Stiff person syndrome (SPS): Literature review and case report

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Stiff person syndrome (SPS) is a rare, debilitating condition which presents with progressive and inconsistent neurological features. The main symptoms are stiffness and intermittent, painful muscle spasms, triggered and exacerbated by stressful and emotional stimuli. The fluctuating clinical nature of SPS, and otherwise normal neurological examination, often lead to a misdiagnosis of conversion disorder. Psychiatric symptoms frequently accompany this disorder and patients are often first seen by psychiatrists. SPS is autoimmune-based: antibodies are directed against glutamate decarboxylase, resulting in dysregulation of gamma-aminobutyric acid (GABA) in the brain which is considered the cause of the neuropsychiatric symptomatology. SPS should be considered in the differential diagnosis of conversion disorder. Effective management requires early detection, a collaborative approach with GABA-ergic medication and intravenous immunoglobulins, and management of concomitant psychiatric disorders. We describe a patient with SPS. Only one other case has been reported in South Africa.

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Stiff person syndrome (SPS) is a rare neurological condition with an intriguing pathophysiology and may result in severe functional disability. Psychiatric disorders are frequently associated with SPS, which may often lead to misdiagnosis of the disorder. Recognition of a case of SPS is important because early initiation of therapy prevents long-term disability.

SPS is estimated to occur in 1 per 1 million individuals.[1-3] Only one other case, in 1979, has been reported in South Africa.[4] In this patient, the diagnosis of SPS was based on clinical and neurophysiological findings. At that stage, it was presumed that SPS was caused by noradrenalin over-activity.

SPS was first described in 1956 as a previously unknown neurological disorder characterised by 'progressive fluctuating muscular rigidity and spasm'.[5] The term 'stiff man syndrome' was coined by Moersch and Woltman.[5] The clinical picture of this syndrome was broad, and had occurred in 14 patients who were diagnosed over a period of several years. What made this syndrome remarkable was the occurrence of pronounced axial rigidity with prominent muscle spasms, while the rest of the neurological examination was normal.[5] Spasms were often triggered by emotional distress and unexpected external stimuli.[6,7]

Since its initial description, several cases of the syndrome have been reported globally in both men and women, as well as children. Consequently, the syndrome has been renamed SPS.[8,9] Several other variants have also been described, such as stiff baby syndrome and stiff limb syndrome.[10] Women appear to be affected more often than men, with a male:female ratio of 2:1. This might be ascribed to the greater incidence of immune-mediated diseases in women.[11,12] SPS can occur from the third to the sixth decade of life,[11,12] although cases have been reported in children younger than 3 years.[13]

Pathophysiology

SPS is currently viewed as an autoimmune disease and may be associated with other autoimmune conditions such as type 1 diabetes mellitus, Hashimoto's thyroiditis, vitiligo, pernicious anaemia, systemic lupus erythematosus (SLE) and coeliac disease.[14-16] Epilepsy may be associated with SPS and is present in 10 - 20% of cases.[14,17] More than 60% of patients diagnosed with SPS have at least one psychiatric diagnosis.[18]

In 1998, Solimena *et al.*[19] were the first to associate SPS with antibodies against the enzyme glutamic acid decarboxylase (GAD). GAD is an antigen found in 60 - 80% of the sera of patients with SPS.[14,20] This enzyme catalyses the decarboxylation of L-glutamate into gamma-aminobutyric acid (GABA). GABA functions in GABA-ergic neurons, which are the main inhibitory neurotransmitter in the brain and spinal cord.[21] Auto-antibodies directed against GAD lower levels of GABA and raise levels of glutamic acid,[21] and this relative GABA deficiency has been proposed as the basis for the pathophysiology of SPS. GAD is also synthesised in non-neuronal tissues, including the beta cells of pancreatic islets, testes and oviducts.[22]

