CLINICAL VIGNETTE

Myasthenia Gravis

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Case Presentation

A 64-year-old male presented to the emergency department with two months of progressive dysphagia and dysarthria. He had difficulty swallowing solid foods and liquids as well as his secretions. Associated symptoms included fatigue, 40-pound weight loss, blurry vision with difficulty fully closing his left eye as well as mild lower extremity weakness. Review of systems was otherwise negative including for fevers, sweats, rashes. Past medical history includes: lupus erythematosus in 2014 with scalp and facial lesions, joint pain and fatigue. He was previously treated with prednisone but had not seen a physician in years due to lack of health insurance. He denied prior surgeries or relevant family history and did not take any medications. He previously smoked cigars occasionally.

Vitals signs were unremarkable. The patient communicated by writing as his speech was dysarthric and dysphonic. Cranial nerve exam was notable for left-sided ptosis and inability to raise the corners of his mouth or purse his lips. Strength was 4/5 in lower extremities and deltoids and 3/5 in neck extensors and flexors. Gait was not assessed however the remainder of the exam was unrevealing. Computerized tomography scan of the chest with contrast on admission revealed a 6.3x4.6x4.5 cm anterior mediastinal mass which was thought to be thymoma.

Neurology was consulted and a presumptive diagnosis of myasthenia gravis was made based on the clinical presentation, exam and imaging. Treatment was initiated with five days of plasmapheresis, and a biopsy of the soft tissue density was obtained while waiting for confirmatory serology. Given the patient's minimal improvement with plasmapheresis, intravenous immunoglobulin and intravenous methylprednisolone was started. Total parenteral nutrition was also initiated due to the risk of aspiration.

Serology resulted later in the admission and confirmed the diagnosis. Acetylcholine Receptor Binding Antibody was 8.4 (0.0-0.4 nmol/L). Acetylcholine Receptor Blocking Antibody was 69 (0-26%). Acetylcholine Receptor Modifying Antibody was 94 (<= 45%). MuSK Antibody was negative. The pathology from the biopsy demonstrated thymic epithelial neoplasm consistent with WHO type AB thymoma.

He was restarted on daily plasmapheresis with a plan for inpatient thymectomy given a lack of significant symptomatic improvement. After surgery, plasmapheresis was decreased to every other day and was scheduled for weekly after discharge. Pyridostigmine 60mg three times daily was started during admission. No steroids were prescribed at discharge. The patient was able to resume an oral diet and had notable improvement in his ability to speak.

Discussion

Pathophysiology/Epidemiology

Myasthenia gravis is an autoimmune neuromuscular junction disorder associated with pathogenic autoantibodies affecting the postsynaptic membrane. Subtypes are based on seropositivity and clinical presentation, and affect prognosis and treatment. Although myasthenia gravis remains a relatively rare disease, the incidence has doubled over recent decades. This in part can be explained by the increased age of our population. A meta-analysis estimated that the global prevalence of myasthenia gravis is 12.4 people per 100,000 population.[1] Another review estimated the prevalence of myasthenia gravis in the United States to be 60,000.[2]

Myasthenia gravis can affect people of all ages and genders. Most commonly it occurs between 50 and 70 years in men and has a bimodal age distribution in women, with the early-onset peak around 20 to 39 years.[2] Genetics are thought to play a role given the associations between HLA antigens and ethnic groups as well as the presence of other autoimmune diseases in patients with myasthenia gravis.[2] Other racial and ethnic associations have been reported. Ocular myasthenia gravis is more common in black men and women.[2] Environmental factors such as stressors, infections and certain medications have been proposed as triggers in those with a susceptible genotype.[2] Myasthenia gravis is associated with other autoimmune diseases, including thyroid disease to neuromyelitis optica spectrum disorder. There is also an association with inflammatory muscle disorders myocarditis and myositis.[3]

Diagnosis

Patients with myasthenia gravis present with fluctuating and fatigable weakness, typically involving the ocular, bulbar and/or proximal limb voluntary muscle groups. Weakness is often worse at the end of the day. Myasthenia gravis subtypes are classified based on disease location (ocular vs generalized), age of onset, and presence of antibodies. The most common antibody acts on the acetylcholine receptor (AChR), however,

others have been identified against muscle-specific kinase (MuSK), lipoprotein-related protein 4 (LRP4), agrin, titin, and ryanodine.[2] A 2016 review article estimated the frequencies of different subtypes. Twenty percent had early-onset generalized myasthenia, 45% had late-onset generalized myasthenia gravis, and 15% had ocular myasthenia gravis.[4]

