CLINICAL VIGNETTE

Eye Fatigue in a Bibliophile

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A 68-year-old male with impaired fasting glucose (HbA1c 5.9) and glaucoma presented for primary care video visit with vision complaints. He reported ptosis and diplopia for the past three years. He was an avid reader and typically read at the end of the day. He also reported food "sticking" when swallowing and drooling with prolonged speaking, as well as fatigue of mastication muscles throughout dinner. He changed meals to smoothies to aid in food intake. Medications included only latanoprost eye drops. Video neurologic exam showed an alert, oriented patient, speaking in full sentences. Neurologic exam was grossly intact with normal upward eye gaze with no fatigue. At follow up one month later, repeat exam showed limited bilateral upward gaze. Horizontal eye movements appeared full, but with diplopia past midline gaze. Face was symmetric with no ptosis. Moderate dysarthria was present with mostly lingual components. His motor exam was otherwise intact.

MRI chest showed a 45 x 30 mm mass abutting the right atrial appendage consistent with a solid, heterogeneous enhancing lesion, possibly a thymoma. EMG/NCS revealed a post-synaptic neuromuscular junction transmission disorder. Labs included elevated acetylcholine receptor antibodies (AChR antibodies) at 13 nmol/L (upper end of reference range is >.5 nmol/L). He was referred to thoracic surgery and underwent robotic thymectomy, bronchoscopy and thoracoscopy with pathology consistent with a thymoma. After surgery, his diplopia and ptosis resolved. He was also treated with pyridostigmine with improvement in swallowing. Prednisone was started and eventually transitioned to mycophenolate, with partial prednisone taper. His pathology showed WHO type B2 thymoma with microvascular capsular invasion, clear margins and no lymph node involvement. He had two myasthenia gravis crises requiring hospitalization. One of his myasthenia gravis crises was after Covid-19 vaccination.

Myasthenia gravis (MG) is a rare autoimmune disorder that causes skeletal muscle weakness. Autoantibodies attach to the post-synaptic acetylcholine receptor of the neuromuscular junction.[1] Other disorders that cause problems with the neuromuscular junction include congenital myasthenic syndromes, toxins like botulism and curare, and Lambert-Eaton myasthenia syndrome. The prevalence of MG is 150-250 cases per 1 million.[1] Women are more commonly diagnosed with MG prior to age 40, and men are more commonly diagnosed after age 50.[2] MG cases have increased in the elderly.[2] Mortality from MG was historically high, but with current therapies mortality is 5%.[2]

The hallmark of MG is fatigable weakness. This means that in MG, weakness worsens with activity and is typically worse at the end of the day. Diplopia and ptosis are seen in 50% of patients with MG.[3] Leg weakness and bulbar symptoms, dysarthria, dysphagia, dyspnea are reported in only 10% of patients.[3] Respiratory failure without any of the above symptoms occurs in 1% of cases. Dysarthria may occur with prolonged speech. Fatigue of the mastication muscles can occur while eating. Dysphagia may present as coughing or choking, or as nasal regurgitation.[2] On physical exam, most patients will have ocular muscle weakness that is fatigable (weakness in closing eyes). Ptosis can be unilateral or bilateral. The muscles that control jaw closure may show weakness. In a physical exam of the extremities, proximal > distal weakness is expected.[2]

The diagnosis of MG is established by consistent symptoms of fatigable weakness and consistent lab testing. Eighty to ninety percent of patients with MG have detectable AChR antibodies.[3] These patients have thymoma in 10% of cases and should be screened with a CT or MRI of the chest. Muscle-specific receptor tyrosine kinase (MuSK) is the second most common antibody in MG, accounting for 5% of all MG cases.[3] Patients with MuSK antibodies typically are young women with neck, shoulder and bulbar symptoms. These patients do not have problems with thymus abnormalities and may be difficult to treat. A third antibody, low-density lipoprotein receptor-related protein 4 (LRP4 antibody) accounts for 1-2% of MG cases.[3] Patients with this antibody tend to have more mild disease. The least likely antibody subtype includes patients with anti-agrin antibodies. Electrophysiological testing is performed when the antibody testing is negative, and MG is clinically suspected. Electromyography and nerve conduction studies can confirm the diagnosis of MG.[4]

Treatment of MG includes cholinesterase inhibitors like pyridostigmine and neostigmine. Pyridostigmine dosing starts at 30-60 mg every four to six hours and may be increased to a maximum of 120 mg every four to six hours.[2] Side effects include diarrhea, abdominal pain and increased secretions. Despite optimal use of cholinesterase inhibitors, most patients require additional medications to control MG symptoms. Other medications used to control MG include steroids, azathioprine, mycophenolate mofetil and cyclosporine.[3] First line therapy is prednisone with azathioprine. Dosing of steroids typically starts with prednisone 60-80 mg/day and 80% of patients will respond to this treatment.[3] During initiation of steroid dosing, weakness

can be severe. Patients with moderate to severe MG should be hospitalized for initiation of steroids as some may require mechanical ventilation.[3] After symptoms are well controlled, the steroid dose should be decreased to the lowest effective dose, typically prednisone 10-40 mg on alternating days.[1]

Azathioprine is used as a steroid-sparing agent. This medication may take many months before clinical improvement is noted. The azathioprine dose to treat MG is 2-3 mg per kg of body weight.[4] Patients with AChR + generalized non thymoma MG should be considered for thymectomy. In a randomized controlled trial of 125 patients who had AChR+ MG, 65 patients were treated with thymectomy and steroids, and 65 patients were treated with prednisone only. This trial reported improved clinical status and prednisone usage in patients who underwent thymectomy.[5] The most recent guidelines from the American Academy of Neurology Practice Advisory for MG recommend discussion of thymectomy in patients between 18 and 65 years with AChR antibody positive MG.[3]

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