Stiff Person Syndrome Questions and Answers For Medical Professionals

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What are the most important symptoms and lab tests to strongly suggest a diagnosis of Stiff Person Syndrome (SPS)?

The most common symptoms of SPS, as reflected in the disease name, are skeletal muscle stiffness. The most common presentation is onset over weeks to months of stiffness in the muscles of the trunk and in thigh muscles, which can also go into spasms (muscle cramping). These symptoms vary in severity, but can be debilitating in many, with associated difficulty walking and falls related to stiffness. An exaggerated startle response is also commonly observed, and patients with SPS can have spasms and falls induced by startle. Less common are focal presentations of stiff person syndrome, which can manifest as stiffness and spasms of a more limited area of the body, most typically a single lower limb or both lower limbs. Also, within the spectrum of stiff person syndrome is a very rare, but more diffuse disorder, called progressive encephalomyelitis with rigidity and myoclonus (PERM) in which the typical features of SPS are present in addition to other severe symptoms of brainstem and autonomic dysfunction and myoclonus.

Clinical recognition is key. SPS must be distinguished from more common disorders such as chronic low back pain, and primary pain disorders such as fibromyalgia. Electrophysiological testing can be helpful in the diagnosis of SPS, including the presence of an exaggerated startle response, and impaired relaxation of muscles manifested as continuous motor unit activity during needle electromyography and co-contraction of agonist-antagonist muscle groups. Laboratory testing which can be extremely useful include testing for known antibodies linked to stiff person syndrome spectrum disorders, most commonly GAD65 antibodies or glycine receptor antibodies (although other antibodies can be linked to SPS as outlined below).

What is the meaning of the GAD65 antibody? Is a positive GAD65 antibody always abnormal?

Glutamic acid decarboxylase (GAD) is an intracellular antigen that is present in presynaptic nerve terminals in the central nervous system, and is important in the formation of gamma-amino-butyric acid (GABA) which is an inhibitory neurotransmitter. (65 refers to the kilodalton molecular weight of this specific subtype of GAD.) GAD65 positivity does not necessarily mean a patient has SPS. GAD65 positivity can be detected in the general population (5-8%--although generally low titer when it is present) and is also linked to other disorders such as Type 1 diabetes mellitus and to other neurological conditions such as cerebellar ataxia, epilepsy, and limbic encephalitis. As a general rule, higher levels of GAD65 antibody (> 20 nmol/L) are more likely to be linked to autoimmune neurological disease. GAD65 antibody levels also tend to be higher in patients with classical SPS than in more limited forms of the disease.

Are there other lab tests including other antibody tests that are closely linked with SPS?

While GAD65 antibodies are the most common autoantibodies detected in SPS, glycine receptor antibodies can also be seen in SPS (and particularly common in PERM). Amphiphysin, Dipeptidyl-Peptidase-Like Protein-6 (DPPX), and gephyrin antibodies have also been linked to some patients with disorders within the SPS spectrum but these are much less common. It is also important to note that some patients will not have any of these antibodies detected, with one large retrospective case series showing approximately 1/3 of cases of stiff person spectrum disorders were antibody negative.

Is there a genetic component to SPS?

Autoimmunity, particularly type 1 diabetes mellitus and thyroid disease, is common among GAD65 autoimmune SPS patients and their family members. Certain immunogenetic background appears predictive of autoimmune SPS. There is a particular susceptibility allele, DQB1*0201, a genetic variant, which is common in patients with SPS and GAD65 antibody, but its presence does not mean someone has or will develop SPS, and as such, is not routinely tested for in SPS or suspected SPS. It is possible that over time, there may be evidence of other genetic variants which may increase susceptibility to development of disease. But SPS is not a disease that is passed down from parent to child.

What would you like primary care providers and general neurologists to do for a patient suspected of having SPS prior to referral to an expert?

It is helpful to have a full careful medical and neurological history and examination. Coexisting autoimmune disease (e.g. type 1 diabetes mellitus or autoimmune thyroid disease) is common in SPS patients, and can help raise suspicion for this diagnosis. If the findings raise suspicion for a spinal cord disease, MRI imaging of the spinal cord to look for mimicking disease may be of utility, as well as blood test or spinal fluid screening for other causes of spinal cord disease. Antibody testing can be extremely helpful as part of the overall evaluation, as high titers of a relevant antibody may be important diagnostically. It is also important to note that sometimes patients are antibody positive in both serum and cerebrospinal fluid, but not in all cases, so paired serum and CSF sampling can often be informative. Electrophysiological testing, as described above, can be useful, but because of the rarity of SPS spectrum disorders, should best be performed by practitioners experienced with this disease process.

What are some of the conditions that can be confused with SPS, causing a delay in diagnosis?

