Stiff Person Syndrome: Current and Emerging Treatments

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Abstract

Stiff Person Syndrome (SPS) is a rare autoimmune neurological disorder that causes muscle spasms and progressive muscle rigidity and stiffness. People with SPS develop antibodies that inhibit glutamic acid decarboxylase (GAD), an enzyme that helps produce the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Inhibition of GAD leads to impaired synthesis and release of GABA, which causes stiffness and spasticity. SPS primarily affects the lower extremities and axial muscles, but depending on the disease's progression or subtype, other areas such as the arms or extraocular muscles may be affected. SPS is relatively uncommon, only affecting about one in a million people. Like other autoimmune diseases, it mostly affects women. Treatment of SPS includes drugs like benzodiazepines, baclofen, and rituximab or therapies like intravenous immunoglobulin or plasma exchange. Despite advancements in diagnosis and treatment, there is still no clear protocol for treatment for SPS, and disease management remains challenging for physicians. The purpose of this research paper is to provide an overview of SPS, review current treatment guidelines, and report on novel and emerging therapies.

Overview

Epidemiology

SPS is an extremely rare disorder with a prevalence of about one in a million people.[1] Since SPS is a chronic disease, the annual number of cases is even lower. This disorder affects females almost twice as frequently as it does males, regardless of race.[1] Symptoms can start appearing as early as twenty years of age, but most commonly start when people are in their thirties and forties. Children are less likely to have SPS, only comprising about 5% of cases.[2]

Pathogenesis

SPS is an autoimmune disorder, and the pathogenesis is linked to antibodies. Patients with SPS tend to have relatively high titers of antibodies against GAD, the rate-limiting enzyme in the production of GABA.[3] GABA is an inhibitory neurotransmitter that helps regulate certain nerve signals in the body. Inhibition of GAD thus leads to impaired synthesis and release of GABA, causing disinhibition of the central nervous system which results in muscle spasms and progressive stiffness (Figure 1).[3,22]

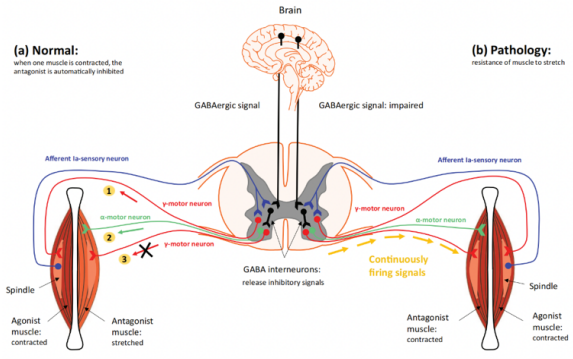

Figure 1: Pathophysiology of Stiff Person Syndrome
a) Normal function: when one muscle is contracted, its antagonist is automatically inhibited. b) Pathology: if the motor neuron is continuously firing signals, while there is no inhibition of the GABA interneuron to the antagonist muscle, the whole muscle will continuously be stimulated and will become hypertonic (spastic), without the ability to stretch (relax), due to concurrent contraction of the agonist and the antagonist muscles, as happens in stiff person syndrome that presents with stiffness and hyperexcitability.

Clinical Presentation

There are several subtypes of SPS including partial SPS, classic SPS, paraneoplastic SPS, and SPS plus. The symptoms of SPS can affect different parts of the body and vary depending on disease progression and subtype. Partial SPS only affects one specific area of the body, typically one of the lower extremities.[4] Classic SPS is the most common subtype and affects multiple parts of the body, particularly the limb and axial muscles (trunk and neck).[5] It is a progressive disorder. Paraneoplastic SPS occurs in the setting of cancer and is associated with a variety of malignancies including breast, colon, thyroid, and lung cancer. In paraneoplastic SPS, symptoms tend to occur before the clinical manifestation of the cancer itself.[6] Finally, in SPS Plus, the classic symptoms of SPS are present but there is also brainstem and cerebral dysfunction that can manifest as slurred speech and double vision, among other symptoms.[7]

Diagnosis

The diagnosis of SPS can be very difficult because the symptoms associated with the disorder can also be caused by more common diseases including Parkinson's, myelopathy, myopathy, multiple sclerosis, and tetanus. Some of the studies that physicians use to diagnose SPS may include, blood tests, electromyography (a test that is used to evaluate muscle function by measuring electrical activity), lumbar puncture, and radiological imaging. The diagnostic criteria for SPS are:

1. Stiffness in the limb and axial muscles, prominent in the abdomen and thoracolumbar region
2. Painful spasms precipitated by unexpected tactile and auditory stimuli
3. Evidence of the continuous motor unit activity in agonist and antagonist muscles demonstrated by EMG
4. Absence of other neurological impairments that could support an alternative diagnosis.
5. Presence of anti-GAD65 or anti-amphiphysin antibodies in the patients blood.
6. Clinical response to therapy with benzodiazepines.[8]

