Diagnosing the elusive stiff-person syndrome

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Introduction

Stiff-person syndrome (SPS) is a rare neurological disorder involving episodic spasms often preceded by sudden stimuli, progressive stiffness of the limbs and trunk, and axial rigidity. Diagnosis of stiff person syndrome can be elusive due to the fact that patients tend to present with non-specific muscle complaints of stiffness, spasms and cramps. These symptoms have a large differential diagnosis, including infectious, toxic, neoplastic, vascular, genetic and autoimmune, and often other diagnoses are considered before stiff-person syndrome. Additionally, the stimuli-induced spasms, social phobia and anxiety experienced by these patients can expand the differential to include psychogenic movement disorders. SPS causes significant disability and in many cases symptom relief can be achieved with treatment. As such, it is important to recognize possible cases of SPS and conduct the appropriate tests for diagnosis. Below is a case report exemplifying an approach to diagnosis of SPS.

Case report

A 66-year-old woman was admitted to the internal medicine service after an 18-month history of complaints of worsening stiffness affecting her lower extremities associated with pain. While the symptoms had started off mild, the patient rapidly progressed to requiring a walker for safe ambulation. The patient's primary caregiver, her son, confirmed this history. Her son also stated that the patient was extremely fearful to attempt walking even when the symptoms were initially mild. The patient denied any symptoms affecting the trunk or her upper extremities. She denied any tremor, apart from that which occurred in the lower extremities upon standing. There were no complaints of autonomic dysfunction. Her speech was normal. By the time she arrived at the hospital, she was no longer able to ambulate even with a walker.

Her past history was positive for a history of anxiety, chronic depression and auditory hallucinations, for which she was followed by the psychiatry service. Other health conditions included hypothyroidism, gastroesophageal reflux (GERD) and osteoporosis. The patient had been treated for her anxiety and depression with a combination of alprazolam 0.5mg three times daily, citalopram 30 mg daily, and risperidone 0.5 mg daily for approximately one year. Other medications included rabeprazole, resiredonate, and levothyroxine.

Because of the neuroleptic exposure (risperidone), the initial thought at admission was that the symptoms might be secondary to neuroleptic malignant syndrome. However, the psychiatry service saw the patient in consultation and felt that the lack of autonomic symptoms, focality of symptoms and lack of delirium argued against such a diagnosis. The patient did have an MRI of the head and spine performed which was unremarkable. Concerns were also raised as to whether or not the patient might be suffering from drug-induced parkinsonism because of the exposure to risperidone. The neurology service was subsequently consulted for a diagnostic opinion.

When examined by the neurology service, the patient was oriented to time and place, and scored 30/30 on the MMSE. She was noted to have full extra-ocular eye movements, but her pursuit movements were very saccadic in nature. The remainder of her cranial nerve examination was unremarkable. There was no evidence of tremor in the extremities at rest or with action. She was noted to be mildly bradykinetic in the upper extremities, but power was fully preserved. There was mild rigidity in the upper extremities on passive movement. In the lower extremities, the limbs were held in rigid extension, such that it was almost impossible to passively move the lower extremities. Her toes bilaterally were held in continual extension. Her sensory examination was unremarkable to pinprick, and only demonstrated elevated vibratory thresholds at the great toes bilaterally. Her reflexes were 2+ in the upper extremities, 3+ at the knees and absent at the ankles bilaterally. There was no evidence of ataxia. Her gait could not be assessed.

After reviewing this woman, it was felt that stiff-person Syndrome could be the underlying diagnosis. Anti-GAD antibodies were obtained and were positive, supporting the clinical diagnosis of SPS. The patient was subsequently started on treatment with diazepam and backofen achieving a dose of 15mg four times daily and 25mg three times daily, respectively. The patient noted a reduction in lower extremity tone and has been able to resume ambulation with a walker. The mobility in her legs has progressively improved while her pain has largely resolved with her current medical treatment.

Discussion

Clinical manifestations

Stiff-person syndrome (SPS) is a rare neurological disorder, affecting the neuromuscular junction in a progressive manner, and has a spectrum of clinical presentations. Several forms of SPS exist; the most common is classic SPS, involving auto-antibodies to glutamic acid decarboxylase (GAD). SPS, however, is a clinical diagnosis and thus the presence of GAD+ auto-antibodies is not a requisite for diagnosis. The classic form of SPS affects twice as many women as men and generally presents in the forth to sixth decades of life. The onset is typically insidious, but progressive in nature. In the early stages of GAD+ SPS, patients
often present with lumbar lordosis and painful muscle spasms induced by stimuli, such as sudden noise, stress or touch.2,5,6 These spasms can cause falls and patients often experience fear of crossing the street and open spaces.7 It is currently unknown if the anxiety and phobias associated with SPS are caused by the pathogenesis or in response to the symptoms.2 SPS can become debilitating, with up to 65% of patients unable to perform routine daily activities due to symptoms of total-body stiffness, fear of falling and anxiety-triggered spasms.2 Depending on the severity of symptoms or possibly failure of treatment, some patients require walkers or wheelchairs and may even become bedridden.2,5