The enzyme has two isoforms, namely a membrane-associated 65 kDa form, GAD65, and the soluble 67 kDa form, GAD67.[21] These isoforms differ in structure and function.[22] Interestingly, GAD67 deficiency in mice has proven to be lethal,[23] while GAD65 deficiency, despite being associated with sufficiently functional levels of GABA, leads to minimally evoked and stress-induced seizures in

mice.[24] In cases of SPS, auto-antibodies directed against GAD65 are present in the sera of up to 80%[16,20] of patients. In 75% of patients, GAD65 antibodies are present in the cerebrospinal fluid (CSF).[25] Auto-antibodies to GAD67 are found in 50% or fewer of SPS patients, although at notably lower titres.[25,26] The CSF titres are 50 times lower than in serum, although the rate of antibody synthesis is 10 times higher in CSF.[27]

Anti-GAD65 antibodies are present in 1% of the normal population and in 5% of patients with neurological disorders other than SPS,[21] such as cerebellar ataxia, temporal lobe epilepsy, and myoclonus and non-paraneoplastic limbic encephalitis.[28,29]

Immunological tests for the detection of anti-GAD antibodies are already in use in some of the hospitals in South Africa, including the Chris Hani Baragwanath Academic Hospital (Johannesburg, Gauteng) and Universitas Academic Hospital (Bloemfontein, Free State).

Endocrine system

Anti-GAD antibodies were first described in type 1 diabetic patients.[30] In diabetics, the titres were found to be elevated 10 times above the baseline,[31] compared with at least 50 times above the baseline in patients with SPS.[3]

According to Pugliese *et al.*,[32] 72% of SPS patients carry the DQB1*0201 allele, which contributes to genetic susceptibility for insulin-dependent diabetes mellitus (IDDM) and other autoimmune diseases.[32,33] A recent study further suggested that a prospective 46% of SPS patients develop type 1 diabetes mellitus after being diagnosed with SPS. Some patients, however, had had diabetes for several months up to 15 years prior to the diagnosis of SPS.[34]

Aetiology

SPS is usually idiopathic, but can also occur as a paraneoplastic condition in 5% of cases.[2] In these cases, the antibodies present may either be anti-GAD or against other pre- and post-synaptic constituents.[35-38] The main paraneoplastic auto-antibodies are directed against amphiphysin, which is a presynaptic cytosolic vesicle protein. These antibodies were found to be present in breast and lung carcinoma.[39] Antibodies directed against gephyrin, a post-synaptic cytosolic vesicle protein, may also be produced.[38]

Clinical features and course of SPS

The onset of SPS is insidious with a progressive course.[40] It has been reported that up to 50% of patients become wheelchair bound, although most patients remain ambulant with treatment.[41]

Symptoms are frequently preceded by psychiatric conditions, months or even years before the onset of the neurological symptoms.[18] SPS initially presents as muscle stiffness, which is progressive and usually involves rigidity of the axial muscles, including the paraspinal thoracic, lumbar and proximal leg muscles.[33] Another debilitating feature is hyperlordosis, which can lead to difficulty rising from a chair or rising from a bed due to the simultaneous contractures of both the paraspinal and abdominal muscles.[33] Intermittent muscle spasms are superimposed on the continuous rigidity. These spasms are often triggered by emotional distress and unexpected external stimuli and can be extremely painful. This in turn can lead to anticipatory anxiety in situations which the patient believes to be unsafe.[42]

Psychiatric conditions associated with SPS

As mentioned earlier, psychiatric conditions are frequently associated with SPS.[18] The prominence of psychiatric symptoms often leads to a misdiagnosis of conversion disorder. Bizarre and fluctuating movement disturbance and the presence of psychological factors contribute to the misdiagnosis.[18] Patients with SPS are often seen by psychiatrists before they come to the attention of neurologists.[7]

Various mechanisms have been proposed to explain the high rate of psychiatric comorbidity in SPS. The aforementioned GABA deficiency has been used to qualify the high occurrence of anxiety associated with the syndome.[43] Panic disorder, post-traumatic stress disorder, generalised anxiety disorders and phobic disorders are frequently associated with SPS.[42,44] Other conditions usually associated with SPS include depression and substance abuse,[42] which have both been linked to dysregulation in the GABA system.[4] Conversion disorder can also occur in association with SPS.

