Stiffness, Spasticity, or Both: A Case Report of Stiff-Person Syndrome

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Abstract

Stiffness and spasticity are common neurologic symptoms that affect limb movements. We describe a patient who presented with ill-defined stiffness and an exaggerated startle response, who on serial examinations had variable degrees of stiffness and marked hyperreflexia but with plantar flexor signs. Stiff-person syndrome (SPS) was considered when axial stiffness became evident and was confirmed with highly elevated anti-GAD antibody titers. A favorable response to a short course of intravenous immunoglobulin treatment was sustained for more than 10 months, an unusual feature to the disease. We review the clinical features, pathologic mechanism, and treatment of this disorder.

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Case Presentation

The patient was a 41-year-old woman referred for further evaluation of cramps, spasms, and fatigue. She described a 2-year history of difficulty walking. Her usual fast pace slowed and she had greater fatigue at the end of a walk that curtailed subsequent activities. She also noticed an initial stiffness for the first 10 steps if she sat for a long time before getting up. A prolonged shaking of her legs occurred when placed in certain positions. Cramps or spasms occurred spontaneously and resulted in contorted postures of her hands and feet. She also described an ease of laughing.

Her medical history was significant for Hashimoto's thyroiditis. Her family history and review of systems were noncontributory. Medications were 5 to 10 mg baclofen twice per day and 2 to 5 mg diazepam twice per day for the past year with no improvement in her symptoms.

On initial neurologic examination she had intact mental status. Cranial nerves were normal. Motor examination revealed no muscle atrophy, normal tone and strength. Deep tendon reflexes were normal at the jaw, but there was spread at the brachioradialis and a brisk response in the legs. Plantar responses were flexor. She rose from a chair easily and her gait was normal. Her sensory examination was normal.

At the end of the evaluation, the impression was cramps and possible spasticity, but physical findings were disparate with mildly brisk reflexes. Her past evaluation included a normal head magnetic resonance image (MRI) and electroencephalography. We performed an electrodiagnostic study, which showed normal nerve conduction values and normal needle electromyography findings, although optimal relaxation could not be achieved in some muscles. Routine blood laboratory tests were normal. A cervical and thoracic MRI scan was ordered to exclude a myelopathy to account for her spasticity. Quinine sulfate was prescribed for muscle cramps.

At her return visit 1 month later, she was accompanied by her husband who provided additional information. Her walking had become very stiff and her husband needed to provide standby assistance for the first few steps. Her walking was much slower and she was no longer able to walk the dog. She experienced episodes of chest tightness with a feeling of shortness of breath. Marked startle responses were brought on by stimuli such as light touch, the ringing of the telephone, or the buzz of her pager. Since her last visit she had stopped taking baclofen and diazepam after noting no benefit from these medications. Examination revealed normal limb tone, but clonus could be elicited in the legs and her tendon reflexes were extraordinarily brisk. Plantar responses remained flexor. Her gait was markedly stiff for the first few steps after sitting. Recent thoracic and cervical MRI scans were normal. The history of startle responses suggested "myoclonus" and she was started on valproic acid.

During her third visit 3 weeks later, her history was reviewed with no new information. Her neurologic examination now showed increased tone to passive manipulation of the legs, and the axial muscles in the upper trunk and lower back appeared rigid. Clonus and extraordinarily brisk tendon reflexes remained in the setting of plantar flexor responses. Stiff-person syndrome (SPS) was considered, and anti-glutamic acid decarboxylase $(GAD)_{65}$ anti-

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bodies were ordered and found to be elevated in serum at 228 U/mL (normal, 0.00–1.45 U/mL). A paraneoplastic antibody panel, including anti-amphiphysin antibodies, was normal. No antibodies to the pancreatic islet cells were found. This patient was given the diagnosis of SPS.

At the next clinic visit 6 months later, the patient reported a decrease in her startle response attributed to the valproic acid. Other symptoms, including stiffness, were unchanged. A decision was made to institute intravenous immunoglobulin (IVIG). Objective and subjective measures were planned to determine the therapeutic response. She received an initial dose of 2 g/kg followed by two additional doses of 1 g/kg 1 month apart. Pre-infusion objective measure of walking 10 meters after sitting for 15 minutes took 14 seconds, which was reduced to 9 seconds after treatment. Tendon reflexes remained pathologically brisk without change. Subjective measurement of stiffness on a scale of 0 to 10 was 7 before treatment and 3 after treatment. Her startle response was unchanged.

Seven months after the last IVIG treatment, she reported that her spasms or cramps had essentially resolved and her stiffness had dramatically diminished. Her only medication was 250 mg valproic acid three times per day. The examination confirmed her report. Her reflexes were only slightly brisk and her gait was normal. However, her anti-GAD antibodies remained elevated at 178 U/mL.

