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CLINICAL VIGNETTE

A Serious Case of Muscle Cramps

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Case Summary

A 46-year-old male with psoriatic arthritis was seen for muscle spasm. In addition to his psoriatic arthritis he also has Grave's Disease complicated by Grave's Ophthalmopathy and hyperparathyroidism status post parathyroidectomy.

The muscle spasms started after parathyroidectomy. He initially noted dysphonia which was thought to be due to post-surgical changes. He also reported muscle spasms occurring seven to eight times per day described as "horrendous." He was advised that the spasms would resolve over time but noticed worsening. Stretching and drinking water or consuming electrolytes would help improve the muscle cramps. However, talking, coughing, sneezing, sleeping in the fetal position and brushing his teeth would trigger spasms. Anger or frustration would also trigger spasms. The cramps could be so severe that he would not be able to get out of bed. He was started on baclofen and lorazepam with some improvement but no resolution of symptoms. He denied fever, chills, night sweats, or weight loss. He denied focal weakness, numbness, or dysphagia.

Patient is originally from Hawaii and most of his relatives are from Guam. He had a twenty pack-year history of smoking. He denied any family history of neuromuscular disorders, neuropathy, or autoimmune diseases. An antinuclear antibody (ANA) test was checked and returned positive at 1:640 and he was referred to Rheumatology for evaluation of possible connective tissue disease as the cause of his muscle cramps.

On physical exam his vital signs were normal. He was able to speak in full sentences. His head and neck exam was normal except for proptosis of the eyes. There were no oral lesions. No evidence of malar rash, erythema of the neck or upper back, and there were no Gottron's Papules. Cardiopulmonary examination was within normal limits. His abdomen was without distension, tenderness, or masses. Neurological exam revealed normal cranial nerves. His muscle exam revealed increased bulk and tone especially of the upper extremities. His strength was 5 out of 5 in all muscle groups bilaterally. His gait was normal. The biceps, brachioradialis, and triceps reflexes were not elicited. His patellar reflexes were normal bilaterally, however, he had ankle clonus and bilateral up-going toes.

Given the positive ANA further serological testing was essentially negative. Infectious labs included negative hepatitis B, C, HIV, RPR, Quantiferon gold and Cocci IgM and IgG. Extensive rheumatologic testing was unrevealing including dsDNA, SSA/

SSB, Sm/RNP, C3/C4 and his antiphospholipid antibodies including anti-cardiolipin, Beta 2 Glycoprotein and DRVVT.

He was also evaluated for occult malignancy given his smoking history. CT abdomen and pelvis with intravenous (IV) revealed pancreatic atrophy and also bilateral sacroiliitis which was consistent with his psoriatic arthritis. CT chest with IV contrast revealed bronchial wall thickening and occasional calcified pulmonary nodules consistent with prior granulomatous disease.

He was referred to Neurology and given the recent parathyroidectomy surgery there was a concern for cervical spine pathology. MRI of the cervical spine revealed no significant spinal canal stenosis. The spinal cord was normal. MRI of the brain with and without contrast was normal. An EMG/NCS was unremarkable.

Initially he was treated with Lorazepam but developed extreme drowsiness so he was transitioned to clonazepam but did not notice any improvement. Given the persistence and severity of the cramping, he underwent more extensive laboratory testing which was negative for Myasthenia Gravis. However, testing revealed a positive glutamic acid decarboxylase (GAD) antibody, which given the clinical context strongly suggestive of Stiff Person Syndrome (SPS). The patient was initiated on monthly intravenous immunoglobulin (IVIG) infusions with significant improvement in symptoms, without complete resolution of spasms. Several months later he developed Type 1 Diabetes Mellitus, which is also seen in patients with anti-GAD antibodies.

Discussion

Stiff Person Syndrome (SPS) is a rare neurologic disorder that causes severe muscle stiffness which progresses to rigidity and spasms.^{1,2} Sometimes the muscle spasms can be visualized and on exam can feel rock-hard.³ The spasms are associated with pain and can lead to extreme stiffness of the truncal muscles which can also affect gait.^{1,4} One of the hallmark clinical characteristics is episodic spasms that can be precipitated by sudden movement, noise or emotional upset.^{1,4} Patients usually describe an insidious onset of stiffness, rigidity and pain in the truncal muscles which slowly progresses to the limbs.^{1,4} Extreme muscle rigidity can be present. Muscles can become hypertrophic due to persistent spasms. Sometimes the stiffness can lead to spinal deformity.¹ The stiffness can affect activities

of daily living and some patients can become so limited that they become bedridden.^{1,5}

The pathogenesis is not fully understood but is thought to be due to an imbalance between excitatory catecholamine and inhibitory GABA neurotransmitters in the brainstem and spinal cords.^{1,4} Recent studies have shown presence of antibodies against glutamic acid decarboxylase (GAD) and anti-amphiphysin in patients with SPS suggesting that it is an autoimmune disorder. The anti-GAD antibodies are commonly seen in SPS patients with other autoimmune diseases like diabetes, autoimmune thyroiditis, myasthenia gravis, vitiligo and celiac disease.¹ Anti-amphiphysin antibodies are commonly seen in the paraneoplastic variant of SPS usually associated with breast or small cell lung cancer.⁵ The true prevalence of SPS is not known.¹

The diagnosis of SPS can be difficult because it is largely based on clinical symptoms. The neurologic exam is usually normal except for abnormal gait and hyper-reflexia in patients with more severe cases. There are no specific neuroradiographic findings for this syndrome.^{1, 4} However, electromyogram (EMG) may show presence of continuous motor unit activity which decreases or resolves with intravenous diazepam.^{1,4} Antibody testing can be helpful with about 60% of patients with anti-GAD antibody positive.¹ Search for underlying malignancy is also important as paraneoplastic SPS is seen in about 10% of all patient with SPS.⁴

Once the diagnosis is established, treatment should be started as soon as possible as it helps slow the course of the disease. But it is important to note that treatment rarely achieves complete remission.⁶ GABA agonist like benzodiazepines and baclofen are helpful to decrease rigidity and muscle spasms. Significantly high doses of benzodiazepines or even intrathecal baclofen are needed for some patient.⁵ Immunotherapy should be considered in patients with severe or refractory SPS like our patient. Steroids and plasmapheresis have variable efficacy but can be helpful especially for patient with life threatening respiratory decline.¹ IVIG has shown efficacy compared to placebo with improvement in muscle spasms, mobility, frequent falls and decrease in anti-GAD titers.^{4,7} Rituximab is another immunomodulating medication that has shown benefit by decreasing the titer of anti-GAD antibodies and leading to improvement in symptoms suggesting SPS is a B cell mediated response.⁸

Because diagnosis is largely based on identification of hallmark symptoms and neurologic exam and imaging can be normal, there may be long delay before treatment is started. Prognosis is variable and some patients experience on-going disability despite treatment.⁴ SPS patients are commonly depressed due to their disability which can significantly decrease their quality of life. Greater understanding and awareness of SPS is needed for earlier diagnosis and reduce significant morbidity.¹

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