



STIFF PERSON SYNDROME: A CLINICAL REVIEW AND RECENT TREATMENT UPDATES

Neurology

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ABSTRACT

Stiff Person Syndrome (SPS) is characterized by rigidity of the truncal muscles with superimposed episodic and often painful muscle spasms, heightened sensitivity to external stimuli, particularly tactile and auditory, and high-titer anti-GAD antibodies. Co-contraction of agonist and antagonist muscles and continuous involuntary firing of motor units at rest are the cardinal pathophysiological hallmarks of the disease. The symptoms range from mild to severe and can progress, resulting in significant disability. The multidisciplinary treatment of SPS is aimed at relief of the painful muscular spasms and extreme rigidity. Currently, the treatment for SPS revolves around improving the quality of life by reducing the symptoms as far as possible with the use of GABAergic agonists, such as diazepam or other benzodiazepines, steroids, plasmapheresis, and intravenous immunoglobulin (IVIG). Intrathecal baclofen therapy has been a very promising treatment option. In this article we will review the presentation, diagnosis and management of SPS.

KEYWORDS

Sps Gad Rigidity Baclofen Perm Ahsct

INTRODUCTION:

Stiff-person syndrome (SPS) is a rare disorder, characterized by progressive fluctuating muscular rigidity and spasms. Most patients with classical SPS have antibodies against glutamic acid decarboxylase (GAD), but there are also paraneoplastic variants, commonly secondary to breast cancer or small cell lung cancer. Both classical and paraneoplastic SPS have an autoimmune basis and are strongly associated with other autoimmune diseases [1]. "Stiff man" syndrome was first described in 1956 by Moersch and Woltman [2,3]. Along with observations from 13 other cases, they described a 49-year-old man with progressive stiffness in his neck, shoulders, and upper back, episodic painful muscle spasms, and difficulty walking. Multiple similar case descriptions have since followed. The term "stiff man" was recently replaced by the gender neutral "stiff person syndrome" (SPS), which gained significant traction after Blum and Jankovic [4] reported that approximately 20 of the 84 reported cases between 1967 and 1991 were female. It was Asher [5], however, in 1958, who first proposed this terminology [6].

EPIDEMIOLOGY:

Stiff-person syndrome (SPS) has an estimated prevalence of one to two cases per million, with an incidence of one case per million per year [7]. Most patients present between the ages of 20 and 50, and women are affected two to three times more often than men. It occurs extremely rarely in childhood [7].

CLINICAL FEATURES:

The natural history of SPS has yet to be completely described. The symptoms range from mild to severe and can progress, resulting in significant disability. Perhaps 65% of patients cannot independently perform normal activities of daily living due to rigidity and stiffness, phobias, unpredictable spasms and frequent falls [7, 8]. The symptom onset is typically insidious. Patients may report intermittent aching and tightness in the neck, paraspinal and abdominal muscles. The rigidity spreads slowly through the proximal muscles and is often asymmetrical [7]. Over time, activities of daily living become severely impaired and patients report difficulty dressing, walking and bending forward, for example, when putting on shoes [8].

In its classical form, SPS is characterized by excessive muscle rigidity of the lumbar, trunk, and proximal limb muscles that is caused by sustained muscular contractions occurring in agonist and antagonist muscles. The clinical hallmark of SPS is an extreme degree of muscle stiffness and rigidity. The persistent nature of these symptoms may lead to fixed spinal deformities such as a pronounced lumbar or cervical lordosis; this is thought to be due to the simultaneous contr

action of opposing paraspinal muscle groups. The onset of stiffness and rigidity in the axial muscles, either lumbar or cervical, is insidious and generally progresses slowly over time to involve proximal limb muscles. Patients walk with a wide-based and unsteady stance ("Frankenstein's gait") with a tendency to fall in a fashion similar to a log tumbling down. They are at high risk for fracture [9]. As patients lose their ability to walk safely, they may develop a heightened sense of fear and anxiety and agoraphobia. As truncal flexibility is lost, ambulation slows considerably; the patient may eventually require assistive devices to walk. Activities of daily living, such as getting into or out of bed, arising from a chair, or dressing, are severely limited; some patients become bedridden. Superimposed episodic muscle spasm precipitated by sudden movement, noise, or emotional upset is a sensitive and specific feature of SPS, known as the startle reflex [10]. Spasms usually begin in the axial muscles and may spread to the extremities. They are painful and can generate sufficient force to fracture bone. The muscle spasm is generally easily visualized; the affected area has a tight, rock-hard appearance and a unique, board-like feel. Palpation may provoke even more intense spasm [2].