Ocular myasthenia gravis is a less frequently seen subtype, typically presenting with ptosis and diplopia. This form tends to generalize within 2 years and is unlikely to generalize after 2 years.[5] Clinical history and characteristic exam findings are key for diagnosis. Serology is commonly used to confirm the diagnosis. Other confirmatory tests include repetitive nerve stimulation and single-fiber electromyography.[6] The tensilon test, which uses the acetylcholinesterase inhibitor edrophonium chloride to assess if there is improvement in strength, is no longer routinely used. Chest computerized tomography is also recommended to exclude thymoma as this occurs in 10-15% of patients with myasthenia gravis.[5] Approximately 30% of patients with thymomas have thymoma-associated myasthenia gravis.[4]

Treatments

Acetylcholinerase inhibitors were the first effective medications for myasthenia gravis in the 19th century and have remained a mainstay of treatment.[7] Pyridostigmine is the most commonly used drug in this category and can be increased to achieve the optimal therapeutic dose. Onset of action is 15 to 30 minutes, and its effects can last up to 4 hours. While this medication acts quickly to improve weakness, it does not affect the course of the disease.[7] Side effects include increased secretions, excess sweating, cramps and loose stools, especially at higher doses. These could be managed with glycopyrrolate, loperamide, and/or hyoscyamine. Due to the effect of increased secretions, these medications are generally not given during a crisis.[7] Additional studies are being done on anti-sense oligonucleotides and their inhibition of AChE R production.[3] Treatment specifics vary based on the subtype. For example, Anti-MuSK and ocular MG are less responsive to ACh inhibition.[7]

Immunosuppression is a key component in the treatment of myasthenia gravis, with corticosteroids being one of the first medications used. Studies show immunotherapy reduces the risk of ocular myasthenia gravis progressing to the generalized form.[7] Although steroids are highly effective for treatment, the systemic side effects associated with long-term therapy have resulted in the use of other immunosuppressants. The anti-metabolite azathioprine is widely used for myasthenia gravis with reported response rates up to 91%.[7] It is used in patients who remain symptomatic on steroids as well as those who have contraindications to or are intolerant of steroids. Azathioprine is generally well-tolerated compared to other steroid-sparing immunosuppressants however it can take up to 18 months to see a therapeutic effect.[7] A number of other agents have been evaluated for treatment. Studies on mycophenolate mofetil and methotrexate have not consistently shown a therapeutic benefit. Cyclophosphamide, cyclosporine, and tacrolimus have demonstrated efficacy. However, their use is limited by tolerability.[7] Monoclonal antibodies such as rituximab and eculizumab also have a role as escalation therapy for those with severe refractory disease.[4]

There are also rapidly-active immunotherapies, with PLEX and IVIG showing comparable efficacy in adults.[7] Indications for both therapies include current or impending myasthenic crisis, patients with worsening symptoms not responsive to other immunosuppressants, or symptomatic patients before thymectomy.[7] PLEX works by removing the pathogenic autoantibodies and cytokines. Symptoms can improve as early as the third treatment, with the effect lasting for weeks.[7] A standard regimen involves a total of 5 sessions done either daily or every other day. Of note, there is not data on chronic treatment protocols. The mechanism of action for IVIG involves immunomodulation, including decreasing antibody production.[7] IVIG can be given over 2-5 days.

Thymectomy is another component of treatment and can result in symptomatic improvement while decreasing the need for immunotherapy. Improvements can be seen as early as 3 months after surgery. Data on efficacy is lacking for patients with non-thymomatous generalized myasthenia gravis as well as those who are MuSK, LRP4, and agrin-antibody positive.

With thymomatous myasthenia gravis, the need for radiation and/or chemotherapy depends on tumor grade, excision margins, and evidence of spread.[7] Treatment should be optimized prior to surgery as weakness can worsen perioperatively.

Medications to Avoid

Medications can either induce or exacerbate myasthenia gravis. Certain drugs result in an autoimmune reaction against the neuromuscular junction. These include immune checkpoint inhibitors and tyrosine kinase inhibitors.[8] A number of medications affect neuromuscular transmission, which can exacerbate or unmask symptoms. Drugs in this category include macrolides, aminoglycosides, calcium channel blockers, class IA antiarrhythmics, and magnesium among others.[8]

Prognosis

Different studies have identified various risk factors for relapse in myasthenia gravis. Shigeaki Suzuki et al. noted an increased rate of relapse among those with anti-Kv1.4 antibodies.[9]

Lili Wang et al. found that the presence of other autoimmune diseases was more common in relapse however there was no significant difference for age, gender, thymus abnormality or symptoms at disease onset.[9]

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