Stiff Person Syndrome

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KEYWORDS

- Stiff person syndrome • Axial spasm • Anti-GAD antibodies
- Autoimmune neuromuscular disorder

KEY POINTS

- Stiff person syndrome (SPS) is a rare autoimmune neurologic disorder presenting with muscular rigidity and trigger-induced painful muscle spasms predominantly affecting the proximal limb and axial muscles.
- SPS is associated with autoantibodies to glutamic acid decarboxylase (anti-GAD).
- Because SPS is frequently underdiagnosed or misdiagnosed, there is limited accurate epidemiologic data.
- Persons suffering from SPS typically do not have pyramidal and extrapyramidal signs.
- There have numerous reports of response of the stiffness and spasms to agents in the benzodiazepine class, such as diazepam or clonazepam.

INTRODUCTION

Stiff person syndrome (SPS) is a rare autoimmune neurologic disorder presenting with muscular rigidity and trigger-induced painful muscle spasms predominantly affecting the proximal limb and axial muscles, with emphasis on the paraspinal muscles, leading to gait difficulties and progressive disability. Sudden death due to autonomic dysfunction may also occur in these patients.[1] The condition was first described by Moersch and Woltman[2] in 1924 based on 14 cases. The term stiff-man syndrome was coined by Moersch and Woltman after their patients used descriptions such as "falls as a wooden man," "falls like a wax dummy," "stiff," or "board like."[2] The term "stiff" was also maintained because of the lack of extrapyramidal features, pyramidal tract dysfunction, or any other known neurologic disorder that could explain the characteristic muscular contractions seen in the patients with the disease.[3]

In 1958, Asher[4] reported the first woman with similar complaints to those reported by Moersch and Woltman.[2] Shortly after this report, Bowler[5] reported the first child with stiff-man syndrome. As the nature of the disease became better understood, it was recommended that the word "person" be used in recognition that the disease can affect both genders.[6]

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PATHOPHYSIOLOGY

SPS is associated with autoantibodies to glutamic acid decarboxylase (anti-GAD).[6–8] GAD is the key enzyme that converts glutamate to gamma-aminobutyric acid (GABA) and exists in two isoforms: GAD65 and GAD67. Both GAD65 and GAD67 function synchronously to produce and regulate physiologic levels of GABA.[9,10] GAD67 produces the basal level of GABA, whereas GAD65 seems to play a role when extra GABA neurotransmitter is required (eg, in times of stress).[9] The production of autoantibodies seen in SPS is primarily against GAD65 and not GAD67. GAD65 is reported to be the target antigen in about 60% of the patients with SPS.[11,12] The structural differences between GAD65 and GAD67 may explain this contrasting antigenicity. GAD65 structure inherent flexibility not present in GAD67 may be the cause of its increase B-cell antigenicity. Also, GAD65 structure displays a strong negative electrostatic field in the C-terminal domain, not seen in the structure of GAD67.[13,14]

Autoantibodies (autoAb) to GAD65 that are found in patients with SPS can inhibit the enzymatic activity of GAD65 and impair the syntheses of GABA, resulting in low levels of this neurotransmitter. GABA is the major inhibitory neurotransmitter of the brain and its impairment seen in SPS may explain the symptoms of stiffness and excessive muscle spasms.[8] GAD65 autoantibodies are detectable in the cerebrospinal fluid and sera of patients with SPS; however, their titers do not seem to correlate with the severity of the disease.[8,14] GAD is also found in nonneuronal tissues, such as beta cells of pancreatic islets, testes, and oviducts. Interestingly, SPS is occasionally associated with endocrine disorders. Thirty percent of patients with SPS have insulin-dependent diabetes and both diseases share autoantibodies to the same isoform GAD65.[8]

GAD65-specific autoantibodies are also seen in some patients with other neurologic diseases, such as myoclonus, cerebellar ataxia, epilepsy, and Batten disease; however, studies suggest that these GAD65 autoAb are organ and disease-specific.[15] IgG from GAD65 Ab-positive patients with SPS administered to the cerebellum of rats induced SPS-like effects in the animals; however, an epitope-specific GAD65-Ab is not yet identified in SPS patients.[8] Despite increasing reports of SPS throughout the world, little is known about the pathophysiological mechanism of the disease. Other known autoantigens described in SPS include amphiphysin, gephyrin, and GABA(A) receptor–associated protein (GABARAP).[16,17] What induces the development of autoimmunity is still not well understood. The autoimmune response to an antigenic stimulus is possibly triggered by a combination of appropriate interactive genetic and environmental factors that culminate in the disease.