Discussion

The first description of this entity was by Moersch and Woltman in 1956.[1] They had examined one patient 25 years earlier and reported on an additional 13 patients. The clinical features included insidious onset of muscle stiffness over several months, but occasionally acutely and subacutely over several days and weeks. Various muscle groups were involved, including those in the limbs, neck, and trunk, but the striking feature was the co-contraction of abdominal and paraspinal muscles leading to trunk stiffness and hyperlordosis. Superimposed painful muscle spasms were common. Patients frequently had startle responses evoked by tactile or auditory stimuli. Examination findings were uniform, with normal sensation, strength, and plantar flexor responses. Interestingly, normal tendon reflexes were reported in their patients. This remarkable series of cases was left with the comment: "thus our story ceases for the present."

Since 1956 the story has continued. In 1988, antibodies to GAD were found in a patient with SPS.[2,3] Patients were also found to have type I diabetes mellitus more frequently than expected. A contemporary review of 20 patients with SPS with positive anti-GAD antibodies reveals the following pertinent features.[4] Average age at the time of diagnosis is 41 years with duration of symptoms before diagnosis from 1 year to 18 years with a mean of 6 years. Women are more commonly affected than men. Asymmetric onset, starting in the leg, is common. The degree and distribution of stiffness progressed in the majority of patients, and hyperlordotic posture representing abdominal and paraspinal muscle co-contraction is common. Rigidity initially has a fluctuating course but became steady. Facial stiffness is a previously unappreciated feature. Falls are frequent, leading to use of ambulatory aids. Stiffness in the chest muscles frequently causes a feeling of shortness of breath. Startle spasms to a variety of stimuli are common. Patients can display anxiety, obsessions, and phobias. A number of associated conditions were found, including a high frequency of insulin-dependent diabetes and thyroid disease in the patients and family members. Occasional patients had pernicious anemia and seizure disorders. A number of antibodies were found in these patients, including antinuclear, antithyroid, anti-parietal cell, anti-RNP, anti-intrinsic factor, and anti-gliadin antibodies.

Our patient had most characteristics consistent with the disorder, including elevated anti-GAD antibody titers. However, her extraordinary brisk reflexes were impressive, whereas her spasticities were only mild. This case emphasizes the wide variances of SPS phenotypes. Other variants of SPS have also been reported, such as focal stiffness,[5] jerking stiff-man syndrome,[6] and SPS with stiff limbs.[7]

Other diseases may resemble SPS, such as myelitis, cervical spondylosis, neuromyotonia, myotonic myopathies, and so on. Detailed discussions of these conditions have been reviewed.[8] Hyperekplexia is a unique disorder and may imitate SPS. It was also named startle disease or hyperexplexia. The disorder may occur sporadically or inherently. Two phenotypes were observed, major and minor forms. The former should be readily differentiated from SPS. Patients show extreme generalized stiffness immediately after birth, which lessens during the first years of life. Excessive startle responses to external stimuli, such as sound or touch, occur inevitably, followed by the augmentation of stiffness. Many patients carry a mutation in the gene encoding the α-subunit of the glycine receptor. In contrast, the minor form has a later onset. Startle reactions are conspicuous but there is no associated stiffness. Although some of the minor forms may possess the mutation of the glycine–receptor gene, others may be sporadic with no alteration of the gene. For the vast majority of patients with hyperekplexia, either major or minor forms, startle reactions are stereotypic. It comprises facial grimacing, retro-flexion of the head, hunching of the shoulder, flexion of the elbows, trunk, and knees. The unique pattern of startle reactions is usually different from what is seen in SPS. Certainly, anti-GAD antibodies in SPS are helpful in discerning SPS from hyperekplexia.[9–15]

The mechanisms of stiffness and pathogenesis of SPS are unknown. Extensive electrophysiological studies have been conducted. Reduced spinal inhibition has been investigated as a source of abnormal motor unit drive. Studies of patients with positive anti-GAD antibodies revealed a complex pattern of changes in inhibitory circuits.[16–18] In most, vibration-induced (GABA-ergic) inhibition was compromised. Reciprocal inhibition (GABA-ergic and glycinergic)

was reduced in some and unchanged in others. Other inhibitory circuits were not altered. It was concluded that not all spinal GABA-ergic inhibitory circuits are uniformly affected in SPS, and there may also be involvement of glycinergic neurons.

Cortical inhibitory activity has been studied by transcranial magnetic stimulation (TMS), a non-invasive technique.[19] A coil is applied over the scalp and generates a transient magnetic field in the motor cortex that activates corticospinal motor neurons and evokes a compound muscle action potentials (CMAP) in extremity muscles. To assess cortical inhibition, a condition–test paradigm has been used with two magnetic stimuli. The first pulse, a subthreshold magnetic stimulus, activated intracortical circuits. The second pulse, a submaximal stimulus, evoked a CMAP. The inhibitory effects of the first stimulus can be explored by varying the time interval between the two stimuli. Inhibition was decreased in patients with SPS. A proposed mechanism includes the following elements. Reduced cortical GABA-ergic inhibition leads to increased corticospinal drive.[20] Reduced GABA-ergic and glycerinergic spinal inhibition contributes to increased spinal motor neuron activity.[19,20] Reduced cortical and spinal inhibition enhances afferent input to exaggerate the startle responses. Cortical disinhibition may impact the cortical–bulbar pathway, leading to "releasing" symptoms like "ease of laughing" seen in our patient.

