

Stiff Person Syndrome

Nancy Theresa Rodgers-Neame, MD, Assistant Professor, Department of Molecular Pharmacology and Physiology, University of South Florida; Director, Florida Comprehensive Epilepsy and Seizure Disorders Program

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Introduction

Background

Stiff person syndrome is rather unique among neurologic diagnoses because of its lack of significant similarity to any other neurologic diseases. Although rare, once observed it is quite unforgettable. Possibly the closest related disease is tetanus because both conditions affect peripheral inhibition via central mechanisms and both conditions inhibit central gamma-aminobutyric acid (GABA) systems.

In 1956, Moersch and Woltmann, who also coined the term *stiff man syndrome*, first clearly described SPS as a neurologic clinical entity at the Mayo Clinic. The eponym for this syndrome, Moersch-Woltmann syndrome, is one of the few instances in which the eponym may be the most inclusive and at the same time the most appropriately limiting name for the disease. The term *stiff person* may be seen to exclude infants, and *stiff man* is inappropriate for children and women; perhaps *stiff individual* most perfectly describes the affected patient.

Clinically, SPS is characterized by muscle rigidity that waxes and wanes with concurrent spasms. Usually, it begins in the axial muscles and extends to the proximal limb muscles, but the severity of the limb muscle involvement may overwhelm the axial muscle involvement (stiff limb syndrome). Some confusion has occurred as a result of cases that include other neurologic findings, such as encephalomyelitis, epilepsy, cerebral palsy, or cerebellar deficits, sometimes in addition to the classic clinical syndrome.

The pathophysiology of the disease is autoimmune. The most common pathologic correlate, anti-glutamic acid decarboxylase (GAD) antibodies, has been associated with a wide range of neurologic diseases. It is also associated with a number of non-neurologic diseases, including diabetes mellitus and thyroiditis.

Pathophysiology

Endocrinologists were excited by a discovery in the 1980s of an antibody to a 65-kd protein that was strongly associated with adult-onset diabetes mellitus and SPS. It is found in a particularly large subset of patients with diabetes, and endocrinologists hoped that it would be the major breakthrough needed to cure this disease in millions of patients worldwide. They were disappointed to find that the 65-kd protein was GAD, an enzyme largely found in the central nervous system (CNS), and, unfortunately, the pathophysiologic link between diabetes and glutamic acid decarboxylase remains unclear.

Since that time, the antibody has been found in patients with a number of neurologic diseases, a scenario that is easier to understand because the pathophysiologic link to

neurologic disease is easier to explain. The range of diseases encountered includes seizures, cerebellar dysfunction, cortical dysfunction, and myelopathy, but the association between function of the enzyme and the consequence of the disease is most clear in patients with SPS.

In SPS, spinal interneurons function to inhibit spontaneous discharges from spinal motor neurons, primarily through the action of glycine. However, this is only one inhibitory input for the motor pathway that includes GABA-mediated inhibition from the cortex, brain stem, and cerebellum. If GAD function is inhibited significantly, then GABA available for these functions is decreased and muscles become continuously stimulated by the motor neurons. Additional possible pathophysiologic etiologies in patients negative for GAD antibody include postsynaptic elements such as synaptophysin, amphiphysin, gephyrin, and GABA-transaminase.

Glutamate is an excitatory amino acid synthesized from glucose via the Krebs cycle. It has several fates within the cell. Glutamate can be packaged for release from synaptic clefts, and it can be acted on by several transaminases to transform it to either glutamine or GABA. Following release from the synapse, glutamate is absorbed either by reuptake mechanisms by the neurons or, more commonly, by astrocytes. GAD is nearly ubiquitous in the CNS and is located in or near the synaptic button. It is rate limited primarily by the availability of free glutamate. However, GAD is not the only source of GABA. The Krebs cycle also serves to synthesize GABA via GABA-transaminase.

However, GAD antibodies alone appear to be insufficient to cause SPS, and GAD antibodies are associated with a broad spectrum of disease; consequently, GAD clearly forms only part of the pathophysiology of SPS. Possibly, postsynaptic GABA-ergic mechanisms, such as the synaptobrevins involved in tetanus, are involved. Research continues to progress on this interesting subject. Some patients clearly have GAD antibody-negative disease and may also be negative for anti-amphiphysin but otherwise fit the clinical picture.