EPIDEMIOLOGY

Because SPS is frequently underdiagnosed or misdiagnosed, there are limited accurate epidemiologic data. The literature reveals it has a tendency to occur predominately in the mid-fifth decade of life and, more often, insidiously following an especially stressful event in life. The incidence is estimated to be equal to or less than one person per million with a 2:1 female/male ratio. There has not been evidence of predominance between races or ethnicities; however, there seems to be a link between diabetes mellitus and SPS.[18,19] Antibodies to amphiphysin have been implicated in paraneoplastic variants of SPS. Antibodies to gephyrin was described in one patient.[17] GABARAP is a protein involved in the trafficking and assembly of GABA(A) receptor, and it is another target antigen in 70% of the subjects with SPS studied.[20] The lack of uniform anti-GAD antibody presence, the lack of what was once viewed as the classic manifestation of axial stiffness and spasms, as well as other variations

on a theme, such as restriction to the lower limbs,[21] confounds accurate compilation of the true incidence and distribution of this disorder. Furthermore, the case report of SPS in a patient after West Nile virus infection suggests possible cross-reactivity and molecular mimicry.[22] SPS manifestations in association with antiamphiphysin antibodies were also found in some patients who had breast cancer or lung cancer, predominately small cell lung cancer.[16,23]

CLINICAL FEATURES

SPS is a disease characterized by muscle rigidity and episodic spasms, often insidious in onset. Stiffness is predominately in the thoracolumbar paraspinal muscles or abdominal muscles with progressive spread to proximal limb muscles over time.[21] Sporadic stiffening and, often painful, muscle spasms can lead to functional impairment with inability to walk and care for oneself. The anxiety of unpredictable exacerbations results in fear of leaving the house and becoming stranded should an attack occur. There is resultant phobia about leaving the home[24,25] and, not unexpected, situational depression. Triggers reflect heightened response to external stimuli, including emotional stressors, sudden unexpected external stimuli (eg, sound or touch), or fast movement in affected muscle groups.[26,27] Though the spasms and rigidity may be localized and sporadic at onset, with improvement during sleep, as the disease progresses the symptoms become static, ultimately leading to loss of independence in daily activities, assistance in walking, and inability to bend at the waist resulting in major functional impairment and disability.[28] A summary of potential features of SPS is provided in **Box 1**.

VARIATIONS ON A THEME

Some patients manifest clinical characteristics localized to a specific region of the body with designations of stiff limb syndrome and stiff trunk syndrome. Barker and colleagues[21] have reported on the association of rigidity with a subacute encephalomyelitis seen at autopsy. In addition, one can see a paraneoplastic syndrome consisting of progressive encephalomyelitis in combination with rigidity and myoclonus (PERM).[29]

Stiff infant syndrome (SIS), or infantile hyperexplexia,[30] manifests at birth or early in infancy and is associated with at least five different genes in a both autosomal-dominant and autosomal-recessive form. These infants will present with hypotonia and diminished rigidity during sleep contrasted with generalized muscle stiffness

Box 1
Potential features of SPS

1. Rigidity which can be generalized or localized
2. Painful muscle spasms
3. The finding of anti-GAD antibodies in up to 60% of patients
4. Lack of an alternative explanation for the rigidity and muscle spasm
5. Potential overlap with other autoimmune disorders
6. Potential relationship with a progressive subacute encephalomyelitis
7. Potential component of a paraneoplastic syndrome
8. Hyperexcitability of spinal motor neurons on neurophysiological studies

and increased rigidity on awakening, including episodes of apnea and exaggerated startle response. As in SPS, these infants will have brisk deep tendon reflexes, though infants with SIS will have a generalized spread of the response. Most patients with SIS will have resolved their stiffness before the end of infancy, with most children being normal by age 3. Recurring episodes of stiffness throughout adolescence and adulthood are not, however, uncommon. Such episodes can be triggered by cold exposure, pregnancy, or startle.