VARIANTS OF SPS:

Since the original description, more limited forms of SPS (sometimes paraneoplastic), including "stiff limb" and "stiff trunk," have been reported (often in patients who are GAD65 antibody seronegative). Furthermore, some patients with high GAD65 antibody values have other neurological disorders coexisting with SPS, including epilepsy and cerebellar ataxia (SPS Cer), brainstem disorders, and myelopathies. Also, a rapidly progressive form with diffuse central nervous system findings, known as progressive encephalomyelitis with rigidity and myoclonus (SPS-PERM), has been described. There is little information about the incidence of SPS (the classic form or its variants) or about long-term treatment responses and outcomes [11].

PATHOPHYSIOLOGY:

The suspicion for an immunologic cause was raised by the observations of frequent comorbid diabetes (up to 35% in some series) and other concomitant autoimmune diseases (vitiligo, celiac sprue, rheumatologic diseases, and thyrogastric disorders) in patients with SPS [6]. Glutamic acid decarboxylase (GAD) antibodies (Anti-GAD) were first documented in association with SPS in 1988. Anti-GAD antibodies inhibited GAD activity and the synthesis of gamma-aminobutyric acid (GABA) in vitro [2]. SPS is characterized by progressive muscle rigidity and gait impairment with superimposed painful spasms that involve axial and limb musculature, triggered by heightened sensitivity to external stimuli. Impaired synaptic GABAergic inhibition resulting from intrathecal B-cell-mediated

clonal synthesis of autoantibodies against various presynaptic and synaptic proteins in the inhibitory neurons of the brain and spinal cord is believed to be an underlying pathogenic mechanism. SPS is most often idiopathic, but it can occur as a paraneoplastic condition. Despite evidence that anti-GAD and related autoantibodies impair GABA synthesis, the exact pathogenic mechanism of SPS is not fully elucidated. The strong association with several MHC-II alleles and improvement of symptoms with immune-modulating therapies support an autoimmune etiology of SPS [12].

The diagnosis of SPS requires a high degree of clinical suspicion in addition to diagnostic testing, with emphasis on specific serological markers such as anti-GAD, GABARAP and amphiphysin antibodies. Anti-GAD antibodies are produced intrathecally, presumably by B cells that have crossed the blood-brain barrier [12]. There is evidence that clonal expansion of B cells, either *in situ* or intrathecally, and circulating autoantibodies play a causative or contributory role in the pathophysiology of many neurological diseases that overlap with SPS, some of which are associated with GAD antibodies such as subacute cerebellar ataxia, drug-refractory temporal epilepsy, brainstem encephalitis, and various forms of organ-specific autoimmune diseases [13]. The occurrence of multiple neurological symptoms and signs in SPS patients, as well as the association of coexisting nuclear and cytoplasmic autoantibodies, may reflect evolving immune responses to multiple CNS and other tissue-specific antigens similar to the phenomenon of 'intermolecular epitope spreading' described in the paraneoplastic setting [14].

DIAGNOSIS OF SPS AND ITS VARIANTS:

SPS is a rare disorder in which patients may have an insidious onset with classical findings being episodic aching and stiffness of the axial muscles slowly progressing to proximal muscles. As the disease progress, the patients may find it difficult to carry out their day-to-day activities. The common clinical scenarios which aid in diagnosis of SPS are as follows –

1. Stiffness starting in the trunk and progressing to the abdomen and lumbar region. Hyperlordosis due to the episodic aching and stiffness of the lumbar spine is a diagnostic hallmark of SPS [15].
2. The stiffness progresses to other muscles in the body, for instance, progression to the thorax muscles causing breathing difficulties. Facial muscle involvement gives an emotionless, masklike appearance [16].
3. Painful spasms are elicited by triggers predominantly auditory or tactile in origin, and they are in sync with those observed in the case of tetanus.
4. Joint dislocations and fracture have been observed in some cases with the sudden onset of spasm.
5. Normal sensation, motor function, and intellect are present.
6. An association with psychological disorders is also seen [16].
7. Electromyography (EMG) findings are supportive of continuous motor activity.
8. Serology testing positive for GAD65 auto-antibodies.

