Title

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CLINICAL VIGNETTE

Myasthenia Gravis Exacerbation Potentially Triggered by Exogenous Thymus Administration

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Case Report

A 67-year-old Asian American man with left eyelid drooping for three weeks. His past medical history includes chronic pain treated with intrathecal pain pump for the past decade as well as chronic diplopia since childhood. He noted increasing difficulty keeping his left eye open which, worsened throughout the day without other vision changes besides his chronic diplopia. He denied any new or worsening muscle weakness although this was hard to assess since he has baseline chronic pain and weakness. His physical exam was notable only for mild to moderate left eye ptosis. Labs were drawn that day returned positive for Acetylcholine Receptor Modulating Antibody (AChR-Ab) but negative for MuSK Quantitative Titers Antibody. A preliminary diagnosis of Myasthenia Gravis was made and the patient returned to discuss the results. On further questioning he revealed that he had sought treatment from an outside medical group to improve his strength and conditioning in an attempt to treat his chronic pain and weakness. As part of that treatment plan, he had been given exogenous thymus peptides, thymosin beta 4 for six months with the last dose two months prior to his symptoms and thymosin alpha 1 started just before his current symptoms began. He also recalled an episode of severe head droop where he was unable to raise his head from his chest for several days and was associated with severe generalized weakness and fatigue. The symptoms occurred towards the end of his treatment with thymosin beta 4 and had never occurred previously and have not recurred since.

The patient was subsequently seen by Generally Neurology as well as a Movement Disorders specialist who confirmed the diagnosis and began treatment with oral pyrostigmine 60mg three times a day with moderate response. Current plans are for continued treatment with efgartigimod 800 mg (~10mg/kg) intravenously weekly for four weeks.

Discussion

Myasthenia gravis is an acquired autoimmune disorder involving blockade of the neuromuscular junction by acetylcholine receptor autoantibodies which arise from thymic hyperplastic germinal centers.[1,2] Diagnosis is bimodally distributed by age, more common in women in their third decade in the early distribution versus men in their sixth decade in the later wave.

Two versions of the disease result in either ocular or combined ocular and generalized weakness syndromes. Generalized is somewhat of a misnomer given patients will complain of weakness and fatigue in specific muscle groups as opposed to the whole body. Classically greater than 50% of patients will present with ocular symptoms including ptosis and diplopia while closer to 15% will present with the bulbar symptoms of fatigable chewing, dysphagia and dysarthria. Only a small percentage will present with isolated peripheral weakness.[3] The paracervical muscles are a common peripheral group which can be specifically affected in late onset myasthenia gravis. This patient likely had this acute finding which resulted in "drooped head syndrome" where the weight of the head overcomes the fatigued and weak neck extensors.[4]

Diagnosis is suspected clinically based on typical symptoms of skeletal muscle weakness which can take the form of ocular, bulbar, peripheral and in late stages respiratory muscles. Physical exam findings and maneuvers such as the ice pack test in which the degree of ptosis decreases or resolves after an ice pack is specifically applied to the eyelid can aid in diagnosis. Edrophonium has a similar affect and was previously administered via intravenous infusion but has fallen out of favor as the medication is no longer available in the United States. The diagnosis is confirmed via serum testing of Acetylcholine Receptor Modulating Antibody and MuSK Quantitative Titers Antibody.[5] Approximately 6 - 10% of patients can be seronegative but if the AChR and MusSk antibodies are undetectable LPR4 antibodies may be measured. LPR4 is associated with agrin induced activation of AChR and MuSK function.[6] Striated muscle antibodies can also offer further insight to the prognosis and cause of MG. These antibodies are highly associated with thymoma in early-onset MG but are more limited by a high false positive rate in patients over 50 years old.[7] There is a high rate of thymomas in MG especially in AChR positive patients. As such, mediastinal imaging with CT or MRI are indicated for virtually all MG patients. Given the autoimmune nature of the disease it is often warranted to check other levels including thyroid stimulating hormone, erythrocyte sedimentation rate, c-reactive protein, rheumatoid factor, anti-ccp and antinuclear antibody titers for evaluation of rheumatoid arthritis Sjogren's disease and Systemic Lupus Erythrematosus.[8]

Treatment begins with pyrostigmine, an acetylcholinesterase inhibitor, but given the autoimmune nature of the disease, most

patients will require immunomodulating medications. Typical regimens include prednisone, cyclosporine or azathioprine. Crises can be mitigated by infusion of IVIG and or plasmaphoresis.[9] Additional investigative therapies with monoclonal antibodies are also being utilized. Given the patient's advanced age and multiple comorbidities the decision was made to administer Efgartigimod which is an IgG antibody that is directed against the neonatal Fc receptor which acts to prolong circulating levels of IgG.[10] There is no clinical benefit to following antibody titers during treatment as they do not correlate with symptomatic progression or disease improvement.

The other two mainstays of treatment are avoidance of exacerbating medications and thymectomy. Multiple classes of medications including macrolides, beta blockers, aminoglycosides and magnesium sulfate can cause myasthenia gravis symptoms and exacerbations. Respiratory depressants such as muscle relaxants and opioids should be avoided or monitored due to the risk of potentiating respiratory muscle fatigue. Given acetylcholine receptor autoantibodies arise from thymic hyperplastic germinal centers, thymectomy can be indicated in patients with generalized disease.[11]

This patient's acute symptoms may have been triggered by the exogenous administration of thymic peptides. His acute episode of "head droop syndrome" came at the end of a course of thymosin beta 4 and his presenting symptoms occurred shortly after the administration of thymosin alpha 1. Thymosin beta 4 is a small peptide naturally occurring in the thymus which has been studied for its induction of angiogenesis and associated acceleration of wound healing.[12] Thymosin alpha 1 is a similar peptide which is being investigated in a variety of illness due to its role in regulating the immune response by augmenting T cell function.[13] Both are also currently being used by functional medicine and "wellness" practitioners as is the case in this patient. Thymosin alpha 1 has been implicated in myasthenia gravis for the past forty years. Studies have shown an increased expression on thymic epidermal cells of myasthenia patients and a subsequent decrease after thymectomy.[13,14] A literature review for thymosin beta and myasthenia gravis returned no published studies but given the close relation to thymosin alpha further investigation is warranted. This patient discontinued, further thymosin infusions after discovery of AChr-Ab and further diagnostic studies for autoimmune causes are planned pending response to current treatments.

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