Patients with SPS continue to be prone to exaggerated startle response to visual, tactile, or auditory stimuli, more so than the average individual is, throughout their lives. This can lead to inability to protect themselves from falls during an unexpected generalized stiffness response. Later in life, they may also exhibit hypnagogic myoclonus as well as periodic limb movements during sleep.[31] One reported form of hypokinetic rigid syndrome in a neonate was attributed to mitochondrial DNA depletion in association with secondary defect in neurotransmission and was progressive and fatal.[32]

ELECTROPHYSIOLOGICAL CORRELATES

Persons suffering from SPS typically do not have pyramidal and extrapyramidal signs. The stiffness occurs from involuntary firing of muscle motor units that will reveal itself as voluntary contraction on electromyography (EMG).[3,33] This is manifested by normal motor unit potential (MUP) configurations and firing rates with lack of denervation.[34] EMG typically reveals continuous MUP firing that can be reduced by administration of benzodiazepines.[34] Muscle spasms can occur spontaneously or by triggering events. Such spasms involve co-contraction of antagonist muscles.[21,26] Subnoxious stimulation of cutaneous or mixed nerves will cause disproportionate spread of reflexes and spasms to distant muscles from the stimulation site that, if confirmed by EMG, can support the diagnosis of SPS.[34] As in hereditary hyperekplexia, which involves loss of glycinergic transmission resulting in disinhibition at brainstem and spinal cord levels, SPS patients have an exaggerated startle response. This can lead to prolonged spasms after loud, or sudden, noises.[34,35] However, unlike hereditary hyperekplexia patients, SPS patients have exaggerated acoustic responses manifested as prolonged spasm of distant muscles, often major motor groups, such as the lumbar paraspinal muscles, neck, and proximal extremities.

The characteristic EMG finding of continuous firing of motor unit activity in SPS is not a result of motor unit disease nor of aberrations in the monosynaptic reflex arc because firing rates and recruitment of MUPs are maintained, as well as conduction velocities, F-waves, H-reflex, and the silent period induced by muscle stretch and mixed nerve stimulation.[34,36] Also, there tends to be a normal interference pattern seen during the spasms. Clinically, patients often have hyperactive deep tendon reflexes and some have clonus, although the Babinski reflex tends to be flexor.[34] The rigidity and the continuous motor unit activity disappear during sleep, as well as during peripheral nerve block and during anesthesia, which seems to indicate a central origin.[2,37]

DIFFERENTIAL DIAGNOSIS

The more typical manifestations of SPS versus variants are being increasingly recognized, as highlighted in a recent review by McKeon and colleagues.[33] As mentioned previously, SPS can reflect an isolated subacute progressive encephalomyelitis with rigidity[21] as well as a paraneoplastic syndrome in combination with PERM.[29] PERM is a rare condition seen in patients with cancer, especially small cell carcinoma of the lung. Unlike SPS, these patients often will have brainstem dysfunction, myoclonus, and spinal rigidity. The clinical features are a result of widespread central nervous