Mortality/Morbidity

Complications of this disease are multifaceted and may occur at any stage of the disease. In general, complications are responsible for the mortality and morbidity and are discussed in more detail in Complications.

Infants with stiff baby syndrome are at particularly high risk of sudden infant death and require monitoring.

- Complications of baclofen pump failure can occur. Cataclysmic exacerbations of the disease have been reported due to baclofen pump failure. At least one death has been reported. In addition, rare malfunctions of the baclofen pump have been associated with excessive release of baclofen intrathecally also resulting in death or permanent disability.
- Psychiatric morbidity from this disease is common. The unpredictability of symptoms and the linkage to stressful events only serve to exacerbate the situation. In addition, GABA mechanisms subserve many of the brain's emotional centers, which may contribute significantly to the psychiatric symptomatology.
- Musculoskeletal complications are common, particularly in later stages of the disease. Joint deformity, joint dislocation, joint contracture, skeletal fracture, and muscle rupture

have been reported.

Age

- The syndrome occurs in children younger than 3 years, most commonly in infants.
- Onset in adults is most frequent in the third to fifth decades of life.

Clinical

History

- Stiff person syndrome
 - Early stages
 - Stiff person syndrome usually begins insidiously in the axial muscles, and, if the patient is referred at an early stage, little objective findings may be found at the initial presentation.
 - In the initial stage of the disease, the patient has an exaggerated upright posture and may report back discomfort or stiffness or pain in the entire back, which is worse with tension or stress.
 - Patients may report disturbed sleep because, although the stiffness is relieved with sleep, when the patient transitions from rapid eye movement (REM) to stage 1 or 2 sleep they may lose the relief from the spasms, which may awaken them.
 - In some patients in the early stages, brief episodes of rather dramatic severe worsening that resolve spontaneously within hours or days may occur. Unfortunately, because of the subtle findings and apparent strong psychological components in the early stages, the patients are labeled as psychogenic, and effective treatment is often delayed.
 - Later stages
 - Later in the disease, proximal limb muscles also begin to be involved, particularly when the patient is stimulated, surprised, angered, upset, or frightened. This sort of stimulus may evoke painful severe spasms in the proximal arm and leg muscles that resolve slowly. The patient begins to move very slowly because rapid movement induces severe spasms. Even the distal extremities may become involved when moved rapidly.
 - Exaggerated lumbar lordosis is present combined with contraction of abdominal muscles.
 - Not surprisingly, depression has been noted as a comorbidity at this stage. The patient's quality of life is affected severely at this point, making it difficult or impossible to drive, work, or have a satisfying social life.
 - End stages
 - In the end stages of the disease, few muscles in the body are spared. Trismus is absent. However, facial and pharyngeal muscles may be affected markedly.
 - Joint deformities may occur. Skeletal fractures and muscle ruptures may occur during spasms.
 - Postsurgically, abdominal incisions are at risk of spontaneous rupture.

Eating, simple movement, and other simple activities of daily living (ADLs) may be problematic.

