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Stiff Person Syndrome Overlapping with Multiple Sclerosis

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Abstract We report the apparent rare association of longstanding relapsing/remitting multiple sclerosis and stiff person syndrome. This middle-aged woman presented with truncal and lower extremities stiffness and spasm not responsive to a course of intravenous methylprednisolone or to high dose muscle relaxants. Her discomfort had progressed, over a one-month period, to being wheelchair bound and considering herself desperate for some type of relief. Of interest, she pursued the medical literature, as a registered nurse, and became convinced that she has stiff person syndrome superimposed on her multiple sclerosis which has not been previously reported. She was found to have an elevated anti-glutamic acid decarboxylase (GAD)-65 antibody titer supporting this association. She was responsive, at least over the short term, to a course of intravenous gamma globulin along with the addition of dantrolene to her regimen.

Keywords: *multiple sclerosis, stiff person syndrome, anti-glutamic acid decarboxylase (GAD) antibodies, progressive encephalomyelitis with rigidity and myoclonus (PERM)*

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1. Case Description

A 53-year-old left-handed Caucasian woman with long standing multiple sclerosis (MS), with multiple brain and cervical spine demyelinating lesions, presented to our medical center on an emergent basis. She had been stable on ocrelizumab, without functional disability, working as a registered nurse, prior to presentation. Ocrelizumab had been started within the past year and she had previously been treated with natalizumab. Her JC virus status was negative. One month prior to admission, on March 11, 2020, she began to experience progressive lower trunk and lower extremity stiffness and spasms with the left leg more involved than the right. The progressive severity interfered with her walking, and she became wheelchair bound spending much of the day in bed in agony. She was under treatment with dextroamphetamine-amphetamine 10 mg a day for fatigue, venlafaxine 75 mg a day for depression, trazodone 50 mg at bedtime to help her sleep pattern, gabapentin 300 mg three times a day for neuropathic pain as well as vitamin D and vitamin B12 supplement. Follow-up MRI scan of the entire neuro-axis, with and without contrast, showed no new lesions or contrast enhancement. Evaluation for a metabolic derangement, deficiency condition or an infectious process was negative. A previous five-day course of intravenous methylprednisolone was ineffective, and she was being continued on baclofen at 80 mg a day as well as tizanidine, a total of 16 mg a day, without response. She reported chronic fatigue, some gait instability with leg weakness, left greater than right, as well as urge bladder incontinence at times.

On examination, following admission, her general physical exam was unremarkable including normal funduscopic exam and musculoskeletal exam. No skin lesions were noted. Her mental status and speech were intact. Cranial nerve examination was remarkable for gaze-evoked nystagmus in all directions. She had good tone, strength, and dexterity in both upper extremities with no dysmetria or tremor. There was increased tone in both lower extremities, left more than right, with strength in the 4+ to 5-/5 range in the right leg and in the 4/5 range in the left leg. She had good tactile sensation throughout with no sensory level noted. Deep tendon reflexes were 3+ in both biceps, triceps, and knees with non-sustained clonus at both ankles. She was unable to ambulate without full assistance. She was started on a five-day course of intravenous gamma-globulin at 0.4 gram/kg daily along with dantrolene for possible stiff person syndrome. Testing for neuromyelitis optica (NMO) and myelin oligodendrocyte glycoprotein antibodies were negative. An autoimmune panel was sent off and this was negative except for the anti-GAD-65 antibody titer elevated at 0.18 nanomole/liter with normal $\leq$ 0.02. She reported significant improvement in her muscle spasm and stiffness during her hospital course and was able to ambulate with limited assistance at the time of discharge on March 16, 2020. She received inpatient rehabilitation therapy during

her hospital course. She has reported persistent, but much more manageable, painful muscle spasms over the several weeks following discharge and is being evaluated for treatment with rituximab. To date, there has been no clinical evidence of a paraneoplastic process. An EMG was recommended, but the patient declined over concern that it might aggravate her pain.

2. Discussion

Stiff person syndrome (SPS) is an autoimmune disorder that can be paraneoplastic disease in etiology. The typical presentation is a progressive axial and appendicular muscle stiffness and spasm. [1] High titers of anti-GAD antibodies are reported as highly specific for the SPS. [2] Our patient's titer was not markedly elevated but only approximately 70% of SPS patients are actually positive for anti-GAD antibodies while anti-amphiphysin antibodies, which were negative in our patient, are primarily positive in association with paraneoplastic SPS. [3]

