Stiff-Person Syndrome

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Definition of Disease

Stiff-person syndrome (SPS) is a rare, poorly understood disorder that affects the central nervous system (CNS) inhibitory mechanisms. The disorder is presumed to be primarily autoimmune in nature. Classical SPS patients present with progressive axial muscle rigidity, which can lead to skeletal deformities and superimposed painful axial and sometimes leg spasms. However, there is a spectrum of symptoms and severity. On one end of the spectrum, the disease has an insidious onset and affects limited muscles (axial or limb muscles), and on the other end, SPS has an acute or subacute onset with diffuse central nervous involvement causing encephalomyelitis, seizures, and myoclonus. Patients commonly have type I diabetes (up to 30%) or other autoimmune diseases such as pernicious anemia, vitiligo, and autoimmune thyroid disease. They frequently carry the DQB1∗0201 allele [1].

The disease was first reported in the literature in 1956 when Moersch and Woltman described 14 patients with a syndrome of progressive fluctuating muscular rigidity and spasm, which they called "stiff-man syndrome" [2]. Four years later, Bowler reported the syndrome in a 7-year-old boy [3]. In 1963, Howard described the dramatic therapeutic benefit of diazepam and suggested a disease pathogenesis involving impaired function of GABA-ergic neurons [4]. The dramatic response to diazepam, which was then confirmed by others, led to inclusion of diazepam response in the stiff-man syndrome criteria [5].

In 1991, Jankovic used the term "stiff-person syndrome" to draw attention to its frequent occurrence in women [6]. Since then, the definition of disease has evolved, and the term stiff-person syndrome spectrum disorders (SPSSD) is now suggested as more appropriate [7].

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The autoimmune nature of the syndrome was suggested in 1988, when a middle-aged woman with grand mal seizures, facial vasomotor phenomena, and painful permanent contractures of the lumbar muscles that caused marked hyperlordosis developed acute-onset insulin-dependent diabetes mellitus. The latter condition suggested an autoimmune pathogenesis, and the patient was found to have autoantibodies to glutamic acid decarboxylase [8]. Two years later, the same authors analyzed the serum of 32 patients with SPS and found autoantibodies to GABA-ergic neurons in 20 patients [9].

Currently, there are three main antibodies associated with stiff-person syndrome: glutamic acid decarboxylase antibodies (GAD65-ab), α(alpha)1-subunit of the glycine receptor antibodies (GlyR-ab), and amphiphysin antibodies. The latter, although rare, are important because of their association with cancer. One can categorize patients either by the clinical phenotype or by the associated antibodies. Using the clinical phenotype, SPSSD can be divided into three subgroups:

1. *Classic SPS*: rigidity in paraspinal and abdominal muscles, sometimes involving proximal limbs, in association with superimposed muscle spasms, resulting in abnormal axial posture
2. *Stiff-limb syndrome (SLS)*: affecting one or more limbs with distal rigidity and abnormal posturing of hands or feet
3. *SPS-plus*, including patients with all or some elements of progressive encephalomyelitis with rigidity and myoclonus (PERM): brainstem dysfunction, myoclonus, upper or lower motor neuron symptoms, sensory deficits, sphincter or autonomic dysfunction, seizures, and cognitive changes or SPS or SLS in association with cerebellar ataxia, epilepsy, or limbic encephalitis.

When using antibodies to qualify the disorder, patients can be divided into four groups: GAD65-abs, GlyR-abs, amphiphysin antibodies, and antibody-negative. This

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immunological characterization appears to be a better predictor of outcome than the clinical phenotype [7].

Pathophysiology of Disease

The hallmark of SPSSD is the dysfunction of central inhibitory mechanisms. This is caused, at least in part, by autoantibodies directed against either pre- or postsynaptic components of inhibitory synapses. The role of antibodies is not fully understood; however, there is gathering evidence of a direct effect. For instance, GAD65-abs appear to limit the synthesis of L-glutamate to γ(gamma)-aminobutyric acid (GABA), which can lead to the depletion of GABA, the major inhibitory neurotransmitter in the CNS [10]. GlyR-abs are believed to disrupt the normal inhibitory glycinergic mechanism [11]. Gephyrin-abs are directed against a cytosolic protein present at the postsynaptic membrane of inhibitory synapses and associated with GABA(A) and glycine receptors [12]. Amphiphysin supports endocytosis at synapses, which regulates the density of GABA-A receptors at the axon membrane. Amphiphysin antibodies are thought to interfere with the expression of GABA-A receptors causing the rigidity seen in SPS [13].

