CLINICAL VIGNETTE

Diagnosis and Prognosis of Ocular Myasthenia Gravis

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Presentation

A 54-year-old man presented to clinic with ptosis of the right eye. His symptoms began about two weeks prior with being unable to voluntarily open the eye. The eyelid droopiness worsened throughout his work day, leaving his eyes "feeling tired" in the evenings. Upon initial evaluation, the patient appeared alert and aware, with no signs of stroke, vision changes, or other neurological deficits. He had experienced isolated episodes like this three other times over the past several years that resolved spontaneous.

Physical exam included normal vital signs. A more detailed eye exam performed while manually opening the eyelid was negative for blurred vision, diplopia, photophobia, pain, discharge, or redness. His pupils were normal, equal, round, reactive to light and accommodation, and all extraocular movements were intact. His neurological exam was unremarkable, as the patient denied dizziness, seizures, loss of consciousness, and headaches. Cranial nerves II – XII were tested with normal responses, with the exception of the isolated ptosis. There was no unusual decrease in sensation or motor strength, and the patient had normal gait without signs of cerebellar dysfunction.

Given the recurrent nature of the patient's ptosis without associated symptoms or other eye abnormalities, an ice test was performed in clinic. An ice pack was applied to the eyes for 2 minutes and then removed, and the quality of the ptosis before and after the ice treatment was compared. The eyelid droopiness improved substantially with ice, increasing suspicion for ocular myasthenia gravis. The patient was referred to neurology and an MRI with/without contrast was ordered to evaluate for central nervous system pathology. The patient was sent home with 40mg po qday prednisone for 5 days and scheduled follow up in two weeks to check for improvement.

Pathophysiology

Ocular myasthenia gravis (OMG) is a variant of the immune disorder myasthenia gravis (MG) which preferentially involves the extraocular eye muscles. The pathophysiology of MG lies at the neuromuscular junction, where antibodies bind and disrupt the activity of the acetylcholine receptor which normally allows for the conversion of the neurological signal into a functional muscular contraction. This dysfunction in the ACh receptor leads to a downstream muscle weakness, which worsens with time and with use. Muscle weakness and fatigability in the extraocular eye muscles leading to ptosis and sometimes diplopia is a common first presentation of MG, and in isolation of other muscular or neurological symptoms and findings constitutes OMG.[1]

Diagnosis

Diagnosing ocular myasthenia gravis can be challenging because it often presents with symptoms for which there is an extensive differential, particularly ptosis. A careful physical exam and certain laboratory tests can increase clinical suspicion for OMG, especially in the case of pupil-sparing ptosis when no additional neurological symptoms are present.

The classic clinical features of OMG are ophthalmoplegia, anywhere from singular extraocular muscle involvement to complete paralysis, and/or ptosis involving the levator palpebrae muscle. These features can be manifested as inability to raise the eyelid exacerbated by prolonged downward gaze. There may also be orbicularis oculi weakness, seen when the patient is asked to close their eyes tightly while the clinicianl tries to open them manually.[2]

Ptosis is associated with several neurological conditions, including myasthenia gravis, third nerve palsy, Botulinum toxin, Bell's Palsy, and Horner's syndrome. In third nerve palsy, there may be ocular deviation, especially to the down-and-out position, and pupillary dysfunction accompanying ptosis. Botulinum toxin can be tested in serum as well as stool or gastric contents, and exposure may be evident in the patient's history. Facial nerve palsy or Bell's Palsy can include twitching, weakness, and paralysis of the face, and facial drooping in addition to ptosis. Other facial muscle involvement is common and more likely than isolated unilateral ptosis alone. Horner's syndrome involves interruption of sympathetic nerve fibers which contribute to raising the eyelid. However, in addition to ptosis, classic signs of Horner's include miosis, anhidrosis, and enophthalmos. Imaging, especially MRI, can confirm the location of the lesion involved.[3]

Simple in-clinic tests including the ice pack test and edrophonium test can be used when clinical suspicion for OMG is high. The ice pack test consists of holding an ice pack over the eyes for 2-5 minutes, and then reassessing the level of ptosis or extraocular eye muscle weakness. In patients with OMG, ptosis improves significantly (by more than 2mm) after ice is applied.

OMG-related ptosis will also improve with rest of the muscle involved.[4] The edrophonium test involves giving the drug, an acetylcholinesterase inhibitor, intravenously to increase the acetylcholine available in the synapse and potentially overcome the antibodies blocking transduction at the NMJ. To prevent side effects of edrophonium (those related to acetylcholine action at muscarinic receptors throughout the body), low-dose atropine can be given prior to the start of the test.

When MG is suspected, a serum assay for acetylcholine receptor antibodies can be performed. However, only around half of OMG patients will have positive serum antibody markers. Other lab tests including that for LDL-related receptor related protein 4 (LRP4) may help with diagnosing OMG when AChR antibody tests are negative.[4] Patients suspected of MG should also have a chest CT or MRI, as up to 15% of patients with MG will have thymoma. These patients are even more likely to have positive AChR antibody tests.[5]

Treatment

Symptomatic and immunosuppressive therapies can be used simultaneously to help patients achieve the best outcomes. The most common first-line symptomatic treatment for myasthenia gravis is acetylcholinesterase inhibitors such as pyridostigmine. These drugs prevent the breakdown of acetylcholine, allowing a larger concentration in the synapse for a longer period of time to better activate the NMJ ACh receptors.[6] To achieve symptomatic relief, pyridostigmine can be titrated from 30mg TID to 150mg QID to reach the patient's optimum dose.[7] For some patients, especially with isolated ocular symptoms, this may be enough and immunosuppressive may be avoided, although this represents a minority of OMG patients

The most common immunosuppressive drug prescribed in MG is prednisone. Like pyridostigmine, prednisone may be titrated from a low dose to achieve therapeutic optimization, however, high dose steroids should be avoided if possible due to systemic adverse effects. There also is some evidence that early treatment with prednisone may help make generalization of OMG less likely.[8]

To achieve immunosuppression, azathioprine and mycophenolate mofetil are also commonly used. Azathioprine can be used in addition to prednisone. However, it may take more than 3 months to see therapeutic effects. Thiopurine methyltransferase activity should be monitored as azathioprine is a purine antagonist which may inhibit the enzyme.[8] These two drugs are options for patients who may not tolerate steroid treatment for OMG. Mycophenolate mofetil shows less efficacy than azathioprine when used in conjunction with prednisone, however, and should not be used in pregnancy.

Prognosis

Many MG patients first present with ocular symptoms such as ptosis, diplopia, and ophthalmoplegia. In the absence of other muscular or neurological involvement, the diagnosis of OMG can be made. Only 15%-20% of all MG patients ever develop ocular symptoms. It is much more common, however, for patients with OMG to eventually develop generalized myasthenia gravis. There is a 90% chance this will never occur if their symptoms were purely ocular in nature for more than 2 years.[9] This was the case for our patient.

In general, OMG is characterized by male predominance, making females with an OMG diagnosis more likely to develop generalized MG over time. Patients with OMG that never becomes generalized have lower seropositivity to AChR antibodies and lower incidence of thymoma than MG counterparts. There is also a positive correlation with age of onset and generalization of OMG.

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