system dysfunction, with the cervical spinal cord most commonly affected. Isaacs syndrome, or acquired neuromyotonia, is an autoimmune channelopathy[38] that manifests as a result of antibodies to voltage-gated potassium channel (VGKC) found along the peripheral motor never axons. This syndrome can be paraneoplastic in origin. VGKC play an important role in nerve cell repolarization after action potential firing. Autoantibodies to the VGKC result in a decrease in higher than normal membrane potential by disrupting potassium efflux leading to inappropriate action potential firing and overrelease of acetylcholine responsible for the muscle cramps, slow postcontraction muscle relaxation, and myoclonus. Other clinical features of Isaacs syndrome include hyperhidrosis, lacrimation, and salivation, which are thought to be a result of antibodies to VGKC in autonomic fibers. An important distinction between SPS and Isaacs syndrome is demonstrated on EMG. Unlike SPS, the EMG in Isaacs syndrome has spontaneous muscle activity as a result of abnormal peripheral nerve firing.[39] In a possible overlap syndrome, Brown and colleagues[40] reported on subjects with lower limb rigidity and spasms without associated anti-GAD antibodies. It was speculated that this variant might be more reflective of a chronic spinal interneuronitis.

Painful rigidity can also be seen with tetanus. Painful muscle spasms are also part of the clinical spectrum of both neuroleptic malignant syndrome and the malignant hyperpyrexia that can been seen with certain anesthetic agents such as suxamethonium and halothane. The serotonin syndrome is characterized by the clinical triad of mental status changes, autonomic hyperactivity, and neuromuscular manifestations that can include rigidity.[41] A compilation of potential challenges in the differential diagnosis of SPS is provided in **Box 2**.

TREATMENT

There have numerous reports of response of the stiffness and spasms to agents in the benzodiazepine class, such as diazepam or clonazepam. In addition, antispasmodic agents, such as baclofen or dantrolene, can also provide some measure of relief. In view of the autoimmune nature of SPS, efforts have been made at immunosuppression with agents such as steroids and rituximab, as well as plasma exchange and intravenous gammaglobulin.[42] No positive controlled clinical trial to establish optimal therapy on evidence-based criteria has been achieved. This is certainly understandable given the rare nature of this disorder as well as the variations on a theme in terms of

Box 2
Differential diagnosis of stiff-person syndrome

1. Hyperekplexia in pediatric population
2. Neuroleptic malignant syndrome
3. Malignant hyperpyrexia related to certain anesthetic agents in genetically susceptible Individuals
4. Tetanus
5. Isaacs syndrome
6. Serotonin syndrome
7. Overlap with paraneoplastic process
8. Component of a subacute progressive encephalomyelitis
9. Chronic spinal interneuronitis

Box 3
Potential treatment options in SPS

1. Benzodiazepines including diazepam and clonazepam
2. Alternative muscle relaxants including baclofen (including intrathecal), dantrolene, and tizanidine
3. Corticosteroid therapy
4. Plasma exchange
5. Intravenous gamma globulin
6. Other immunosuppressive agents, such as mycophenolate, cyclophosphamide, azathioprine, methotrexate, and rituximab
7. Vigabatrin
8. Gabapentin
9. Sodium valproate
10. Levetiracetam
11. Botulinum toxin injections

pathogenesis. Sevy and colleagues[43] reported on successful treatment using rituximab with an intractable patient with SPS who had failed alternative immunosuppressive therapy. Of interest, despite clinical improvement in terms of reduced stiffness and spasm frequency, the blood and cerebrospinal fluid levels of anti-GAD antibodies increased during the course of treatment. A 12-year-old patient was also recently reported to have a significant response to rituximab.[44] However, in a recently reported controlled clinical trial, rituximab was not found to be superior to alternative therapy.[45]

An example how the overlap of manifestations can affect therapeutic response was provided by Cabo-López and colleagues.[46] They described a 28-year-old woman with psychogenic mutism. While hospitalized, this patient developed axial and proximal limb stiffness with hyperreflexia and prominent muscle spasms. She was found to have anti-GAD antibodies, as well as antibodies to parietal cells, microsomal thyroid peroxidase, and thyroglobulin. A partial response was observed with a combination of benzodiazepines, muscle relaxants, and corticosteroids.

Other immunosuppressive agents that have been tried include cyclophosphamide and mycophenolate. Additional agents reported in the literature include tizanidine, piracetam, and phenobarbital, as well as sodium valproate,[47] levetiracetam,[48] gabapentin,[49] vigabatrin,[50] and propofol.[51] Also, there have been reports of some response to botulinum toxin injections.[52] Potential treatment approaches are provided in **Box 3**.