- Stiff baby syndrome
 - The clinical presentation of stiff baby syndrome is somewhat different.
 - Babies and young children are less rigid between attacks. Involvement of the distal muscles is often more evident, particularly during paroxysms. Opisthotonic posturing is more prominent.
 - Startle or stress is a frequent and prominent precipitant of the attacks.
 - Its clinical characteristics are within a broader descriptive category known as hyperekplexia. Differentiation of a particular case as stiff baby syndrome sometimes is considered dependent upon the presence of anti-GAD antibodies. In addition, stiff baby syndrome may be more persistent or more frequently recurrent, although this is not invariable.
 - Diagnosis can also be more complex because other etiologies (eg, other neuromuscular disorders, seizures, withdrawal or intoxication from maternal drug abuse) need to be excluded.
- Associated diseases
 - Diabetes mellitus: Although different epitopes for the GAD antibodies in diabetes have been identified, SPS and diabetes have demonstrated comorbidity. This comorbidity occurs in association with a finding of positive GAD antibodies. Early distal involvement and involvement of a single limb is more frequent in patients with diabetes mellitus. Stiff person syndrome has also been associated with diabetes mellitus and ICA 105 pancreatic autoantigen with and without the presence of anti-GAD antibodies.
 - Thyroiditis: An association with thyroiditis has been described. This may be due to comorbidity of multiple autoimmune entities or may be a more direct association. At least one group has suggested a link due to neuromuscular hyperactivity.
 - Breast cancer: A variant of SPS occurs rarely in patients with breast cancer. The antibodies involved are to a synaptic protein, amphiphysin. Anti-GAD antibodies are absent.
 - Epilepsy: Anti-GAD antibodies have been described in patients with medication-resistant focal epilepsies. In one series, 4 of 19 patients with anti-GAD–positive SPS were also found to have localization-related epilepsy.
 - Cerebellar ataxia: A number of case studies report the presence of cerebellar ataxia (with or without SPS) associated with anti-GAD antibodies.
- A form of familial spastic cerebral palsy has been described with a missense mutation in the GAD-67 gene. This is a different isoform of glutamic decarboxylase; however, it demonstrates that the pathophysiology of SPS is likely due to abnormalities in the function of glutamic acid decarboxylase.

Physical

In general, increased muscle tension, which may be more marked proximally than distally, is present. Frequently, lower extremities are most severely affected. Rarely, upper and lower extremities are affected. One limb may be affected, sparing other muscle groups. In most if not all patients, opposing muscle groups are noted to be tense, and tonic contraction with long relaxation times (myotonia) may be noted following percussion of the muscle. In most

patients, the neurologic examination findings are otherwise normal. Anxiety is common.

Variations and stages are as follows:

- Early in the disease, patients may report stiffness of the back and sometimes the neck; very little objective findings are revealed. Patients may walk and sit with an exaggerated upright posture (classic "tin-soldier" appearance).
- Later in the disease, response to stimuli becomes marked. Startle may lead to very uncomfortable and prolonged spasms. The symptoms worsen significantly with stress or anxiety, and the worsening of symptoms causes anxiety, often causing a disturbing self-perpetuating cycle.
- Late stages and acute exacerbations of the disease are accompanied by crippling involvement of the extremities. Skeletal fractures and muscular rupture have been observed in late stages of disease
- One variation of the disease known as stiff limb syndrome is observed more frequently in patients with diabetes mellitus. In this variation, the axial involvement is less marked, and one or (rarely) more extremities are affected.
- In stiff baby syndrome, distal findings may be more pronounced than in adults. Smaller babies may have increased tonic extension of the leg at the hip. Younger patients frequently have a more pronounced response to startle than adults, and hyperekplexia must be considered in the differential.

Causes

Currently, 3 autoantibodies associated with SPS are identified. The idiopathic form is most often associated with glutamic acid decarboxylase antibodies. The paraneoplastic form is most often associated with amphiphysin antibodies. One case report identifies gephyrin antibodies associated with SPS.

Workup

Laboratory Studies

- Obtain the following laboratory tests and interpret the results as outlined in Pathophysiology:
 - Hemoglobin A1C: This is obtained because of association with diabetes mellitus.
 - Complete blood count: An association with pernicious anemia has been reported.
 - Comprehensive metabolic profile
 - Thyroid-stimulating hormone: Thyroiditis is sometimes associated.
- Special tests
 - Anti-GAD antibodies
 - Anti-pancreatic islet cell antibodies
 - Anti-amphiphysin antibodies

Imaging Studies

- MRI or CT scanning of the brain is only indicated if cortical or corticospinal tract signs

are present on examination, for example, frontal lobe signs, increased reflexes, clonus, or abnormal plantar reflexes.

- Chest CT may also be indicated. Several individual case studies have reported thymoma in SPS.

Other Tests

- Electromyography (EMG): Characteristic continuous motor unit activity with normal morphology is especially prominent in the paraspinal muscles. Myotonic potentials are absent. Activity resolves with sleep and abates with benzodiazepines (diazepam). Simultaneous continuous motor activity is noted in opposing muscles.
- Electroencephalography: EEG is indicated when episodic or paroxysmal stiffness occurs or signs of cortical abnormalities are present on examination. Rare cases of SPS with associated refractory partial epilepsy have been reported.

