



UNDERSTANDING STIFF PERSON SYNDROME

This neurological disease thought to be caused by an autoimmune response can leave patients unable to leave home. But treatment can help many to control the disease, and a possible cure may be on the horizon.

By Ronale Tucker Rhodes, MS

IN 2014, SALLIE Rhodes was a normal, happy 25-year-old “with an apartment, roommates, a passion for jogging and a good job as a pediatric nurse.” But, one day, her life was turned upside down. Her body kept locking up from searing spasms that made her legs stiff, her head and neck rigid and the muscles in her torso extremely tense, causing her to suffer concussions, cuts and other injuries. She suffered two years before finally being diagnosed with stiff person syndrome (SPS), a very rare disease of the nervous system.¹

While SPS affects approximately only one in a million persons, for those few, it is a frightening disease that leaves some too afraid to leave home, fearing stimuli will trigger painful spasms, and others unable to leave home because they can’t walk or move. SPS, also known as “tin man syndrome,” can occur in people of all ages, even infants, although it mostly occurs in individuals between 30 years and 60 years of age. It is twice as prevalent in women than men, but there is no link to any race or ethnic group.² And while no genetic link has been established, there have been isolated familial cases.³

SPS was first described by Frederick Moersch, MD, and Henry Woltman, MD, in a 1956 paper that covered 14 patients (10 men and four women with an average age of 41 years) collected over 32 years. Initially named Moersch-Woltman syndrome in their honor, the two coined the term stiff man syndrome.⁴ The name was later changed to SPS to reflect that the disorder can affect individuals of any age and of either gender.⁵

What Is SPS?

According to the National Organization of Rare Disorders, SPS is a rare acquired neurological disorder whose severity and progression varies from person to person. In addition to classic

SPS, which is found in the majority of cases, there are several variants often referred to as “stiff-man plus syndromes”: 1) stiff limb syndrome characterized by a focal onset of stiffness and rigidity in one leg followed by more widespread involvement later on in some patients; 2) progressive encephalomyelitis with rigidity and myoclonus (PERM) that presents with more rapid neurological decline with features of brainstem dysfunction (nystagmus [involuntary eye movement], opsoclonus [uncontrolled eye movement], ophthalmoparesis [weakness or paralysis of the eyes], deafness, dysarthria [poor speech articulation] and dysphagia [difficulty swallowing]) and profound autonomic dysfunction; 3) paraneoplastic SPS (approximately 5 percent of SPS cases), which presents with stiffness and rigidity in the neck, upper torso and arms, and is most commonly associated with breast, ovarian and lung cancer; and 4) others that present with a mixture of signs and symptoms superimposed on classic features of SPS, including cerebellar dysfunction, gait instability, oculomotor dysfunction, dysarthria, peripheral neuropathy, vertigo, parkinsonism and seizures.⁶

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The exact cause of SPS is unknown, but it is believed to be an autoimmune response in the brain and spinal cord, and it often occurs alongside other autoimmune disorders. Related disorders

include diabetes mellitus (occurring in approximately 35 percent of SPS patients), thyroiditis, breast cancer, epilepsy, vitiglio, cerebellar ataxia and myasthenia gravis.^{5,7}

Most people with SPS have antibodies to glutamic acid decarboxylase (GAD), a protein in inhibitory nerve cells involved in the creation of gamma-aminobutyric acid (GABA) that helps to control muscle movement. When the immune system mistakenly attacks certain nerve cells that produce GAD, this leads to a deficiency of GAD in the body. It is unknown what role a deficiency of GAD has in developing SPS. Some individuals with SPS have no detectable antibodies to GAD. But GAD-65 is the most common antibody produced by people with autoimmune diabetes.⁵

Less commonly, individuals with SPS will have antibodies to amphiphysic, a protein involved in the transmission of signals from one nerve cell to another. These antibodies pose a higher risk for developing breast cancer.³

In infants and young children, the disease is termed stiff baby syndrome, which is somewhat different because it typically affects the lower legs and arms and feet and hands. Spasms usually occur due to stress or being startled, and it may be more persistent or more frequently recurrent. In addition, the syndrome is dependent upon the presence of anti-GAD antibodies.⁷

Symptoms of SPS

SPS is characterized by progressive muscle stiffness (rigidity) and repeated episodes of painful muscle spasms, as well as back pain, sleep disturbance, impaired movement, emotional disturbances, lumbar lordosis, muscle and skeletal ruptures and fractures and joint deformity.^{4,8} In addition, symptoms reported by 80 percent to 99 percent of individuals with SPS include anxiety, EMG abnormality, falls and hyperhidrosis. And, 30 percent to 79 percent of individuals report agoraphobia [a fear of leaving home], autoimmune antibody positivity, difficulty walking, emotional lability, exaggerated startle response and paraspinal muscle hypertrophy.³

There are three different stages of SPS: early, advanced and end. Symptoms vary from case to case and depend on the stage in which the person is diagnosed.