The discovery of antibodies to GAD in patients with SPS is a remarkable landmark in exploring the disease. The antibodies have been found in high titers in the serum and cerebral spinal fluid in 60% of patients with a clinical diagnosis of SPS.[3] GAD catalyzes the conversion of glutamate to gamma-aminobutyric acid (GABA). There are two GAD isoforms, GAD_{65} and GAD_{67}. GAD_{65} is a cytoplasmic enzyme in synaptic vesicles and pancreatic beta cells, and is the isoform of interest. Anti-GAD antibodies have been found in patients who do not have SPS but in low titers.[21] These patients commonly have insulin-dependent diabetes and other autoimmune diseases.[2,3,21] There is an association between SPS and HLA-DR and DQ alleles.[4]

The pathogenic role of anti-GAD antibodies in SPS is uncertain. Anti-GAD antibodies appear to cause a functional impairment rather than a structural change because patients with SPS can recover with treatment, and the few postmortem examinations have not disclosed cellular destruction.[22] The concentration of GABA is reduced in cerebral spinal fluid,[21] which correlates with reduced levels of intracerebral GABA assessed by magnetic resonance spectroscopy.[20] These data are in keeping with reduced inhibition in the motor cortex.[19] However, how anti-GAD antibodies exert their effect is not clear. Serum from patients with anti-GAD antibodies in an *in-vitro* preparation inhibits GAD synthesis.[23] How this occurs *in vivo* is uncertain because antibodies circulate in extracellular space but the GAD is intracellular. Data suggest that antibodies may penetrate the cellular membrane.[23] Alternatively, GAD may be converted to a membrane-associated protein, exposed as an antigen.[24]

A rare group of patients, described recently, have muscle stiffness similar to SPS, but have antibodies to amphiphysin,[25,26] a protein in presynaptic nerve terminals whose role is unknown. The protein may be involved in the endocytosis of synaptic vesicles. Anti-amphiphysin antibodies represent a paraneoplastic syndrome, and have been associated with intraductal breast, small cell lung, and ovarian cancers. Associated paraneoplastic syndromes include SPS, encephalomyelitis, limbic encephalitis, sensory neuronopathy, and the Lambert-Eaton myasthenic syndrome.[25,26] Interestingly, another autoantibody against a protein, named gephyrin was detected in a single case with SPS-like presentation and mediastinal tumor. Gephyrin is a cytosolic protein distributed in inhibitory post-synaptic membranes, where $GABA_A$ or glycine receptors may be associated.[27] These findings raise the issue of the need for a malignancy work-up in patients with SPS. An evaluation is reasonable in patients who have atypical clinical features, and are anti-GAD antibodies-negative or anti-amphiphysin antibodies-positive.[20] There has been little knowledge on mechanisms in the patients who have antibodies to amphiphysin or gephyrin.

Treatment

A variety of treatments have been tried for SPS that focuses either on increasing GABA-ergic inhibitory activity or dampening antibody activity. Most reports on therapeutic responses are case descriptions or small case series, and there is only one controlled study. Diazepam was the first drug to show an effect[28] and has been the benchmark drug, in does up to 100 mg per day, but not every patient responds.[4,29] Baclofen has been used as an analog of GABA, and total oral doses of 80 to 90 mg per day have been found to be more effective than diazepam alone.[30] Baclofen has been used intrathecally in daily doses from 120 to 1200 μg and also found to be more effective than diazepam alone.[31] Valproic acid has been used, and in a case report a total dose of 2000 mg per day was more effective than diazepam alone.[32] Plasma apheresis has been used to remove antibodies, but responses vary from a striking and long-lasting effect with five exchanges over 12 days in one patient to no effect in another patient.[33] Corticosteroids have been used for the immunomodulating effect, and 100 mg prednisone per day followed by a taper has been effective.[34]

IVIG has multiple actions on the immune system.[29] In case reports, initial doses of 2 g/kg (divided into five consecutive daily doses of 0.4 g/kg) followed by supplementary doses of 0.5 to 2 g/kg every 3 to 4 weeks were found to be more effective than other drug combinations.[35] In the only controlled trial for SPS, 2 g/kg IVIG was given monthly for 3 months in a randomized and blinded crossover design with placebo.[29] There was a significant improvement in

objective measurements of stiffness. Anti-GAD antibody titers fell to variable degrees with IVIG treatments. Effects lasted from weeks to 1 year. In our patient, the response to a brief course of IVIG treatment was unusual in that she had a mild initial response to IVIG, followed by a more dramatic response months after her last dose that has endured at least 10 months after the last treatment. Her anti-GAD antibodies remain elevated, but antibody titers have not been found to correlate closely with the response to IVIG.[29]

In summary, perhaps the key features that should raise the question of SPS are stiffness resulting from muscle co-contractions, the distributions of the stiffness, and the startle response.

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