Central Nervous System/Peripheral Nervous System Syndromes

Classic Stiff-Person Syndrome

SPS is a rare disease. It is estimated to have a prevalence of 1 per one million individuals. Women are more affected than men [7, 14]. Patients can present at any age, though most commonly it affects people in the fifth decade [7, 14, 15]. Patients with classic stiff-person syndrome present with progressive muscular rigidity affecting axial muscles with superimposed episodes of spasms. The symptoms can progress over months to years and then stabilize. The rigidity frequently involves the proximal leg muscles but also may spread to the arms, face, and bulbar muscles. The rigidity is caused by continuous contraction of agonist and antagonist muscles. This continuous contraction frequently leads to skeletal deformities and patients typically have exaggerated lumbar lordosis and board-like appearance. The rigidity will cause limitation of forward flexion. Affected muscles feel very rigid and tender to touch. This muscle rigidity may fluctuate. Walking becomes slow and unsteady. Some patients will need assistance walking, ranging from using a cane to a wheelchair, causing significant disability and depression.

The spasms are superimposed on the rigid muscles. They resemble myoclonic jerks and may last a few seconds to several minutes. They frequently cause significant pain. These spasms can lead to frequent falls, and because of the severe rigidity, patients may appear to be falling like a log or statue. Occasionally, the frequency and severity of the spasms may result in apnea, necessitating respiratory support. Spasms can be spontaneous or precipitated by auditory stimuli such as loud noise, unexpected tactile stimuli, or strong emotions such as anger or fear. This may lead to misdiagnosing patients as being hysterical. Recurring spasms can lead to phobia and depression. Some patients may have pronounced sympathetic autonomic stimulation leading to increased temperature, sweating, pupil dilation, increased heart and respiration rate, and increased blood pressure. Sudden death has rarely been reported in SPS.

The examination of patients with SPS will reveal a pronounced lumbar lordosis and slow, effortful, unsteady gait. When asked to bend forward, the patients will have significant restriction. One may notice masked facies. Vitiligo may be observed on examination of the skin. An exaggerated startle response to acoustic or tactile stimulation may be noted. Careful examination of eye movements may reveal nystagmus, ocular misalignment, limited eye movements, deficient smooth pursuit, and impaired saccade initiation [16, 17]. Affected muscles may feel rock-hard to touch, and tone may be increased. There is no cogwheel rigidity or spasticity. Tendon reflexes are normal or mildly brisk, but typically there is no spread, Hoffman's or Babinski sign, or brisk jaw jerk. There are no abnormal movements. Muscle strength is normal despite occasional complaints of subjective weakness.

Focal or Segmental Stiff-Person Syndrome

Patients with focal or segmental SPS were initially thought to have stiff-leg syndrome [18]. In their original case series, Brown et al. reported four patients with stiffness and painful spasms of the legs. The onset was asymmetric. Spasms induced jerking of the foot and resulted in falls. In general, there was no associated truncal rigidity or hyperlordosis. Patients showed rigidity of the affected muscles as well as abnormal posturing. No pyramidal or extrapyramidal signs were noted. Strength was normal.

Patients with focal or segmental SPS have a relapsing and remitting course and may develop symptoms or signs of brainstem involvement and sphincter dysfunction. They have greater degree of disability than those with SPS [19]. The electrophysiology, imaging, and laboratory testing are similar to those with SPS. However, the incidence of GAD-ab-negative patients is greater, and patients are more refractory to treatment [19].

Stiff-Person Syndrome Plus

This group of patients presents with some or all the elements of progressive encephalomyelitis with rigidity and myoclonus (PERM): brainstem dysfunction, respiratory failure, ophthalmoparesis, ptosis, myoclonus, upper or lower motor neuron symptoms, sensory deficits, sphincter or autonomic dysfunction, seizures, hallucinations, and cognitive changes**.** Another subset of patients with SPS plus are those with SPS and cerebellar ataxia, dysarthria, and oculomotor dysfunction [20].

A cerebrospinal fluid (CSF) pleocytosis is frequently observed. Most of these patients will have GlyR-ab in the serum and sometimes in the CSF. Some will also have GAD-abs or amphiphysin-abs. Untreated, the prognosis is guarded, but with adequate immunosuppression, patients can do well [7, 21].

Laboratory Features

On lab testing, there may be evidence of autoimmunity such as positive antinuclear antibodies (ANA), anti-islet cell, thyroid microsomal, gastric parietal cell, and smooth muscle antibodies [19]. An elevation of the muscle enzymes can be observed, especially following severe spasms. The CSF may show a mild elevation in cell numbers or protein concentration [15]. Oligocolonal bands are commonly present [15, 19].

Antibody Testing

GAD65 are present in about 60–80% of patients in both serum and CSF [7, 14]. Although GAD-ab may be seen in patients with type I diabetes mellitus (T1DM), the titers are 100-fold higher in patients with SPSSD. Elevated titers of GAD-ab are associated with other neurological syndromes besides SPSSD [22].