In the early stage, individuals experience an exaggerated upright posture (rigidity) primarily in the trunk and abdomen that fluctuates. They may also have discomfort, stiffness or pain in the entire back that worsens with tension or stress. Sleep disturbance is common when transitioning from rapid eye movement to stage one or two sleep due to the loss of relief from spasms, which may awaken individuals. In some people, brief episodes of severe worsening symptoms resolve spontaneously within hours or days.

In the advanced stage, rigidity usually ensues in the proximal limb muscles along with muscle spasms that occur randomly and can be triggered by stimuli such as a sudden noise, touch or emotional stress. These stimuli cause individuals to begin to move very slowly to avoid rapid movement that induces severe spasms even in the distal extremities. In addition, exaggerated lumbar lordosis (inward curvature of the lower back) is present combined with contraction of abdominal muscles. Depression is a comorbidity since the individual's quality of life is severely affected. Approximately 65 percent of SPS patients are unable to function independently during this stage.

Finally, in the end stage, facial and pharyngeal muscles may be markedly affected, and joint deformities may occur. During spasms, fractures and muscle ruptures may occur. And, eating, simple movement and other activities of daily living may be problematic.⁷

Diagnosing SPS

Because SPS symptoms vary so widely, a diagnosis is often difficult. Indeed, diagnosis is frequently delayed considerably by an average of 6.2 years.⁹

A diagnosis of SPS begins by identifying characteristic symptoms and obtaining a detailed patient history and thorough clinical evaluation.¹⁰ Table 1 provides a list of characteristics physicians look for when conducting an

Table 1. What Physicians Look for During an Examination for SPS

- Increased tone in the axial/truncal muscle groups
- Increased tone in the legs (symmetric or asymmetric)
- Normal power in the upper and lower limbs, unless at an advanced stage of the disease
- Possible hyperreflexia, without plantar extension
- Normal sensory function and coordination
- Hyperlordosis of the lumbar spine (resulting from cocontraction of abdominal and paraspinal muscles)
- “Woody” feel on palpation of the muscles, due to spasms
- Slow, wide and cautious gait
- Intact cognitive function
- Normal sphincter function

Source: Hadavi, S, Noyce, AJ, Leslie, RD, and Giovannoni, G. Stiff Person Syndrome. *Practical Neurology*, 2011;11:272–282. doi:10.1136/practneurol-2011-000071. Accessed at www.rareconnect.org/uploads/documents/stiff-person-syndrome-review.pdf.

examination. In addition to these, more specific tests are needed to support or confirm a diagnosis, as well as to rule out other conditions. This is because while SPS lacks any significant similarity to other neurologic diseases, it presents with overlapping symptoms. For instance, tetanus is perhaps the closely related disease to SPS because both conditions affect peripheral inhibition via central mechanisms and both inhibit central GABA systems.¹¹

Antibody testing can measure levels of GAD in the blood. While absence of GAD antibodies doesn't rule out SPS, the presence of high levels of them strongly supports a diagnosis. In most people, GAD antibodies are commonly associated with diabetes, but these individuals have low levels making the distinction between high and low levels important. Very high GAD antibodies make SPS more likely.¹⁰

Electromyography is another important diagnostic tool that measures electrical activity in skeletal muscles. In SPS, the typical finding is continuous (low-frequency) motor unit activity simultaneously occurring in agonist and antagonist muscles.¹⁰

Additional tests that can support a diagnosis include hemoglobin A1C, complete blood count, comprehensive metabolic profile and thyroid-stimulating hormone. And, a lumbar puncture to detect oligoclonal bands that are seen in approximately two-thirds of SPS patients can rule out other diseases.³

There are clinical criteria for diagnosing SPS that were established in 1967 by Edward E. Gordon, MD. Later, those criteria were expanded by other physicians, including Marinos C. Dalakas, MD, who broadened the criteria to include tightness of the axial muscles, the progression of stiffness to the limbs, painful spontaneous muscle spasms, and an elevation of positive GAD or amphiphysin antibodies. Today, the Dalakas criteria are used worldwide to diagnose classic and variants of SPS (Table 2).⁹

Treating SPS

The goal of treatment is to provide symptom relief and to modulate the immune response causing SPS. Unfortunately, because the disease is so rare, the quality of treatment is limited because clinical drug trials are hindered by the low numbers of patients.¹²