Important differences between SPS and conversion disorder need to be highlighted to prevent a delayed diagnosis. Generally, SPS has a progressive course, while conversion disorder rarely lasts longer than a year. Additionally, the presence of antibodies directed at GAD may help distinguish between these two conditions.[45]

Diagnosis

The diagnosis of SPS is mainly made on clinical findings. Several similar sets of criteria have been proposed. The first set of diagnostic criteria was published by Gordon *et al.*[46] in 1967. The main clinical findings are (*i*) stiffness of axial muscles and progression to involve proximal limb muscles due to continuous co-contracture of agonist and antagonist muscles usually involving the lower limbs; (*ii*) abnormal axial posture with increased lumbar hyperlordosis; and (*iii*) superimposed muscle spasms.[40,47] Emotions and unexpected tactile, auditory or emotional stimuli often precipitate attacks of spasms or increasing stiffness.[44]

In addition to the clinical picture, anti-GAD antibodies in the serum and/or CSF strongly support the diagnosis.[45]

In SPS patients, improvement is assessed on clinical findings rather than anti-GAD titres.[27,48] Electromyography (EMG) demonstrates continuous involuntary motor unit activity with normal morphology, affecting the paraspinal muscles most. Myotonic potentials are not present on the EMG. The motor activity subsides with sleep and is attenuated with benzodiazepines (diazepam).[49]

Treatment of SPS

As noted, decreased GAD activity reduces GABA levels and raises levels of glutamate, a disequilibrium that causes muscle rigidity. Diazepam is commonly used in high dosages as the first-line treatment for SPS.[50] Other GABA derivates such as baclofen and valproate have been reported to be effective adjuvants in treating some patients.[19] Other treatment options include immunomodulatory agents and plasmapheresis.[51-54]

With regard to immunomodulatory treatment, Dalakas *et al.*[53] conducted one of the pioneering studies on the use of intravenous immunoglobulin in SPS. The study had a randomised, double-blind, placebo-controlled cross-over design and investigated treatment with intravenous immunoglobulin G (IVIg) in 16 patients with SPS. The treatment resulted in a statistically significant improvement in stiffness. In our case (reported below), the improved clinical outcome obtained was very similar, where objective data were obtained

through reproducible instruments that measured the stiffness and sensitivity to stimuli that triggered spasms.[53]

Management of patients with SPS should be a collaboration between neurologists and psychiatrists to optimally minimise the patients' suffering and disability. The predominance of psychiatric symptoms in SPS makes this a truly neuropsychiatric condition.[6]

Case report

Approval to report this case was granted by the Ethics Committee of the Faculty of Health Sciences of the University of the Free State. The patient gave written informed consent for publication and patient confidentiality was protected at all times.

We present a case of a 45-year-old black female with progressive pain and stiffness of the lower extremities which occurred over the course of 2 years. She originally came from Maseru in Lesotho, a small country neighbouring South Africa. Her condition started after her husband had passed away. She was a member of the police force and had to stop working due to her illness. She consulted several healthcare professionals in her home country, but she continued to deteriorate and eventually had difficulty walking and worsening stiffness of the muscles of her trunk and back.

Initial management was symptomatic until she was referred to hospital for further management. A preliminary diagnosis of spinal cord tuberculosis (TB) was made and she was started on TB treatment. After one month of treatment in her home country, she had not improved and was referred to the Department of Neurology at Universitas Academic Hospital in Bloemfontein, South Africa, approximately 130 km from Lesotho.