Prognosis and Complications

There are a multitude of factors that influence the prognosis of patients with SPS, including symptomatic presentation, complications, and response to treatment. Patients with SPS are at a high risk of developing joint deformities and muscle atrophies that can lead to more frequent falls.[9] As the disease progresses, SPS can also cause dysautonomia (dysfunction of the autonomic nervous system) which manifests as elevated heart rate, hypertension, and hyperthermia.[10] Since there is no cure for SPS and it is a chronic, debilitating condition, it is crucial to initiate diagnosis and treatment early to prevent long-term complications and reduce the progression of the disease.

Standard Treatments

Treatment of SPS can be broken down into two main categories: symptomatic management and disease-modifying therapy or immunotherapy. These approaches are used independently and concurrently depending on the subtype and severity of SPS.

Symptomatic management is the standard treatment approach utilized in patients when they are first diagnosed with SPS. Symptomatic management focuses on lessening the pain from the muscle spasms, the stiffness, and the rigidity of the disorder. Medications such as benzodiazepines, baclofen, gabapentin, and vigabatrin – which promote GABA's inhibitory effects in the central nervous system – are commonly employed for symptomatic management.[11] Benzodiazepines potentiate the effects of GABA by binding to the GABA receptor and increasing the frequency of chloride channel opening. The movement of chloride ions into a neuron causes it to become hyperpolarized which makes it less likely to fire an action potential leading to the inhibition of nerve impulses (Figure 2).[12,21]

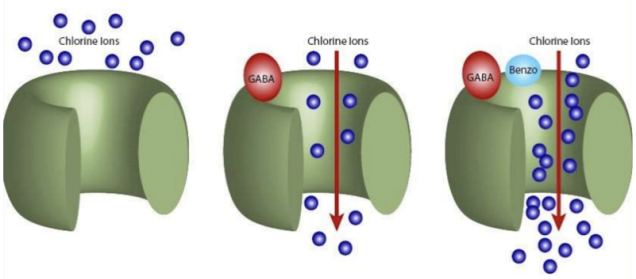

Figure 2: Mechanism of Action of Benzodiazepines
Left: No chlorine influx because GABA has not bound to receptor. **Middle:** Normal chlorine influx resulting from GABA binding to the receptor. **Right:** Increased chlorine influx resulting from both GABA and benzodiazepines binding to the receptor.

Though benzodiazepines are the first-line treatment for SPS, patients can develop tolerance to these medications causing them to become ineffective. Baclofen is a GABA agonist that directly binds to GABA receptors and inhibits the transmission of reflexes at the spinal cord, lessening the impact of muscle spasms.[11] Baclofen can be administered orally, intravenously, or intrathecally (direct injection into the cerebrospinal fluid of the spinal canal). Gabapentin binds to voltage-gated calcium channels in neurons and reduces the release of monoamine neurotransmitters thereby dampening pain responses.[13] Vigabatrin inhibits GABA degrading enzymes thereby increasing GABA levels in the nervous system. Some other muscle relaxants that are used for symptomatic management of SPS include dantrolene and tizanidine.[14] In addition, some anti-epileptic (such as Levetiracetam)[5] and antidepressant medications have been used to effectively treat SPS in patients with seizures and psychiatric comorbidities.[5]

Disease-modifying therapy is a specific type of immunotherapeutic treatment that functions by reducing or removing the antibodies present in the bloodstream. Intravenous immunoglobulin is the most effective treatment in this category that has been shown to provide clinical improvement in SPS patients for up to a year.[15] Another treatment is plasma exchange; however, this is still a newer treatment method, and its benefits are not yet fully established. Plasma exchange is the process of "cleaning" the blood by removing some of the liquid plasma which contains antibodies then returning the patient's blood with donated plasma that has no GAD-specific antibodies.