There are several disorders that can be confused with stiff person syndrome. Parkinson's disease or other parkinsonian syndromes are sometimes considered in these cases, because of muscle stiffness and falls. Because patients with SPS can have hyperreflexia, primary diseases of the spinal cord are sometimes considered, as well as upper motor neuron syndromes such as primary lateral sclerosis. Hereditary spastic paraparesis is sometimes suspected in the context of hyperreflexia and significant lower extremity predominant symptoms. A more rapid onset of symptoms of muscle stiffness and spasms should raise greater suspicion for SPS. Sometimes musculoskeletal injuries can present with similar symptoms, but absence of temporal relationship to trauma would argue against it. Sometimes SPS can be misdiagnosed as a functional disorder, particularly when anxiety accompanies SPS symptoms. Musculoskeletal back pain and fibromyalgia are other diagnostic considerations.

H**ow do you approach treatment for a patient newly diagnosed with SPS?**

There are different strategies for management of patients with SPS, and the approach is individualized based upon severity of symptoms, tolerance of medications, and comorbidities which may affect treatment options. Symptomatic management is very important in patients with SPS. Patients usually have a significant response to benzodiazepines, with diazepam very commonly used with good effect. Another option for symptomatic treatment is oral baclofen. Some patients with mild disease or disease extremely well controlled with benzodiazepines or baclofen are treated with those alone.

Treatments that modify the immune system are often necessary for good control, with good data for the use of intravenous immunoglobulin (IVIG), and some patients are also tried on corticosteroid medications and/or plasma exchange. In severe disease which is not well-responsive to the aforementioned strategies, rituximab or cyclophosphamide can be considered to improve control of disease. There are multiple other agents which are slower acting, but can be helpful in maintaining a remission from disease symptoms, including azathioprine or mycophenolate mofetil. It is important to note that none of these strategies for treatment of SPS are side effect-free and treatment plans always need to balance symptom control with side effect burden for the greatest improvement of function and quality of life for the patient.

In addition to approaches directly targeting the disease, it is important that attention is paid to safety issues and function in activities of daily living, for instance physical therapy and occupational therapy assistance can be crucial to reduce risk of falls and improve safety in the home and/or workplace.

What is the recent thinking about stem cell transplants for SPS?

There is increasing interest in the use of hematopoietic stem cell transplantation (HSCT) for patients with stiff person syndrome who are refractory to standard treatments for this disease, with several reports of patients with a good response to HSCT. A recently reported trial of 23 patients with SPS receiving HSCT showed a response in 74% of the patients, with 47% of the responders staying in remission over a mean 3.5 year period (Burt RK et al. Neurology, 2020). Responders were more likely to have GAD65 antibody positivity in the CSF, normal reflexes, and intermittent muscle spasms, while nonresponders were more likely to have "lead pipe rigidity," EMG evidence of simultaneous contraction of agonist/antagonist limb muscles. Outcomes were also noted to be worse in patients using SSRI or SNRI medications prior to the stem cell transplant. There is much work to be done to determine the appropriate role of HSCT in the treatment of SPS, which can be difficult because the rarity of the disease limits the ability for large scale trials, and outcomes can be harder to measure given the subjective nature of many of the symptoms of SPS. Particularly given the potential risks of HSCT, it will be important to clarify which patients will be able to achieve a sustained response from this treatment. At present, this treatment strategy is generally reserved for patients with severe disease who are poorly responsive to standard medical care.

Since SPS is a very rare illness, what would you like to see happen to improve our understanding of SPS and to develop more effective therapies?

We would like for more sensitive and specific (and accessible) autoimmune and electrophysiologic biomarkers to be developed and become available for clinical practice to improve early recognition and hence the potential for early treatment. We would favor pathophysiologic studies to identify immune biomarkers predictive of treatment responses to a suite of immune and symptom-directed therapies. We would like for regenerative medicine to develop paradigms for healing of injured interneuronal pathways. We would like to see development of SPS-specific rehabilitative programs.

Links:

Sharing Mayo Clinic: Diagnosed with stiff-person syndrome - Mayo Clinic News Network
April 14, 2019
Story of Dr. Tara Zier, founder of The SPSRF
https://newsnetwork.mayoclinic.org/discussion/sharing-mayo-clinic-diagnosed-with-stiff-person-syndrome/

Mayo Clinic Center for Multiple Sclerosis and Autoimmune Neurology
https://www.mayo.edu/research/centers-programs/center-multiple-sclerosis-autoimmune-neurology/about/center-leadership?_ga=2.138551856.2029153769.1638057117-640834309.1638057117

Mayo Clinic Autoimmune Neurology program
https://www.mayoclinic.org/medical-professionals/neurology-neurosurgery/news/autoimmune-neurology-evolving-care-for-immune-inflammatory-diseases-of-the-cns/mqc-20480947?_ga=2.177332646.2029153769.1638057117-640834309.1638057117