabine)	vigabatrin: 2-3 g; valproate: 0.6-2 g; gabapentin 3600 mg; levetiracetam: 2000 mg; tigabine: 6 mg	Augmentation of GABA signaling
Antispasticity Agents		
Baclofen	10-60 mg	$GABA_B$ agonist
Tizanidine	6 mg	Central α2-adrenergic action; inhibits norepinephrine release
Dantrolene	200-400 mg	Dissociates excitation-contraction coupling and blocks release of Ca^{2+} from the sarcoplasmic reticulum
Botulinum toxin A	–	Neuromuscular junction blocking; prevents acetylcholine exocytosis
Immunotherapies		
IV immunoglobulin	2 g/kg	Immunosuppression/modulation
Rituximab	2 g (in two divided doses)	B-cell depletion
Plasmapheresis	5-6 passes	Immunosuppression/modulation
Corticosteroids	Up to 60 mg	Immunosuppression/modulation
Immunosuppressive agents (e.g. azathioprine, methotrexate, mycophenylate mofetil)	azathioprine: 2.5-3 mg/kg; methotrexate: 15-20 mg; mycophenylate mofetil: 2-3 g	Immunosuppression/modulation
Adapted from: Dalakas MC. Stiff person syndrome: advances in pathogenesis and therapeutic interventions. Curr Treat Options Neurol 2009;11:102-10		

SPS is strongly associated with a variety of other autoimmune disorders, and the presence of these co-morbidities can be helpful in correctly diagnosing SPS. Autoimmune diabetes occurs in up to 35% of patients with SPS.[2] In addition to anti-GAD antibodies, islet-cell antibodies have also been detected in the serum of patients with SPS and diabetes.[12] Other autoimmune disorders, including thyroiditis, pernicious anemia, and vitiligo, have also been observed in patients with SPS. Patients with SPS presenting with these co-morbid autoimmune conditions have elevated levels of their respective autoantibodies, including thyroglobulin antibodies, thyroid peroxidase antibodies, and gastric parietal-cell antibodies.[12]

Historically, the mainstays of treatment for SPS were GABA-enhancing medications and anti-spasticity drugs. However, as the autoimmune pathogenesis of SPS was identified, the utility of immunotherapy for SPS was investigated and has been validated. Currently, treatment of SPS consists of a combination of GABA-ergic and anti-spasticity medication as well as immunotherapy (Table 4).[2]

Key Points

This patient's case displays many of the clinical features classically observed in SPS. There was a prodrome of severe anxiety and she was able to identify a significant psychological stressor that triggered her functional decline. She developed progressive stiffness of the axial muscles leading to hyperlordosis and then developed stiffness of the extremities with the lower extremities locked in extension and upper extremities locked in flexion. She also had painful spasms elicited by auditory or tactile stimuli and she displayed autonomic instability on telemetry. She had markedly elevated anti-GAD65 antibodies and had co-morbid autoimmune disorders (autoimmune thyroiditis, latent autoimmune diabetes of adults) with associated circulating autoantibodies. Finally, she showed clinical improvement after treatment with diazepam.

Unfortunately, our patient did not display any clinical improvement following treatment with IVIG. However, in the clinical trial that demonstrated benefit of IVIG therapy for patients with SPS, bedridden patients were excluded.[13] Thus, this case highlights the importance of early diagnosis of this severely debilitating neurologic condition, as the least disability is observed in patients treated early in the course of their disease.

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"Sulfur and Steam, Yellowstone"
photograph by Andrew Zabolotsky