The last immunomodulatory drug that is used to help patients with SPS is Rituximab. Rituximab is a monoclonal antibody against CD20 antigen on B cells, which are responsible for producing the antibodies against GAD. Rituximab is effective because it targets and destroys B cells thereby slowing down the production of the antibodies. It

has been shown to have long-lasting benefits in nonrandomized trials.[16, 5]

Emerging Therapies

Physical Therapy

Several case reports have demonstrated the utility of physical therapy (PT) for symptomatic treatment of SPS.[17] The mean age of patients involved in these case studies was 30-60 years old. Since SPS is more prominent in females, there were more females than males in these studies. All of the case reports suggested that the condition affected the axial skeleton which includes cervical lordosis (exaggerated inward curve of the spine), thoracic kyphosis (exaggerated forward curve of the spine), and lumbar lordosis. There were also reports of a few deformities of hip, knee, and ankle musculature and joints. The most common PT interventions used in these case reports were massage, electrotherapeutic modalities, hydrotherapy, relaxation, and stretching. Balance and coordination exercises, along with flexibility exercises, were also a part of the treatment. PT was intended to treat both emotional stressors along with spasms. Length of treatment varied from two weeks to one year, where patients would have PT weekly or daily. The results of the studies were positive; goniometric measurements (joint range measurements) confirmed the improvement in range of motion outcomes when assessed for joint ranges.[17] Furthermore, muscle strength and power were also improved. Functional Independence Measure (the functional status of a patient as determined by the degree of assistance which they require) gave a clear picture of the flexibility improvement, which meant an improvement in daily activities and overall quality of life.[17]

Tacrolimus

Tacrolimus is another type of drug that could help treat the autoimmune aspect of SPS. It acts through inhibition of the calcium calcineurin (CaN) pathway and exerts its immunosuppressive effect by reducing the proliferation of activated T cells. T cells help to activate B cells leading to antibody production. Therefore, Tacrolimus is suspected to indirectly decrease GAD-65 antibody production by inhibiting T cells. In a case study by Nakane *et al.,*[18] it was used as an immunosuppressive drug in conjunction with muscle relaxants such as baclofen. The results indicated that the use of tacrolimus was successful. It was able to decrease the production of anti-GAD B cells in the patients. Since tacrolimus also inhibits CaN, it also increased hyperflexibility within the patients which helped alleviate symptoms of stiffness.

Propofol

Propofol is a widely used short-acting IV anesthetic agent. The drug increases the effect of GABA, through modulation of the GABA-A receptor.[19] Propofol is highly lipid soluble and therefore penetrates readily into the CNS. Since it has a rapid effect onset and a short half-life, it makes for a good short-term anesthetic. In a case report by Hattan *et al.,* a patient with SPS refractory to benzodiazepines was given IV propofol, which resulted in spasm relief and the ability to properly walk again.[19] Since SPS patients commonly develop tolerance to benzodiazepines, propofol may be useful in providing immediate relief of spasms until a longer-lasting therapy (such as an

intrathecal baclofen pump) is implemented.

Autologous-Haematopoietic Stem Cell Transplantation

Autologous-hematopoietic stem cell transplantation (auto-HSCT) is an immunotherapy given to patients with SPS. Auto-HSCT involves the replacement of a patient's bone marrow with that of a healthy donor, thereby replacing the dysfunctional immune system of the patient with a healthy immune system. In a study by Kass-Iliyya *et. al.*, four patients with SPS were treated with auto-HSCT because conventional immunotherapies were ineffective in the management of their condition.[20] The results of the study showed that all patients improved symptomatically, allowing them to terminate all forms of immunosuppressive therapy. Two of the patients were also able to get out of a wheelchair, and another increased their walking distance from 300 meters to 5 miles.[20] Two patients even became seronegative for anti-GAD antibodies and normalized their neurophysiological abnormalities.[20] The results of the study suggest auto-HSCT may be useful in the management of patients with SPS refractory to standard therapies.

Discussion

The treatments of SPS yield different results in different people. The more conventional treatments have shown efficacy in clinical studies, however, even those are not 100% effective. Some of the newer treatments seem to be effective in many patients. For example, auto-HSCT is an alternative for patients who cannot use other immunotherapies that are more conventional. Unlike plasma exchange, where the benefits have not been fully established, auto-HSCT has had tangible results in helping patients even more than the other immunotherapies that currently exist. Additionally, the integration of physical therapy as a regular part of treatment helps patients with their mobility and has shown efficacy in several case reports. Furthermore, propofol can be useful as a therapeutic bridge when changing symptomatic treatments. For example, if patients need to switch to a different form of treatment but cannot immediately, propofol can provide temporary relief of pain.

Conclusion

Stiff Person Syndrome is an autoimmune disorder that causes muscle spasms and contractions in different areas of the body. Currently, there are many different treatments to reduce its symptoms and several therapies that attempt to mitigate its autoimmune effects. In addition, there are several case reports that suggest that some newer treatments may work better than the presently established ones. However, there still is no cure for SPS. Since it is a rare disorder, there are not many clinical trials investigating treatments or cures for this debilitating disease. Additionally, it is a variable disease meaning that different patients may respond to different treatments quite differently, making it difficult to find a cure that works for all patients. Continuing to research SPS and synthesizing information from clinical trials and case reports is key to helping find a cure for SPS.

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