CLINICAL VIGNETTE

Diagnosing Ocular Myasthenia Gravis

Lillian Chen, MD and Gurveen Sandhu, MD

Case Presentation

A 65-year-old man with type 2 diabetes, hypertension, and hyperlipidemia presented with intermittent diplopia for 1 year. It was most noticeable when watching TV and reading. He did not notice any correlation between direction or distance of gaze with his symptoms. He denied difficulties speaking, chewing, swallowing, breathing, standing from a seated position, or lifting heavy objects.

Physical exam revealed normal vital signs. His pupils were normal, equal, round, reactive to light and accommodation. He had subtle ptosis on the left. Extraocular movements were intact, however he reported diplopia on primary gaze to the right. Cranial nerves II – XII were otherwise intact. The rest of his neurologic exam was unremarkable including normal speech and 5/5 bilateral upper and lower extremity strength.

Labs including a complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, and free T4 were normal. Due to the concern for myasthenia gravis, acetylcholine receptor antibody (AchR-Ab) was obtained and returned positive. Acetylcholine receptor binding antibody was also positive. MRI brain was normal and MRI chest was negative for thymoma. He was referred to a neurologist who diagnosed him with ocular myasthenia gravis and started pyridostigmine 60 mg three times daily as needed as well as prednisone 20 mg daily. One month later, the patient reported his diplopia had essentially resolved and that he had not taken any pyridostigmine for the week prior. He was started on mycophenolate 500 mg twice daily. Six weeks later, a taper of the prednisone was initiated. He is now 18 months after his diagnosis, doing well on mycophenolate.

Discussion

Myasthenia gravis (MG) is a rare acquired autoimmune disorder characterized by skeletal muscle weakness and fatigability. The pathophysiology involves antibody-mediated blockade of the nicotinic acetylcholine postsynaptic receptors at the neuromuscular junction of skeletal muscles leading to impaired signal transduction. The hallmark of MG is fluctuating fatigable muscle weakness that varies in severity, worsens with activity, and improves with rest. Approximately 60% of patients with MG present with ocular symptoms, and most of these patients will develop generalized myasthenia gravis (GMG) over time, while 15% continue to have only ocular involvement, termed ocular myasthenia gravis (OMG).[1] Most patients who convert to GMG will do so within the first 2 to 3 years.[2,3]

Patients with OMG may present with a triad of ptosis, oculomotor paresis, and, less commonly, orbicularis oculi weakness. Ptosis is often unilateral or asymmetrical at initial presentation. Eyelid fatigability may be assessed by comparing the position of the upper lid margin in primary position then retesting after 1-2 minutes of sustained upgaze. Alternatively, having the patient maintain a sustained downgaze for over 15 seconds followed by a quick return to primary gaze may elicit Cogan's lid twitch, which is positive when the upper eyelid overshoots or twitches upward before returning to its previous ptotic position. This clinical sign has a sensitivity and specificity of 50-75% and 90-99%, respectively.[4,5] The "curtain sign," in which manual elevation of the ptotic eyelid by the examiner leads to contralateral eyelid ptosis, or "enhanced ptosis," in which manual elevation of the less affected eyelid leads to worsening ptosis of the other eyelid, are other findings that may be observed due to Hering's law of equal innervation. However, these may be seen with other causes of ptosis. In the ice pack test, ice is applied to the ptotic eyelid for at least 2 minutes. A positive finding is improvement of ptosis by at least 2 mm which occurs due to rest as well as enhanced neuromuscular transmission at cold temperatures. A retrospective cohort study reported a sensitivity of 92% and specificity of 79%.[6]

Cardinal positions of gaze should be tested to evaluate for oculomotor dysfunction and diplopia. Diplopia can be horizontal or vertical depending on the muscles involved. Testing of the orbicularis oculi is performed by having the patient forcefully close their eyelids. Easy ability of the examiner to separate the eyelids leading to a visible sclera is consistent with a positive "peek sign." Pupil involvement is not seen with MG and should prompt investigation into other diagnoses. Strength of other facial, bulbar, and limb muscles should also be examined thoroughly as weakness indicate GMG. The differential of OMG includes Graves ophthalmopathy, chronic progressive external ophthalmoplegia, muscular dystrophy, and brainstem and motor cranial nerve palsies.