Procedures

Lumbar puncture and associated CSF studies should be obtained in patients with a presentation that is consistent with SPS to rule out other etiologies. Oligoclonal bands can be observed in approximately two thirds of patients with antibody-positive SPS. In addition, lumbar puncture can add needed information if the patient's presentation is unusual or complex.

Treatment

Medical Care

Initial medical treatment may involve either baclofen or a benzodiazepine. Although no studies have been performed, tizanidine (Zanaflex) may be a less sedating alternative. Other medications that have been tried include antiepileptic medications, dantrolene, and barbiturates, but no clinical trials have been performed.

- **Intrathecal baclofen therapy**
 - Some patients may be candidates for intrathecal baclofen therapy for long-term treatment. Because symptoms may be variable, an externally programmable pump may be the best option.
 - Evaluation for intrathecal baclofen therapy by an experienced evaluator, the neurosurgeon involved, and the neurologist caring for the patient should coordinate the procedure so that the goals of therapy are clear. Deaths have been reported in SPS from baclofen pump failure; share this fact with the team and the patient. **Baclofen pump therapy should not be considered the sole therapy for the disease.**
- **Plasmapheresis (plasma exchange)**
 - In some patients, plasmapheresis has been demonstrated to be of clinical utility in the treatment of SPS.
 - No real prescribed dosage exists for plasmapheresis. The time of plasmapheresis, amount of supplementary albumin, and other parameters are controlled on a patient-by-patient basis by the pathologist running the blood

bank involved in the procedure. A 5-treatment series administered every other day is considered a standard regimen for autoimmune diseases, but longer and shorter regimens have been used.

- The efficacy is then evaluated and further treatment is decided on a patient-by-patient basis, usually as a collaborative effort with the insurance company physicians because it is such an expensive procedure.
- Possible adverse effects include hypotension, bleeding, arrhythmias, and infection.
- **Intravenous immunoglobulin**
 - Intravenous immunoglobulin (IVIG) has also been used in the inpatient setting for the treatment of SPS. The usual dose is 2 g/kg, administered over 2-5 days.
 - The length of the series is variable and dependent upon patient response. Treatment may extend past the inpatient period. (Documentation of patient response is usually necessary for ongoing reimbursement by third party payers.)
 - Remember that IVIG is contraindicated in patients with IgA deficiency because of increased anaphylaxis in these patients.
- **Physical therapy and occupational therapy**
 - Physical therapy and occupational therapy are critical to the recovery of the patient under treatment. Medical treatment may make the patient feel weak, a feeling that may respond well to therapy.
 - The patient may also have a great deal of problems with voluntary movement and fine motor skills.

Consultations

Psychiatry may be consulted especially when symptoms of depression or anxiety are prominent. The psychiatrist should be made aware of the pathophysiology of SPS and that the anxiety symptoms may be directly related to the presence of glutamic acid decarboxylase antibodies in the central nervous system. If possible, consult a psychiatrist that has shown interest in the disease.

Activity

Exercise or physical therapy may be helpful in preserving range of motion and in relieving symptoms related to prolonged muscle tension. In addition, muscular biofeedback may be helpful, although careful studies of physical therapy treatments have not been done. Keep in mind that activity or exercise may exacerbate spasms.

Medication

The goals of pharmacotherapy are to reduce symptoms, reduce morbidity, and prevent complications.

Benzodiazepines

Most frequently cited as useful in the treatment of SPS. Activate the GABA-A receptor to enhance central inhibitory circuits. Benzodiazepines include diazepam (Valium) or lorazepam (Ativan).

Diazepam (Valium)

Depresses all levels of CNS (eg, limbic and reticular formation), possibly by increasing activity of GABA.

Individualize dosage and increase cautiously to avoid adverse effects.

Lorazepam (Ativan)

Sedative hypnotic with short onset of effects and relatively long half-life.

By increasing the action of GABA, which is a major inhibitory neurotransmitter in the brain, may depress all levels of CNS, including limbic and reticular formation.

Immune modulators

These agents alter immune response to antigens. IVIG can be used.