The diagnosis of SPS is established by clinical findings and exclusion of pyramidal and extrapyramidal disorders, with supportive evidence from electrophysiological findings on EMG studies and serological and CSF testing that show elevated anti-GAD antibodies. Conventional MR imaging studies of the nervous system are usually normal [12]. Magnetic resonance spectroscopy has demonstrated a significant regional decrease in GABA levels in the motor cortex, providing supportive evidence of deficient GABAergic inhibition as a pathophysiological mechanism in SPS. Diseases that should be differentiated from SPS include myelopathies, dystonias and other extrapyramidal diseases, neurodegenerative disorders such as spinocerebellar degenerations, primary lateral sclerosis, neuromyotonia or 'Isaacs syndrome', as well as rare forms of chronic tetanus and psychogenic disorders. Magnetic resonance imaging studies of the brain and spine are useful to exclude certain structural disorders, such as myelopathies. Electromyography plays an important role in establishing a diagnosis of SPS by demonstrating the characteristic involuntary firing of motor units [12]. Standard Dalakas's criterion can be utilized for diagnosis of SPS [Table 1] [7].

Table 1: The Dalakas criteria for the diagnosis of typical stiff-person syndrome [7]

<ul style="list-style-type: none"> • Stiffness in the axial muscles, prominently in the abdominal and thoracolumbar paraspinal muscle leading to a fixed deformity (hyperlordosis).
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<ul style="list-style-type: none"> • Superimposed painful spasms precipitated by unexpected noises, emotional stress, tactile stimuli.
<ul style="list-style-type: none"> • Confirmation of the continuous motor unit activity in agonist and antagonist muscles by electromyography.
<ul style="list-style-type: none"> • Absence of neurological or cognitive impairments that could explain the stiffness.
<ul style="list-style-type: none"> • Positive serology for GAD 65 (or amphiphysin) autoantibodies, assessed by immunocytochemistry, western blot or radioimmunoassay.
<ul style="list-style-type: none"> • Good response to diazepam

TREATMENT OF SPS:

The multidisciplinary treatment of SPS is aimed at relief of the painful muscular spasms and extreme rigidity. Several pharmacological agents used such as benzodiazepines, antispasmodics like baclofen or dantrolene, immunosuppressive agents such as steroids, rituximab, and plasma exchange or intravenous immunoglobulins. Other treatment modalities are physiotherapy and occupational rehabilitation [8]. First line treatment is benzodiazepines such as midazolam or diazepam. Failure to improve on benzodiazepines, are treated with oral baclofen, where some patients show good clinical outcome while others fail to improve. As the disease progresses intrathecal baclofen can be initiated with good results [8].

INTRATHECAL BACLOFEN -

Intrathecal baclofen results in higher CSF bioavailability, as CSF penetration of baclofen is limited for oral baclofen. Almost 50 times higher CSF levels of drug are achieved at much lesser fraction of intrathecal baclofen versus oral administration [17]. Silber et al in a double blinded placebo controlled trial of intrathecal baclofen proved a significant improvement in the electrophysiological activity of SPS patients. Baclofen is a GABA-B agonist and can be used in combination with benzodiazepines. Patients are started on an oral maintenance dose at 5-60 mg in divided doses. Intrathecal baclofen at 50-100 µg/day is used for severe spasticity. However, the clinician has to be cautious about the drug delivery rate as a drop in intrathecal baclofen drug delivery rate can cause severe withdrawal and also prove fatal [18,19]. Chaudhari DM et al reported a case that upon receiving intrathecal baclofen as a symptomatic treatment for SPS, a good clinical outcome was observed [17].