The prevalence of SPS is roughly one to two cases per million making it a rare disorder. However, this might be reflective of its being misidentified as severe fibromyalgia, polymyalgia rheumatica or a chronic pain syndrome. SPS was proposed as having two primary features, truncal and proximal limb stiffness, by Dalakas. [4] He proposed diagnostic criteria which needed to be satisfied including: muscle stiffness leading to hyper-lordosis, superimposed painful muscle spasms set off by auditory or tactile stimulation, electromyography evidence of continuous motor activity in agonist and antagonist muscles, absence of an alternative neurological explanation and positive serology in support of SPS. [4] However, despite this "classic" expression, there have been variations on a theme such as isolated limb involvement termed stiff limb syndrome. A review of 23 patients with SPS identified three groups, stiff trunk (man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity and myoclonus (PERM). Sarva et al reviewed the "ample" phenotypic and serologic variations with this disorder designating it as a spectrum of manifestations [5]. This is, in part, reflective of anti-GAD-65 antibodies being found in a number of autoimmune and paraneoplastic process such as type 1 diabetes mellitus and immune checkpoint inhibitor associated with limbic encephalitis. [6]

PERM is considered an SPS variant reflective of the rare spectrum of SPS-type illnesses [7,8]. Another rare association includes an association with antibody-associated epilepsy. [9] Anti-GAD-65 antibody prevalence has been reported to be up to 70 % in SPS [2] with less than 5% in some other neurological disease as well as reports of positivity, in low titers, in the general population. [10] In a retrospective study of 56 patients with positive anti-GAD-65 antibody in serum and /or CSF with neurological manifestations, 36 patients had high Anti-GAD-65 concentrations, defined as serum concentration > 10,000 IU/mL or CSF concentration >100 IU/mL, and 20 patients had low titers. Thirty four of the 36 patients with high titers (94%) had a known neurological syndrome: 7 patients had stiff-person syndrome, 3 patients had cerebellar ataxia, 9 patients had chronic epilepsy , 9 patients had overlap syndrome ,and 9 patients had limbic encephalitis. Twelve of the 20 patients with low concentrations had a heterogeneous array of diagnoses including one with PERM.

Although the presence of anti-GAD 65 antibody and an increased risk of MS are associated with same HLA subtype HLA-DRB1*1501, [11] there does not appear to be a common coexistence of SPS and MS based upon review of the literature. In a reported case of a middle-aged woman with classical SPS, along with high anti-GAD-65 antibody titers, developed neuromyelitis optica (NMO) spectrum disorder. This was confirmed with MRI and positive aquaporin-4 (AQP-4) IgG antibody titer and was reported by Jassam. [12] Newsome et al described five patients who presented with an MS-like picture with bilateral lower extremity and axial rigidity with nonspecific white matter changes on brain MRI. Based upon the clinical course, and significant elevated anti-GAD 65 antibody titer, it was determined that these patients most likely had SPS. [13] In another potential overlap case, a middle aged male patient, with long standing MS, presented with slowly progressive bilateral upper and lower extremity weakness and stiffness as well as speech and swallowing difficulty. Based upon his progression, with elevated serum GAD-65 antibody titer, he was eventually diagnosed with PERM. [14]

There have been no randomized trials which have addressed the optimal treatment of SPS. Benzodiazepines, which our patient did not receive, are considered the first line for symptomatic therapy. Diazepam tends to be preferred, given its long half-life, with dosing up to 80 mg daily in divided doses. [15] Alternative benzodiazepines include clonazepam and lorazepam.

In a Mayo Clinic study of 193 patients with SPS, all received diazepam and reported improvement of stiffness and spasms in all patients with classical and partial SPS with a median dose of 40 mg per day. Eighteen out of 23 patients reported further improvement with adjunctive baclofen. [15] There have been also anecdotal reports of a significant response with combined gabapentin and dantrolene. [15]

For patient resistant to benzodiazepines, the use of IVIG or IV steroids is supported by some studies. Karlson et al reported three patients disabled by SPS refractory to benzodiazepines and steroid therapy who had good functional recovery after IVIG infusion. [16] However, in a recent study of six patients with SPS treated with either IVIG or intravenous steroid, no difference in clinical improvement was noted. [17] In patients with SPS refractory to standard therapies, there are reports of the B-cell depleting agent rituximab being of benefit. [2]

3. Summary

SPS is an autoimmune disease that can potentially overlap with or masquerade other immune mediated neurological disorders such as MS and NMO spectrum disorder. In our patient, despite not having documented so-called classical SPS, her clinical presentation, in association with elevated anti-GAD-65 antibody titer, highlights the possible association of SPS with an autoimmune demyelinating disorder, such as MS. Such

recognition can help guide effective treatment in what can be an intractable, severe, and disabling condition.

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Ethics/Informed Consent

Informed consent was obtained from the patient and an IRB was sought which was approved by Ochsner-LSU.

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