On arrival, her condition had deteriorated even further. She was unable to walk and developed urinary retention and chronic constipation. The upper limbs were spared, but she reported painful muscle spasms in her lower limbs. Clinical examination revealed normal systemic findings. On neurological examination, her mental status evaluation demonstrated normal cognitive functions, although she showed signs and symptoms of depression and became tearful when she talked about her late husband.

She had no cranial nerve fallout. On motor system evaluation, however, the patient was found to be severely stiff when lying on her abdomen, with axial rigidity and spasticity in the lower limbs. The power in all the extremities tested normal. The patient had normal reflexes with absent ankle reflexes. Flexor plantar responses were present. Sensory and cerebellar examinations were normal. During hospitalisation, it was noted that the patient also experienced intermittent spasms which would flare up in response to stressful stimuli. She also experienced brisk jerk movements followed by tonic movements when startled. When asked to count to three and sit up on the third count she was able to do so, but could not otherwise perform this movement due to abdominal and paraspinal spasms. After careful consideration, taking into account the history and clinical examination, the differential diagnosis included spastic paraparesis and its subset of differential diagnosis, SPS and conversion disorder.

Routine blood tests yielded normal results. Tests for the human T-lymphotropic virus types 1 and 2 were negative. The patient's vitamin B_{12} and red cell folate levels were normal. She tested negative for HIV and syphilis. The patient had a positive antinuclear antibody test with a titre of 320 and positive antiparietal cell antibodies with a titre of 160. Magnetic resonance imaging of the spine showed no abnormalities. A lumbar puncture was attempted on several occasions, but could not be performed successfully due to the patient's severe paraspinal muscle rigidity. At that stage the patient had already been started on GABA-ergic medication and the EMG recorded normal motor units. The GABA-ergic medications were prescribed to combat the severe axial rigidity and spasticity in the lower limbs. She was put on baclofen, a derivative of GABA, to which she showed a mild clinical response. The baclofen was increased weekly over a 2-week period to a maximum dose of 25 mg 8-hourly.

The inconsistent clinical findings associated with a psychological stressor and the presence of depression prompted psychiatric consultation, with a preliminary diagnosis of conversion disorder and comorbid major depression. The patient was put on a selective serotonin reuptake inhibitor and received psychotherapy.

During her fourth week in hospital, her serum anti-GAD result returned positive with an anti-GAD65 titre of >100. A diagnosis of SPS was made and oral diazepam was added to her treatment. The dose was increased weekly over a 4-week period to 10 mg 8-hourly. During the fifth week, valproic acid was added at 300 mg 12-hourly, to which she responded to some extent. She was able to lie on her back and had improved mobility of her limbs.

Also during the fifth week of hospitalisation, the patient was given a five-day course of intravenous Polygam (IVIg; National Bioproducts Institute, Pinetown, South Africa). The decision to add IVIg was based on her limited clinical response to the treatment given to date, and on studies reporting the efficacy of intravenous administration of immunoglobulin.[54-57] During the following week, she had fewer spasms and was able to sit up on her own. She continued improving in the following 2 weeks, being able to transfer from her bed to a chair and eventually to walk with a walking frame after another 3 weeks. She regained bowel and bladder control and was discharged from hospital.

The patient was followed up one month after her discharge and received a single dose of 0.4 g/kg Polygam administered over 24 hours. After 10 weeks, she was able to mobilise on her own without a walking aid and became completely independent. She received a second dose of Polygam at 14 weeks follow-up.

The administration of immunoglobulin therapy had led to the patient's improvement with less reported stiffness. She could mobilise indoors without using any aid and could perform her household activities for the first time in several years. During her 9-month follow-up consultation, she reported that she continued to mobilise independently at home. Her anti-GAD titres were repeated and were found to still be elevated, with an anti-GAD65 titre >100. Her condition improved with each follow-up visit.

Conclusion

SPS is a rare disorder and may present with co-existing psychiatric symptoms. Although rare, SPS should always be included in the differential diagnosis for patients presenting with a psychogenic movement disorder.

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