Immune globulin intravenous (Gamimune, Gammagard, Sandoglobulin)

Neutralizes circulating antibodies through anti-idiotypic antibodies. Down-regulates proinflammatory cytokines, including INF-gamma; blocks Fc receptors on macrophages; suppresses inducer T and B cells and augments suppressor T cells; blocks complement cascade; promotes remyelination; may increase CSF IgG (10%).

Skeletal muscle relaxants

These agents increase activity of central inhibitory systems. Theoretically less sedating in relationship to GABA-A agonists such as benzodiazepines. Baclofen can be used.

Baclofen (Lioresal)

May induce hyperpolarization of afferent terminals and inhibit both monosynaptic and polysynaptic reflexes at the spinal level.

Follow-up

Further Outpatient Care

- Ongoing physical therapy and occupational therapy
 - Physical and occupational therapists can help with long-term muscle control and also serve as an adjunct to clinical observation for worsening signs and symptoms. They can also use passive muscle relaxation techniques that can help to relieve symptoms of long-term muscle spasm and to avoid loss of range of motion.
 - Be sure to encourage therapists to send reports or call staff about changes.
- Medications
 - Symptomatic medications, particularly benzodiazepines, may need to be changed or rotated often to avoid receptor down-regulation.

- Because the disease is rare, do not overlook novel medications that have not been reported but that have potential utility.
- Intravenous immunoglobulin
 - Outpatient IVIG can be used in patients with responsive symptoms as ongoing therapy.
 - Appropriate monitoring of vital signs should be available, and the procedure should be performed in an approved chemotherapy unit.
 - As in the inpatient setting, response should be documented carefully.

Inpatient & Outpatient Medications

- Baclofen
 - Baclofen is a specific GABA-B receptor agonist. The dramatic response of many patients with centrally mediated spasticity to this medication, including those with SPS, implies the importance of this underresearched receptor in the CNS.
 - The oral dosage is 10-30 mg every 8 hours, while the intrathecal dosage is in the range of micrograms per day.
 - The major adverse effect with oral dosage is somnolence. The major adverse effect with intrathecal dosage is hypotonicity. Other, more severe complications related to baclofen pump failure have been reported.
- Benzodiazepines
 - Diazepam and other benzodiazepines are also useful in the treatment of stiff man syndrome. In milder cases, small dosages can be used (2 mg q8h), but resistant severe cases can require very large doses (ie, 15-20 mg q8h; do not administer initially to benzodiazepine-naïve patients).
 - Benzodiazepines have the added benefit of relieving the inevitable anxiety associated with the disease.
- Pain management
 - Muscle pain is often a problem with patients and can cause worsening of the spasms and a cycle of spasms, pain, more spasms, and more pain.
 - Nonsteroidal anti-inflammatory medications can be used for less severe cases.
 - Long-term therapy with amitriptyline or similar tricyclics may be helpful. Time-release opiates may also be of benefit.
- Novel medications
 - Novel medications that may be of use because of their utility in other centrally mediated causes of spasticity include tizanidine (Zanaflex) and gabapentin (Neurontin).
 - Hypothetically, botulinum toxin type A (BOTOX®) may also be helpful in selected cases. However, the number and size of the muscles involved would possibly limit its usefulness. Complications of BOTOX® therapy are more frequent when multiple muscles are injected with larger amounts of toxin.
 - Although these medications have not been reported specifically in SPS, they have been used with success in other cases of spasticity.

Transfer

- Transfer to a tertiary or university medical center is often a difficult decision for a

clinician. The clinician may feel that it reflects on him or her personally as a physician. However, in reality, even in some major metropolitan areas, hospitals have found offering the full range of facilities and expertise to be impossible. These resources extend beyond those of the individual clinician so that even though the treatment of the patient may be within the capability of the physician, it is not within the capability of the facility. Therefore, when patients approach the point at which they strain the capability of the facility, transfer should be initiated.