Drugs known as benzodiazepines such as diazepam and clonazepam are used to treat muscle stiffness and episodic spasms. However, these muscle relaxants often need increasing doses for symptom relief, which sometimes cause troublesome side effects. In conjunction with benzodiazepines, baclofen is usually given to treat spasticity. Other options to treat spasticity include

Table 2. Dalakas Criteria for Diagnosis of Typical SPS

- Stiffness in the axial muscles, prominently in the abdominal and thoracolumbar paraspinal muscle leading to a fixed deformity (hyperlordosis)
- Superimposed painful spasms precipitated by unexpected noises, emotional stress, tactile stimuli
- Confirmation of the continuous motor unit activity in agonist and antagonist muscles by electromyography
- Absence of neurological or cognitive impairments that could explain the stiffness
- Positive serology for GAD-65 (or amphiphysin) autoantibodies, assessed by immunocytochemistry, Western blot or radioimmunoassay

Source: Physiopedia. Stiff Person Syndrome. Accessed at www.physio-pedia.com/Stiff_Person_Syndrome.

dantrolene and tizanide, which are commonly combined with other muscle relaxants. Anti-seizure medications such as tiagabine, valproate, carbamazepine and gabapentin have also shown to benefit a small number of people with SPS. However, vigabatrin, another anti-seizure medication, is rarely used because of its potential for visual field constriction.^{5,12}

Immune-modulating therapies include intravenous immune globulin (IVIG), plasmapheresis, rituximab and corticosteroids.

IVIG is considered a second-line treatment for severe or refractory SPS, and in addition to its immune-modulating effects, it has shown to improve many SPS symptoms.¹¹ The usual dose is 2 g/kg administered over two to five days, and the length of the series is variable and dependent upon patient response.¹³ Case reports show significant improvements in stiffness, startle, functional status and clinical examination, as well as radiographic and serological improvements. In a randomized, double-blinded, placebo-controlled crossover trial of monthly IVIG, results showed a significant decrease in stiffness, which stabilized during washout and increased again when switched to a placebo. Patients reported improvements in symptoms and ability to participate in activities of daily living, which lasted between six weeks and one year. And, GAD autoantibody titer also fell after IVIG.^{3,12}

With plasmapheresis (or plasma exchange), blood is removed from the patient and blood cells are separated from the plasma. The plasma is then replaced with other human plasma, and the blood is retransfused into the patient.³ There is no real prescribed

dosage for plasmapheresis, and the time of plasmapheresis and other parameters are controlled on a patient-by-patient basis. However, a standard regimen for autoimmune diseases is a five-treatment series administered every other day. There are possible adverse effects, including hypotension, bleeding, arrhythmias and infection.¹³ While no controlled studies have been conducted of plasma exchange, case reports show conflicting results, with some patients' symptoms and serological markers improving, and others showing no improvement.¹²

Rituximab, which depletes mature B cells, has been shown to give symptomatic and serological remission in patients with refractory SPS.¹² In 2010, a patient with SPS associated with a thymoma, diabetes mellitus, autoimmune thyroiditis and the presence of anti-GAD and anti-amphiphysin autoantibodies experienced a partial improvement following a thymectomy and the administration of prednisone, IVIG and mycophenolate mofetil. When treated thereafter with rituximab, the patient had complete sustained remission of SPS and the disappearance of serum anti-amphiphysin antibodies.¹⁴

Corticosteroids have been used as either monotherapy or combined with other therapeutic agents and have shown to improve spasms and autoantibody titers. However, again, there have been no clinical trials performed to determine their overall role in treating SPS.¹²

In addition to these therapies, physical and occupational therapy are critical to recovery since treatments may make patients feel weak. Exercise or physical therapy may also be helpful for preserving range of motion and relieving symptoms related to prolonged muscle tension. In addition, muscular biofeedback may be helpful.¹³

THE GOAL OF TREATMENT IS TO PROVIDE SYMPTOM RELIEF AND TO MODULATE THE IMMUNE RESPONSE CAUSING SPS.

A Possible Cure?

Most recently, autologous hematopoietic stem cell transplantation (auto-HSCT) has shown success in curing patients with SPS. In 2014, researchers at the Blood and Marrow Transplant Program at the Ottawa Hospital Research Institute in Ontario,

Canada, performed transplants on three women with SPS, two of whom were in clinical remission following the transplant and have now returned to normal functioning.

