

CLINICAL VIGNETTE

Stiff-Person Syndrome – A Case for Early Diagnosis

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Introduction

Stiff-person syndrome (SPS), formerly called stiff-man syndrome, is a rare, distressing neurological disorder first described in 1956.¹ Patients have been described as “tin soldiers” with “titanic” muscle spasms characterized by progressive muscle stiffness, rigidity and spasm involving the axial muscles, resulting in severely impaired ambulation.¹ We present a case of a patient with significant neuromuscular findings who was diagnosed with SPS 18 months later. Although this is a rare condition, early recognition of clinical clues could lead to earlier diagnosis and prevent unneeded therapies.

Clinical Case

A 40-year-old Hispanic-American veteran presented with multiple complaints including back pain and spasms, finger pain, and posterior neck stiffness and tightness. He denied bowel or bladder incontinence or trouble with mentation. His symptoms had progressed to the point that he required a cane and eventually a wheel chair for mobility.

His past medical history was significant for hypertension, dysthymic disorder, sleep apnea, vitamin D deficiency, and transaminitis of unclear etiology. His family history was unremarkable for any illness.

Physical examination revealed a wide-based, slow to turn, mildly spastic gait. His lower extremities were hyporeflexic with increased tone, but his upper extremities were normoreflexic with normal tone. Strength and bulk were normal throughout. His fundi were sharp with clear margins of his optic nerves and flat maculae with good foveae reflex. However, there was hippus on pupillary response to light on both sides. His retinal vessels as well as his peripheral vision were normal.

Lumbosacral spine x-rays showed normal bone structure without abnormalities. Initially, he was treated conservatively with the use of capsaicin and a heating pad. However, his symptoms worsened; he developed trapezius and paraspinal stiffness, which made gait initiation difficult. He also reported difficulty moving his left knee, as it had “a mind of its own” and developed new onset visual disturbance and dizziness that was similar to being drunk. He otherwise denied changes to acuity, double vision or sensation of motion. An outside

physician started him on cyclobenzaprine, which did not improve his symptoms. Further imaging including cervical spine and knee x-rays as well as Magnetic Resonance Imaging (MRI) of his brain were unremarkable other than mild C2-C5 degenerative disc disease.

A few months later, he reported new onset of “vertigo,” which he described as a nauseous sensation upon lying down that resolved when he sat up without perception of environmental motion. Due to his progressive symptoms, neurology, audiology, head and neck, and physical medicine and rehabilitation were consulted.

Despite multiple consultants, his condition continued to deteriorate. His neurologist started a trial of escitalopram and sertraline, but his symptoms worsened. An EMG showed continuous motor activity in his lower extremities including the medial gastrocnemius, tibialis anterior and peroneus longus. A fludeoxyglucose (FDG) 18 was also performed with normal findings. During his FDG 18, he was found to have elevated glucose and he was diagnosed with diabetes mellitus with a hemoglobin A1C that had increased from his prior baseline of 5.8 to 13.9.

His symptoms began to improve when clonazepam was initiated at a later date. He was referred to the neuromuscular clinic for further care where he was noted to have positive anti-GAD and anti-islet cell antibodies, suggesting the diagnosis of type 1 diabetes. A lumbar puncture was notable for elevated levels of IgG anti-GAD antibodies, albumin, glucose and protein. He also had an increased intrathecal IgG synthesis rate and increased trans-blood brain barrier albumin leakage. This established the diagnosis of Stiff Person Syndrome (SPS).

Visual Evoke Potentials (VEPs) revealed prolonged P100 latencies bilaterally, which were suggestive of bilateral demyelinating lesions anterior to the optic chiasm.

In addition to clonazepam, he was also started on mycophenolate mofetil. However, after a few months, he elected to discontinue both medications. He was later started on baclofen and intravenous immune-globulin (IVIG) due to worsening symptoms and spasticity. Concurrently he developed dizziness and lightheadedness that prevented him from walking alone, looking downward, and lying down.

Despite improvement of spasms while on baclofen, he switched to tizanidine because he was unable to tolerate the side effects. In the meantime, repeat MRI of his brain was unremarkable for demyelinating disease but showed progression of mild cerebellar atrophy.

The patient later stopped all his medications as he wished a holistic approach to his treatment with the use of herbs and supplements. Clinically, his condition and symptoms progressed with significant muscle tension, neck spasms, visual impairment, and vertigo.

Discussion

SPS varies from mild to severe, but if untreated it can be progressive and disabling. It is felt to be caused by increased muscle activity due to decreased inhibition of the central nervous system (CNS) that results from the blockade of glutamic acid decarboxylase (GAD), an enzyme critical for maintaining inhibitory pathways. This is followed by a decline in the levels of γ -aminobutyric acid (GABA) in the CNS, which causes a loss of neural inhibition.² SPS is often associated with autoimmune disorders such as type 1 diabetes mellitus (T1DM), suggesting a shared pathology. Rarely, it is a paraneoplastic process associated with an occult malignancy.

Although progress has been made in understanding and treating SPS, the disease remains underdiagnosed, thus delaying treatment. Antibodies against GAD provide an excellent diagnostic marker, but their role in disease pathogenesis is uncertain. Research focused on identifying new autoantigens has provided evidence that GABA_A receptor-associated protein (GABARAP), a 14-kD protein localized at the postsynaptic regions of GABAergic synapses, is an antigenic target. Circulating anti-GABARAP antibodies that inhibit GABA_A receptor-associated protein expression on GABAergic neurons have been found in up to 65% of SPS patients. The impairment of GABAergic pathways and reduction of brain GABA results in clinical manifestations of stiffness, spasms, and phobias.³

Current standard therapy for SPS includes pharmacological therapy, plasmapheresis, and immune-modulating therapies like IVIG, Benzodiazepines and other GABA-acting medications remain essential to managing the stiffness and spasms of SPS.⁴ Patient education and behavioral and physical therapy can be helpful in minimizing symptoms.

Our case presented a diagnostic challenge with trials of multiple medications, which delayed the diagnosis. In retrospect the patient's response to clonazepam, a medication used to treat the early stages of SPS, was a clue to the underlying condition. The alarming progression of weakness, muscle stiffness and movement limitation should also prompt early subspecialty referral to neuromuscular service. The diagnosis of diabetes, which could have led to anti-GAD measurements and possibly a CSF examination, may have led to earlier diagnosis. However, despite clinical clues, the diagnosis of SPS is difficult in its early stages.

Our patient's unusual visual processing delay and other non-specific vision changes were unusual for SPS. SPS patients

typically present with extraocular movement dysfunction. His visual evoked potentials were suggestive of demyelinating disease, but MRI found no evidence. Thus, the abnormalities were thought to be due to retinopathy secondary to his SPS, as GABA receptors are also present in the retina.

Though treatment options for SPS are limited and sudden withdrawal of medications is life threatening, our patient elected to use alternative medicine due to side effects from conventional therapy. He has remained stable with frequent flares despite the alternative medicine therapies.

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