- Questions to be answered are as follows:
 - Does the treating facility have regular availability of plasmapheresis? Is intravenous immunoglobulin therapy available on a regular basis at the treating facility?
 - Does the treating facility have rehabilitation-grade physical therapy and occupational therapy?
 - Does the treating facility have excellent inpatient psychiatric consultation for patients with chronic diseases? Do consulting psychiatrists have knowledge and interest in patients with chronic diseases, or are they mostly consulted for chemical restraint or behavior problems?
 - Does the treating facility have an intensive care unit that is used for neurologic acute care, or does staff of the intensive care unit perform primarily cardiac, respiratory, and end-of-life care?
 - Does the treating facility have an associated rehabilitation center capable of handling unusual diseases and physiatrists interested in unusual diseases?
- Most patients with the early stages of SPS do not require specialized care and do not require transfer by an experienced clinician. They can be treated successfully in an outpatient setting. However, attention to the above issues can alert a concerned physician to the need for transfer and help the physician justify the transfer to the patient, family, and insurance providers.

Complications

- Early stages
 - The earliest and most common complications of the disease are anxiety and depression. Unfortunately, the nature of the disease and the reaction of physicians and family to the problems may act in concert to produce this comorbidity.
 - The function of GAD is to convert glutamate to GABA. Although this is not the only source of GABA for the CNS, it is a significant source; depending on the situation, GABA can be depleted rapidly. GABA serves as a natural antianxiety compound. The most potent antianxiety medications are based on augmentation of the GABA-A receptor. Because a significant portion of patients with SPS have antibodies to GAD, not surprisingly patients also have anxiety. Tragically, anxiety worsens the spasms.
 - In the early stages, signs of the disease are often subtle to physicians and other health care workers. The patient feels uncomfortable and is aware of the stiffness, but his or her daily life is not disrupted significantly. Unfortunately, the failure of physicians and family to respond to the problem may result in increased anxiety and lead to dysphoria on the part of the patient. Ironically, the anxiety and dysphoria may become more disruptive to the patient's quality of life

than the disease, and the patient may be diagnosed with a somatization disorder.

- Late stages
 - Difficulty swallowing: Patients may have spasm of the pharyngeal muscles, making swallowing difficult and necessitating alternative methods of feeding.
 - Skeletal fractures: Severe paroxysms of spasms may result in skeletal fractures, particularly of the vertebral elements. They also have been reported in long bones.
 - Muscle rupture: Muscle rupture has been reported in severe cases during spasms.

Prognosis

- Prognosis is variable. Many patients have an indolent course that is primarily asymptomatic and is punctuated by occasional episodes of stiffness. Other patients may have a much more aggressive course, rapidly progressing to the late stages of disease.
- Other forms of the disease have been described that are accompanied by cerebellar findings, encephalopathy, and other CNS abnormalities, but whether they are separate diseases or different manifestations of the same disease is unclear.
- Prognosis for stiff baby syndrome is perhaps better. It is generally believed to be self-limiting and resolves with maturation of the CNS. Unfortunately, long-term follow-up studies are lacking.

Miscellaneous

Medicolegal Pitfalls

- The major medicolegal pitfalls involving SPS are misdiagnosis and delay in diagnosis, which can result in inappropriate medication adverse effects, prolonged morbidity, or both.
- However, remember that SPS is a rare condition and that patients commonly are not diagnosed with this syndrome until they have been evaluated by one or more neuromuscular specialists.
- Because of the nature of the disease, the risk for falling (resulting in possible injury) in patients with SPS is increased compared to healthy individuals. The proper precautions at home (especially while ambulatory) should be taken. Consultation with a physical medicine specialist may be appropriate.
- The condition is most commonly misdiagnosed as conversion disorder, particularly because SPS is often accompanied by increasing anxiety. This anxiety state may be physiologic and due to disruption of the mechanism for synthesis of GABA from glutamate, or it may be due to prolonged inadequate therapy.
- Careful assessment by a physician or physical therapist is necessary to determine the patient's level of motor skills (eg, driving, activities of daily living [ADLs], occupational) to ensure that he is not a danger to himself or others.
- Because presentation frequently does not follow a classic pattern or because it may be associated with other disorders, a high degree of alertness for the unusual patient

reporting stiffness increases the likelihood of early diagnosis.

- Baclofen pump failure has been described. Although rare, failure to deliver medication can result in catastrophic exacerbation of disease. Another rare complication is sudden delivery of high doses of baclofen intrathecally resulting in respiratory failure. Either complication can lead to significant morbidity or death.