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Clinical Medicine Insights: Case Reports

Stiff Man Syndrome: A Diagnostic Dilemma in a Young Female with Diabetes Mellitus and Thyroiditis

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ABSTRACT: Stiff Person Syndrome (SPS), is a very rare neuroimmunologic disorder characterized by progressive muscle pain, rigidity, stiffness, and spasms. It can be very debilitating if misdiagnosed or not recognized in time. Herein we discuss a case of a female in her 20s who presented with an unsteady gait, lower extremity weakness, persistent leg pain, and stiffness few weeks after uncomplicated childbirth. She has type 1 diabetes mellitus (DM) and was diagnosed with thyroiditis in the course of her illness. The triad of thyroiditis, DM, and stiffness with normal neuroimaging in a young female patient is an unusual occurrence.

KEYWORDS: stiff person, autoimmune, thyroiditis, diabetes

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Introduction

Stiff Person Syndrome (SPS), previously referred to as Stiff Man Syndrome, is one of the rare causes of rigidity and spasm. This can be difficult to diagnose if there is no high index of suspicion. It is a noninfectious disorder that often affects the axial muscles, which eventually can make ambulation difficult. There is a strong association with some autoimmune-mediated disorders such as type 1 diabetes mellitus (DM1), pernicious anemia, and thyroiditis. It can also present as paraneoplastic or idiopathic variant depending on the clinical syndrome.

Case Summary

A female in her 20s with a past medical history of asthma, DM1, and postpartum depression presented to the emergency department because of difficulty ambulating associated with lower extremity weakness and worsening leg pain. The lower extremity weakness, mainly in the left leg, was associated with difficulty in walking, which began a month prior. The pain was only in the left leg, which started in her left lateral thigh and radiated down to left foot. It was very severe (10/10), described as muscle cramp-like in nature, and had progressively gotten worse over the course of five days prior to presentation. She also stated that the left foot was swollen previously, which was not related to trauma. These symptoms were preceded by newly diagnosed DM1 with diabetic ketoacidosis and profound unintentional weight loss. Her family history was positive for rheumatoid arthritis. On review of her symptoms, the patient admitted blurry vision, occasional headaches, and occasional back pain. She denied any loss of sensation or tingling in her extremities, change in bladder or bowel habits, dizziness or falls, or any recent infection. She had been in her usual state of good health until a month after delivery.

Upon physical examination, vital signs were within normal range, except for a heart rate of 93, presumably due to pain. The patient weighed 46 kg with a BMI of 16.9. There was tenderness on palpation of the left ankle and foot. On neurological examination, cranial nerves 2–12 were grossly intact, deep tendon reflexes were 2+ bilaterally in the upper

and lower extremities, and the strength in the left and right lower extremities were noted as 3/5 and 5/5, respectively. The rest of her physical examination was noncontributory. Laboratory findings were pertinent for hemoglobin of 10.9 gm/dL, mildly elevated chloride level of 110 mmol/L, and asymptomatic urinary tract colonization. A lower extremity venous Doppler study was negative for deep vein thrombosis. A lumbrosacral CT imaging study showed mild to moderate curvature of the lumbar spine with no evidence of neural compromise. X-ray imaging study of the left foot was negative for fractures and found moderate hallux valgus. She received oxycodone/acetaminophen for pain and alprazolam for anxiety.

A couple of days later, the patient continued to have difficulty ambulating, even with the assistance of a roller walker. In addition, the patient exhibited dragging of her left foot when ambulating. She also complained of a numbness and tingling sensation in the toes of her left foot. MRI studies of the head and spine were negative for pathologies, and the X-ray imaging of the hips were also negative for fractures/acute phase of avascular necrosis. About a week into admission, she developed several episodes of diaphoresis and sinus tachycardia with a heart rate in the 200–220 bpm range. Electrocardiogram (EKG) revealed sinus tachycardia; carotid massage and adenosine only temporarily improved the tachycardia. As part of tachycardia work up, thyroid-stimulating hormone was done, which revealed a low level of 0.015; however, free T4 and total T3 were normal (1.2 and 1.36, respectively). Further evaluation with thyroid scan showed low uptake of 1.2%, and thyroid-stimulating immunoglobulin was also negative. The patient was transferred to the medical intensive care unit because of worsening symptoms. The patient's home medications of mirtazapine and quetiapine, which she was taking for her postpartum depression, were held for possible serotonin syndrome. Her heart rate improved, but remained tachycardic in the range of 100–160 bpm, likely associated with her not-well-controlled pain. Gabapentin was added to help control pain, thinking that diabetic neuropathy might be a comorbidity. Psychiatric consultation revealed that diagnosis of conversion disorder was not probable.

In the intensive care unit, the patient had several episodes of generalized body jerking and stiffness, which were associated with severe pain. During each episode, she held the rails of the bed while jerking, shaking the entire bed. She was very diaphoretic and always awake, oriented but did not make eye contact as she stared at the ceiling. Each episode lasted two to three minutes. Elevated creatinine kinase was also noted; however, video EEG did not reveal any seizure activity. Her left foot was now found to be inverted, and bilateral lower extremities were fully extended and rigid on passive attempts to manipulate them; occasional twitch-like movements were also seen. Repeat X-ray imaging study of the left foot showed four angulated metatarsals with no evidence of fracture, arthritis, or osteomyelitis.