SUMMARY

The recognition of an intriguing, but disabling, neuromuscular disorder, SPS, is vitally important in the clinical realm. SPS is an uncommon, if not rare, disorder characterized by a sense of body stiffness associated with painful muscle spasms. Like many illnesses, the manifestations can vary in terms of location and severity. The syndrome has been subdivided into stiff trunk versus stiff limb presentation as well as a progressive encephalomyelitis associated with rigidity. Stiff person-type syndrome can also reflect a paraneoplastic picture. Most patients demonstrate exaggerated lumbar lordosis. Roughly 60% of patients have anti-GAD antibodies in the blood and the

cerebrospinal fluid. The differential diagnosis includes tetanus, serotonin syndrome, encephalomyelitis, neuroleptic malignant syndrome, and malignant hyperpyrexia. There have been reports of response to muscle relaxants, including benzodiazepines, immunosuppressants, intravenous gamma globulin, plasma exchange, several anticonvulsants, and botulinum toxin.

Case study

A 54 year old right-handed African-American woman is referred to you because of increasing sense of "stiffness" and painful spasms. She has a several year history of type II diabetes mellitus and hypertension. She has been in otherwise good health, but reports a several month history of diminished appetite with a 20 lb. weight loss. She is being treated with an oral hypoglycemic agent for her diabetes and an angiotensin converting enzyme inhibitor for her hypertension. She has never smoked, drank alcohol or used illicit drugs. She has had a total abdominal hysterectomy with retention of her ovaries and this was related to uterine fibroids.

Family history is pertinent for hypertension and diabetes with both of her parents dying in their 60's from recurrent stroke. She has a brother, age 47, who is on hemodialysis for end-stage renal disease attributed to hypertensive nephropathy. Review of systems is pertinent for a generalized sense of weakness, a sense of "stiffness" of her axial musculature, and increasing painful muscle spasms of her extremities, especially her legs, along with the diminished appetite and weight loss.

On exam, her vital signs are stable except for a blood pressure of 154/94 mm Hg. She has no rash. Funduscopic exam reveals arteriolar narrowing. You noted some cervical lymphadenopathy. She also has some abdominal distension. Her mental status and speech are intact. Cranial nerve exam is normal. She has fairly good tone and strength throughout but muscle spasms of her lower torso and proximal lower extremities are noted during the exam. There is no evidence of cerebellar dysfunction. Her sensory exam reveals somewhat diminished vibratory sensation in a stocking-type distribution which you attribute to her diabetes. No sensory level is noted. The deep tendon reflexes are prominent in the 3/4 range with the Babinski response flexor on both sides. Her gait is somewhat antalgic related to her muscle spasms, but no actual truncal ataxia is noted.

Your differential diagnosis includes possible demyelinating disease, possible Lyme disease with spinal cord involvement, diabetic amyotrophy, or a paraneoplastic syndrome. The creatine kinase is normal at 154 with normal thyroid profile, normal B12 and folate level but a surprisingly elevated sedimentation rate of 87. A diligent medical student has been assigned this patient and does an extensive review of of possible explanations for the sense of body stiffness with painful muscle spasms. A diligent medical student has been assigned this patient and does an extensive review of possible explanations for the sense of body stiffness and painful muscle spasms. This leads to the sending off of a serum anti-glutamic acid decarboxylase antibody titer which comes back elevated at 1.2 nmol/L (normal = $\leq$ 0.02 Nmol/L). Unfortunately, the chest x-ray reveals multiple lesions felt to reflect metastatic disease and the CT scan of the abdomen reveals advanced ovarian carcinoma.

During presentation at Neurology Grand Rounds, at the medical center where the patient was admitted, it is felt by most attendees that his presentation represented stiff person syndrome as paraneoplastic manifestation of her metastatic ovarian carcinoma.

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