Pathophysiology

In classic SPS, the majority of cases are associated with auto-antibodies against glutamic acid decarboxylase (GAD).1,2 The GAD enzyme is involved with the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) from the excitatory neurotransmitter precursor, glutamate.4 Antibodies against GAD prevent this conversion, thus dampening the GABAergic inhibitor pathway and causing accumulation of glutamate.6 It is proposed that the muscular symptoms of stiffness and spasms result from the auto-antibodies affecting interneurons in the spinal gray matter and intracortical inhibitory neurons.2,6

Glutamic acid decarboxylase is most abundantly present pre-synaptically in the CNS, but is also present in pancreatic β cells.2,6 Interestingly, SPS is highly associated with autoimmune type 1 diabetes mellitus.2,6 In fact, the majority of patients diagnosed with SPS either have diabetes or will subsequently develop it.2 While many diabetics have auto-antibodies against GAD, these auto-antibodies target a different epitope than in classic SPS and are present in low titres.2,6,9 Thus, the vast majority of diabetics do not develop SPS.2,9 When considering other autoimmune disorders in addition to type 1 diabetes, up to 80% of SPS patients will be affected by another autoimmune co-morbidity.6 SPS responds well to immunotherapy, further supporting the autoimmune pathogenesis of SPS.2

Treatment

There are two general strategies to treatment of SPS; the first approach is to treat the neurotransmitter imbalance directly and the second to treat the auto-antibody titres, treating the imbalance indirectly.9 In the first case, medications such as benzodiazepines and baclofen can be used to improve GABAergic inhibition.2,6,9 The doses of these medications however are limited by adverse cognitive side-effects.9 Additionally, monoaminergic inhibitors, such as clonidine and tizanidine, can also improve symptoms.6

The second approach applies particularly to GAD+ SPS patients due to the autoimmune nature of their condition. These patients may benefit from immunosuppressive therapy such as steroids and intravenous immunoglobulin (IVIg).2,6 In a randomized, cross-over study, 16 patients were treated with either placebo or IVIg for 3 months, followed by a 1-month washout period and treatment with the alternative agent for 3 months.5 Significant improvements in stiffness and heightened-sensitivity scores improved for both groups during the IVIg treatment period.5 Furthermore, a case has been reported describing significant symptom improvement using rituximab, an anti-CD20 antibody that binds mature B cells and targets them for removal.10 Plasmapheresis is another option available for treatment of antibody-related SPS.2,6 This allows direct removal of excess auto-antibodies, however the beneficial effects are short-term.2,6

Diagnosis

SPS a very rare disorder, with an estimate of 1:1,250,000 affected.6 Additionally, because its symptoms lead to a broad differential diagnosis, SPS can easily be mistaken for other disorders.2 In early stages, patients with SPS often present with reports of intermittent muscle spasm, but have a normal neurological exam.2 Additionally, if treated with diazepam, the EMG findings associated with SPS – continuous low frequency motor activity – are masked, which can further complicate the diagnosis.2,5,6,8 As the condition progresses, patients often develop phobias and anxiety.2 This psychological aspect of SPS can lead physicians to look for a psychogenic source for the problem.2,4 As such, SPS diagnosis can be elusive, but should not be forgotten in this clinical picture. While diagnosis of SPS can be made based on clinical findings, auto-antibody titres for GAD can support the diagnosis.2,6,8 Thus, although 60-80% of these patients will have serum anti-GAD antibodies, the absence of such antibodies does not rule out SPS.1

Conclusion

Stiff-person syndrome is an important diagnosis to consider when patients present with muscle stiffness, spasms and cramps.1 Patients with SPS often describe stimulus-triggered spasms and falls, and phobia of open spaces, which may lead clinicians to misdiagnose the condition as psychogenic movement disorder.2,4 However, it is crucial to test for this condition as SPS causes significant morbidity and, in most cases, can be treated to alleviate symptoms.1,2,5,6 Furthermore, SPS can present as a manifestation of an underlying neoplasm, such as breast cancer, SCLC, lung adenocarcinoma or mediastinal carcinoma, and may indicate the presence of or predisposition to diabetes.2

References

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