The demonstration of a high titer of GAD-ab in the serum ($\geq$ 2000 U/ml by RIA) or GAD pattern on immunohistochemistry is a critical feature in making the diagnosis of SPSSD [23]. A positive CSF GAD-ab will confirm intrathecal production. Using epitope recognition can help differentiate GAD-ab related to T1DM versus SPSSD.

One study observed that patients with glutamic acid decarboxylase antibodies carry a worse prognosis than patients with glycine receptor antibodies or patients who tested negative for antibodies [7]. Those with GAD65 antibodies are more likely to be female and have systemic autoimmune or endocrine disorders.

Antibodies to the α(alpha)1-subunit of the glycine receptor (GlyR) are present in 12–18% of patients with SPS [7, 24]. Patients with GlyR-abs frequently develop SPS-plus instead of classic SPS. They frequently have a CSF pleocytosis and often improve with therapy.

Antibodies to amphiphysin are present in 2–10% of patients and are frequently associated with breast or small-cell lung carcinoma [7, 14, 25, 26]. Compared to patients with GAD-ab-associated SPS, those with amphiphysin-abs are older and are more likely to have arm and neck involvement [25]. The presence of one antibody does not preclude the presence of other antibodies.

Radiological/Electrophysiological Features

Needle or surface electromyography (EMG) may show continuous motor activity in affected muscles, despite attempts to relax the muscle. Recording simultaneously from antagonist muscles, for example, the gastrocnemius and tibialis anterior muscles, will demonstrate an absence of relaxation from the antagonist muscles when activating the agonist muscles [27]. Muscle spasms can be elicited and studied using surface EMG. This may demonstrate excessive and poorly habituating activity in affected muscles [28]. H-reflexes have been used with mixed results and are difficult to interpret [27]. These can show reduced vibration-induced inhibition of the H-reflex, with normal Hmax/Mmax ratios and normal Ia reciprocal inhibition [27].

In classic SPS, imaging of the spine may demonstrate lumbar hyperlordosis. Magnetic resonance imaging (MRI) of the brain and spine does not demonstrate any unique findings in patients with SPS.

Treatment

Most patients with SPS respond to diazepam, baclofen, or both [14]. Leviracetam may offer some benefits as well. High doses are often needed to control symptoms, which may lead to the development of side effects such as sedation. When side effects of these drugs become significant or if the disease is aggressive or if the patient has SPS-plus, immunomodulatory treatment is warranted. One randomized trial supported use of immune intravenous gamma globulin (IVIG) [29]. If effective, it can be maintained for long-term use. Plasma exchange has been attempted in refractory cases with mixed results. Other immunomodulatory agents such as rituximab, azathioprine, mycophenolate mofetil, and prednisone have demonstrated limited success [7, 14, 25].

Though patients with Gly-ab may have more severe symptoms, they appear to respond better to immunomodulation than other patients [7]. Patients with amphiphysin-ab should be screened for cancer since their stiffness may be paraneoplastic in origin.

Case Vignette

A 45-year-old woman presented to the neuromuscular clinic because of difficulty walking and back spasms. Her referring physician suspected progressive lateral sclerosis. The patient recalled progressive low back pain and rigidity 1 year prior to presentation. In the past 6 months, she has been experiencing increasing difficulty bending down to pick up groceries and a slow, effortful gait. She started using a walker. In the last 2 months, she has been having severe back spasms, especially when startled. Occasionally, these back spasms have caused her to fall. She reports being recently diagnosed with T1DM following significant polydipsia and polyuria.

Her examination revealed a hyperlordosis, stiff back muscles that felt hard to touch, and rigid hip flexion and extension. Deep tendon reflexes were normal. There was no Babinski sign. There was no tremor. During examination, the patient experienced painful low back spasms during sensory testing. Electromyography revealed continuous motor units activity in the paraspinal muscles. Blood test revealed GAD-ab elevated at 1091 units/mL. Screening for cancer was negative. The patient was prescribed diazepam 5 mg, three times daily, and showed improvement in her gait and stiffness as well as reduction in spasms. She eventually increased her diazepam to 20 mg three times daily and tolerated this regimen.

Conclusion

SPSSD consists of a rare set of diseases characterized by severe muscle stiffness and rigidity with decline in function. Although poorly understood, an underlying autoimmune disorder interfering with the CNS inhibitory mechanism is likely the culprit. The spectrum ranges from a mild disease affecting focal muscles to a severe form that also includes the development of seizures and myoclonus.

GAD-abs are frequently positive, especially in classic SPS. In SPS-plus/PERM, GlyR-abs are more commonly found. Patients with amphiphysin-ab should be screened for cancer. Treatment includes the GABA agonists, especially diazepam and baclofen. Patients with SPS-plus or refractory forms of the disease should be treated with immunomodulation, especially IVIG.

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