During the first part of auto-HSCT, a patient's cells that can regrow bone marrow are retrieved and put into a preservative and stored in liquid nitrogen. The patient is then given a conditioning regimen that includes chemotherapy and antilymphocyte antibodies to try to kill their immune system. The preserved cells are then thawed and reinfused into the patient, which redevelops their immune system from scratch. After the procedure, the patient is prescribed medications to prevent unusual viral or fungal infections. Six months posttransplant, the patient has to be revaccinated. While the patient's blood counts recover within a few weeks after transplant, the immune system recovery can take from three months to six months.

The first woman to receive a transplant was diagnosed with SPS in 2005 at age 48. She presented with progressive leg stiffness, hyperreflexia and falls, and she walked with an abnormal "tin solder" gate. MRI findings were normal, but anti-GAD antibodies were present at a very high titer (127 U/mL). And, over the years, her symptoms worsened. A month following her transplant, her symptoms resolved. After two months, her GAD antibody titer was 87 U/mL. "Despite continued circulating anti-GAD antibodies, at six months, she was fully mobile, had returned to work and was enjoying skiing and biking." And, as of 2014, she had remained asymptomatic four years and eight months following the transplant.

The second woman was 30 years old in 2008 when diagnosed and presented with episodic leg muscle stiffening with normal neurologic exams between attacks. She also had a low titer of anti-GAD antibody. After transplant, she experienced two episodes of severe muscle spasms in the first two-and-a-half months, followed by a third and a fourth, but those were less severe and shorter in duration. As of 2014, she had also returned to work and not had symptoms related to SPS in more than year.

Neither of these women had unexpected treatment-related toxic effects, and neither needs immunomodulatory or immunosuppressant medication.

The third woman was recovering and her symptoms were going away at the time of the reporting.

According to Christopher Bredeson, MD, head of malignant hematology and stem cell transplantation at Ottawa Hospital and senior scientist at Ottawa Hospital Research Institute, while the results so far are "favorable," the treatment approach involves an approximate 5 percent mortality risk, the recovery period is long and it's unclear if the effects are permanent. However, he

added, “In select patients who have sort of exhausted other things, it proves the principle, and we are encouraged to continue and try to develop the approach.”¹⁵

In the U.S., the Fred Hutchison Cancer Research Center in Seattle, Wash., has an ongoing clinical trial testing the efficacy of high-dose immunosuppressive therapy and auto-HSCT in more than a dozen neurological autoimmune diseases, including SPS, that don’t respond to conventional therapy. Led by George Georges, MD, the trial accepted Sallie Rhodes after other treatments failed, and her condition deteriorated. While U.S. insurance doesn’t pay for the \$450,000 procedure, Rhodes’ company made an exception and approved it.

On May 5, 2014, Rhodes underwent the procedure even though the doctors were worried her condition was so severe that muscle spasms could stop her breathing or that nausea from chemotherapy could result in her choking on her own vomit. However, more than five months after transplant, her symptoms were much better; her upper-body motion was much improved, and her spasms were less frequent and severe when they occurred. Unfortunately, improvement hasn’t been as dramatic as they’d hoped, and at the time of the reporting, she never entirely stopped having spasms, including episodes severe enough to send her regularly to the emergency room. But, the treatment is still deemed a success.¹

Future Outlook

While this disease has been recognized for more than half a century, much more research has been conducted in the last two decades to develop new treatments and possibly even a cure for SPS. According to the National Institute of Neurological Disorders and Stroke that conducts research related to SPS and supports additional research through grants to major medical institutions across the country, current research is focused on understanding the cause of the disease and the role of anti-GAD antibodies.¹⁶

Clinicaltrials.gov lists five studies on its site, three of which have been completed, one that has been terminated and another that is still recruiting. The completed studies focused on rituximab as treatment, IVIG as treatment, and the cause, development and progression of the disease. The currently recruiting study began in 2014 and is studying stem cell transplantation for SPS.¹⁷ In fact, great hope is being placed on auto-HSCT, with Dr. Georges presenting in May at the American Society for Apheresis 2017 Annual Meeting on “Autologous Hematopoietic Stem Cell Transplantation for Autoimmune Neurologic Diseases: Multiple Sclerosis and Stiff Person’s Syndrome.”

Until more is discovered about SPS and how to cure it, patients are left with available treatments that help to manage their condition. Fortunately, symptoms of SPS can be well-controlled for many with appropriate treatment. Regrettably, that is not the

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case for all as many patients continue to live housebound out of fear of freezing or falling unexpectedly. At this point, because the immune system appears to be at the root of the problem, procedures like auto-HSCT, and even potentially others, could eventually lead to alleviating this traumatic disorder. ■

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