Confirmation of suspected OMG may be seen with acetylcholine receptor antibody (AChR-Ab) testing. However, a negative result does not preclude this diagnosis, as it is only positive in about 50% of those with OMG as compared to

nearly 90% of those with GMG.[7] A small percentage of OMG patients may have antibodies to muscle-specific tyrosine kinase (MuSK) and LDL-related receptor-related protein 4 (LRP4), which are post-synaptic proteins necessary for AChR function and aggregation. Testing for these may be obtained in those who are AChR-Ab negative.

If serological testing is non-diagnostic, further evaluation includes repetitive nerve stimulation or single-fiber EMG. Those with suspected OMG should also have a CT or MRI chest to evaluate for thymoma. If not already performed, thyroid function should be checked as patients with OMG may have coexisting autoimmune thyroid disease.

In patients with mild symptoms, nonpharmacologic options may include eyelid adhesive tape for ptosis, or an eye patch, occlusive contact lens, eyeglass occlusion, or prism lenses for diplopia. Once ocular symptoms are stable for at least 6 months to a couple years, surgery for ptosis or strabismus may also be considered.

Initial pharmacologic treatment typically consists of an acetylcholinesterase inhibitor, most commonly pyridostigmine. Unfortunately, only 20 to 40% of patients with OMG will have a satisfactory response to pyridostigmine alone, particularly those with diplopia rather than ptosis alone.[8] Therefore, pyridostigmine is used as an adjunct to immunosuppressants in most cases. Prednisone is usually the first-line immunosuppressant agent and is started at a low dose. Steroid sparing agents are second-line and include mycophenolate, cyclosporine, and rituximab. Plasmapheresis and intravenous immune globulin may be used for short term if symptoms are debilitating. Thymectomy is recommended for OMG patients with thymoma and considered in patients without thymoma who are AChR-Ab positive who do not respond to or cannot tolerate medical therapy.

Conclusion

Although ocular myasthenia gravis is rare, it is important to have a high index of suspicion in a patient who presents with diplopia and/or ptosis. As serologic and electrodiagnostic studies are less sensitive in OMG as compared to GMG, a thorough history and physical exam is paramount in securing the diagnosis and excluding mimics in order to initiate appropriate treatment.

REFERENCES

1. **Gilhus NE, Verschuuren JJ**. Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurol*. 2015 Oct;14(10):1023-36. doi: 10.1016/S1474-4422(15)00145-3. PMID: 26376969.
2. **Gilhus NE**. Myasthenia Gravis. *N Engl J Med*. 2016 Dec 29;375(26):2570-2581. doi: 10.1056/NEJMra1602678. PMID: 28029925.
3. **Hendricks TM, Bhatti MT, Hodge DO, Chen JJ**. Incidence, Epidemiology, and Transformation of Ocular Myasthenia Gravis: A Population-Based Study. *Am J Ophthalmol*. 2019 Sep;205:99-105. doi: 10.1016/j.ajo.2019.04.017. Epub 2019 May 9. Erratum in: *Am J Ophthalmol*. 2020 Jul 3;: PMID: 31077669; PMCID: PMC6744973.
4. **Singman EL, Matta NS, Silbert DI**. Use of the Cogan lid twitch to identify myasthenia gravis. *J Neuroophthalmol*. 2011 Sep;31(3):239-40. doi: 10.1097/WNO.0b013e3182224b92. PMID: 21654336.
5. **Van Stavern GP, Bhatt A, Haviland J, Black EH**. A prospective study assessing the utility of Cogan's lid twitch sign in patients with isolated unilateral or bilateral ptosis. *J Neurol Sci*. 2007 May 15;256(1-2):84-5. doi: 10.1016/j.jns.2007.02.020. Epub 2007 Mar 21. PMID: 17374543.
6. **Fakiri MO, Tavy DL, Hama-Amin AD, Wirtz PW**. Accuracy of the ice test in the diagnosis of myasthenia gravis in patients with ptosis. *Muscle Nerve*. 2013 Dec;48(6):902-4. doi: 10.1002/mus.23857. Epub 2013 Sep 11. PMID: 23536427.
7. **Provenzano C, Marino M, Scuderi F, Evoli A, Bartoccioni E**. Anti-acetylcholinesterase antibodies associate with ocular myasthenia gravis. *J Neuroimmunol*. 2010 Jan 25;218(1-2):102-6. doi: 10.1016/j.jneuroim.2009.11.004. Epub 2009 Nov 26. PMID: 19942297.
8. **Evoli A, Batocchi AP, Minisci C, Di Schino C, Tonali P**. Therapeutic options in ocular myasthenia gravis. *Neuromuscul Disord*. 2001 Mar;11(2):208-16. doi: 10.1016/s0960-8966(00)00173-5. PMID: 11257479.