As this diagnostic dilemma continued, a lumber puncture (LP) was done. She had to be sedated with propofol to relax her muscles to attain a fetal-like position for the LP, as any attempt to bend her would cause severe discomfort. Cerebrospinal Fluid (CSF) analysis revealed clear appearance, White Blood Cell (WBC) of 29/μm with 100% lymphocytosis, glucose of 81 mg/dL, elevated protein, normal myelin protein, negative for Herpes simplex virus (HSV), amphiphysin protein, but very significantly elevated glutamic acid decarboxylase antibody (GAD65 Ab, 253 nmol/L). Further evaluation of the 100% lymphocytosis with immunofixation of the CSF did not reveal any monoclonal protein. Electromyogram and nerve conduction studies revealed continuous motor unit activity, which was significantly decreased after IV diazepam injection. At this juncture, a diagnosis of SPS most likely autoimmune type was made. She was treated with a benzodiazepine, baclofen, and Intravenous Immunoglobulin (IVIG). The patient clinically showed significant signs of improvement in rigidity and stiffness and was eventually transferred back to the general medical floor where she was eventually discharged to a short-term rehabilitation facility.

Discussion

SPS is a rare disorder characterized by progressive muscle stiffness and rigidity, with superimposed spasms. Symptoms usually begin in adulthood. Insidious in nature, the stiffness often first affects the axial muscles and slowly progresses to the proximal limb muscles. Postural reflexes and muscle control diminish and afflicted patients are prone to falls and fractures. It can present in different ways depending on the variant; autoimmune, paraneoplastic, or idiopathic. The real incidence and prevalence are not known. The intensity of the contraction can be so severe, sometimes generating enough force to fracture bone.[1] The spasms have been described to be precipitated by sudden movements, noises, or emotional upset.[2] Our patient preferred a quiet, dim-lighted room. She most likely had autoimmune variant considering the DM1, thyroiditis, elevated anti-GAD antibodies, and family history of rheumatoid arthritis. However, some thought was given to the paraneoplastic type as well once the CSF showed 100% lymphocytosis. Nevertheless, absence of a monoclonal band made this less likely. Elevated lymphocytosis in the CSF has also been described in the patient with SPS.[3]

Due to its rarity, SPS is not readily recognized. Diagnosing SPS requires a very high index of clinical suspicion. SPS is currently thought to be an autoimmune process in nature; polyclonal and oligoclonal antibodies are typically elevated that target GABAergic (gamma amino butyric acid) neurons, the major inhibitory neurotransmitter in the brain. More specifically, the dominant antigen recognized by these antibodies is the GABA-synthesizing enzyme, GAD, which is present in approximately 60% of patients with SPS.[4] There are two GAD isotypes, GAD65 and GAD67. Anti-GAD65 antibodies are found in 80% of patients with newly diagnosed DM1. SPS is

still rare in patients with DM1 despite the high frequency of patients with DM1 with elevated anti-GAD65 autoantibodies. The titer of anti-GAD autoantibodies in those with SPS is far higher than that observed in patients with just DM1, often differing by 100- to 500-fold.[5] Our patient had elevated levels more than 126,000 times greater than the upper limit of normal, which is consistent with organ-specific neurological autoimmunity disorder. Other known antibodies of SPS include those against amphiphysin, gephyrin, and GABA(A) receptor-associated protein. Amphiphysin, which was negative in our patient, is seen in only 5% of the patients with SPS.[6]

It may be difficult to differentiate SPS from other causes of stiffness, such as tetany, neuromyotonia, and familial startle disease. High level of anti-GAD antibody and persistent motor stimulation on Electromyogram (EMG) make diagnosis of SPS more likely.

Because of the rarity of this disorder, randomized clinical trials have not established a strict guideline for therapy. Benzodiazepines, such as diazepam, are considered first-line treatment for SPS.[7] It is thought to modulate the levels and activity of GABA. Antispasmodic agents, such as baclofen, can provide relief, given that it is a GABA agonist.[8] Considering the autoimmune nature of SPS, immunosuppressive therapy can be used in patients with severe disease unresponsive to benzodiazepines and baclofen. Glucocorticoids have been shown to be an effective treatment in some patients.[9] IVIG and rituximab have also been proved as effective alternative treatment options.[10,11] Our patient did respond well to triple therapy: diazepam, baclofen, and IVIG.

SPS is a very rare disease with debilitating nature if not recognized in time. A high index of suspicion is needed to diagnose this treatable illness.

Author Contributions

Conceived the concepts: HE, MP, AG, EA, JN. Analyzed the data: HE, MP, AG, EA, JN. Wrote the first draft of the manuscript: HE, MP, AG, EA, JN. Contributed to the writing of the manuscript: HE, MP, AG, EA, JN. Agree with manuscript results and conclusions: HE, MP, AG, EA, JN. Jointly developed the structure and arguments for the paper: HE, MP, AG, EA, JN. Made critical revisions and approved final version: HE, MP, AG, EA, JN. All authors reviewed and approved of the final manuscript.

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