IVIG (INTRAVENOUS IMMUNOGLOBULINS) AND PLASMA PHERESIS -

As per the European Federation of Neurological Societies (EFNS), IVIG (2 g/kg over two to five days) should be reserved for patients who have no symptomatic relief after the use of diazepam and/or baclofen and have a severe disability in carrying out daily activities [20]. The result of a randomized, double blinded, placebo-controlled, crossover trial on patients treated with IVIG has showed improvement in their symptoms with a significant decrease in stiffness and decrease in GAD autoantibodies [21]. The GAD autoantibody titre also decreased after administration of IVIG [21]. IVIG is usually safe but has higher chances of adverse reactions as compared to plasmapheresis, ranging from mild to severe in patients with IgA deficiency and, hence, is contraindicated in them. On the other hand, plasmapheresis therapy has shown promising results in 56% patients registered in the study approved by John Hopkins Institute (JHH) where first-line treatment failed [22]. Studies have shown that plasmapheresis is well tolerated with adverse effects seen in just 4.75% of patients receiving it [23].

RITUXIMAB -

Rituximab, a monoclonal antibody that binds to the B-lymphocyte cluster of differentiation (CD) surface antigen, has been tried as an effective drug to manage SPS. It is administered as at least two doses each of 350-375 mg/m² infusion with spacing of seven to 14 days or as four weekly infusions, which have resulted in a substantial decrease in the severity of symptoms [24]. Though very few papers have reported the effective use of rituximab, it should still be considered as an alternative treatment for patients with SPS when the treatment with benzodiazepines and other conventional antispasmodic immunotherapies have failed to produce the desired effect [25].

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (AUTO-HSCT)-

Role of Autologous hematopoietic stem cell transplantation (auto-HSCT) for SPS has recently gained interest worldwide. Based on prior experience using auto-HSCT for autoimmune diseases, the Ottawa

Hospital Blood and Marrow Transplant Program performed auto-HSCT on 2 patients with severe SPS based on a regimen used for patients with multiple sclerosis [26]. Sanders et al, described 2 patients with severe SPS who are in clinical remission after intensive immunosuppression followed by auto-HSCT. Both patients remain in remission without ongoing immunomodulatory or immunosuppressive medication, and both have returned to their normal premorbid functioning [27].

Another recent trial studies 9 cases with severe SPS underwent AHSCT: 4 females, 5 males, mean age 42 (25–50), mean years since diagnosis 5.3 years (1–14.7), all disabled and unable to work, most required assistance for ambulation. Baseline median distribution of stiffness index (DSI), a standardized measure of stiffness ranging from 0–6, was 5 (3–6). No engraftment complications, severe or unexpected adverse events occurred. The initial treatment response varied; 7 of 9 patients experienced some improvement of DSI and functional status at 1 month post-AHSCT. However, by 1 to 2 years post-AHSCT all 9 patients achieved very significant and sustained reductions in DSI and neurological disability. EMG findings improved or normalized in all patients, anti-GAD65 titers decreased, and the majority of patients were able to taper off all benzodiazepine and anti-spasm medications and some were able to return to full-time work. These preliminary findings suggest that AHSCT is well-tolerated and may be a highly effective therapy for selected patients with treatment-refractory, severe SPS.

CONCLUSIONS:

- SPS is a rare and frequently misdiagnosed disease. Hence, stiff person should be considered in the differential of a patient with painful, intermittent progressively worsening, muscular spasms. Especially in females, due to higher female predilection.
- SPS is a rare disorder and is very difficult to diagnose. With a timely recognition of the disease and prompt treatment, the quality of life of SPS patients can be improved. Though the first line of drugs for SPS is benzodiazepines and baclofen, their dose-related adverse effects are of major concern.
- The diagnosis of SPS is often questionable, but the presence of anti-GAD antibody is an important clue. Anti-GAD antibody is primarily involved in the pathogenesis of SPS, and several autoimmune diseases can be associated with SPS.
- The prognosis for patients with SPS is variable. Patients with more limited disease may continue to function normally for extended periods, but gradual functional decline is generally noted.
- Several different options may be tried in patients resistant to treatment with IVIG, including B cell depletion with anti-CD20 (rituximab), plasma exchange, immunosuppressive agents and intrathecal baclofen infusion pump, but studies are very limited, and responses have varied substantially between patients. AHSCT is well-tolerated and may be a highly effective therapy for selected patients with treatment-refractory, severe SPS.

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