Ocular and Generalized Myasthenia Gravis: A Teaching Case Series

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Abstract

Myasthenia gravis is an autoimmune disease affecting acetylcholine receptors in skeletal muscle. Ocular symptoms include variable ptosis, diplopia and/or blurred vision. Ocular manifestations may be the initial symptoms in undiagnosed disease, prompting patients to seek eye care. Symptoms of shortness of breath or difficulty swallowing may indicate myasthenic crisis, a life-threatening condition. We present two cases of myasthenia gravis, one with ocular and the other with generalized disease. These teaching cases exemplify the importance of optometric in-office history skills, diagnostic testing and clinical decision-making necessary to effectively diagnose and manage emergent and non-emergent cases of myasthenia gravis.

Key Words: *diplopia, ptosis, ocular myasthenia gravis, generalized myasthenia gravis, myasthenic crisis*

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Background

The following case reports are to be used as a teaching guide for optometry students and residents and are relevant for all levels of training. Myasthenia gravis can be a diagnostic challenge because it mimics any pupil-sparing ophthalmoplegia. Neuromuscular anatomy and physiology are reviewed. Ocular and generalized findings for myasthenia gravis are presented as well as the most current treatment options available. These cases exemplify the importance of optometric in-office history skills, diagnostic testing and clinical decision-making necessary to effectively diagnose and co-manage emergent and non-emergent cases of myasthenia gravis.

Student Discussion Guide

Case Descriptions

Case 1

A 67-year-old white male presented to the urgent care optometry clinic reporting sudden onset right eye ptosis and binocular, vertical, diplopia, worse at the end of the day, of one week duration. **(Table 1)** The patient denied difficulty swallowing, breathing, hoarseness or generalized weakness. His medical history was positive for hypertension, atrial fibrillation and high cholesterol. He reported good compliance and control of these conditions with atenolol, simvastatin, Niaspan, and coumadin. He was a non-smoker and had no drug allergies. He was oriented to person, place and time.

Due to the variable and fatigable ptosis and diplopia, which improved with ice pack testing, and without symptoms of generalized involvement, the patient was diagnosed with presumed ocular myasthenia gravis. The following blood work was ordered: acetylcholine receptor antibody (AchR) test and thyroid function tests (T3, T4 and TSH). A chest CT was also ordered to rule out thymus gland abnormality. AchR antibody testing was positive and thyroid function tests returned normal. The chest CT was normal, with no evidence of thymoma. The patient was referred to a neurologist, who confirmed the diagnosis, for treatment and management of his ocular myasthenia gravis. He was started on a course of oral pyridostig-

Table 1
Case 1 Initial Presentation

	OD	OS
Best-corrected visual acuity	20/20	20/20
External exam	Ptosis (variable); + orbicularis oculi weakness; + Cogan's lid twitch	Normal
Pupils	ERRL, -APD	ERRL, -APD
Extraocular motility	Full	Full
Confrontation visual field	FTFC	FTFC
Cover test		4-16 prism diopter intermittent, left hypertropia distance and near; variable and fatiguing
Ice pack test	See Figures 1 & 2	See Figures 1 & 2
Prolonged upgaze test	See Figures 3 & 4	See Figures 3 & 4
Biomicroscopy	Normal	Normal
Intraocular pressure (GAT)	14 mmHg	14 mmHg
Dilated fundus exam	Pink, flat, optic nerve distinct borders; 0.3 c/d; flat, intact retina 360	Pink, flat, optic nerve distinct borders; 0.3 c/d; flat, intact retina 360

FTFC = full to finger count; ERRL = equal, round and reactive to light; APD = afferent pupil defect; GAT = Goldmann applanation tonometry.

Figure 1
Case 1: Before Ice Pack Test

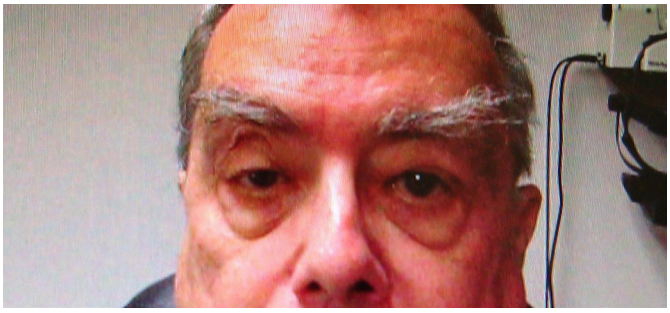


Figure 2
Case 1: After Ice Pack Test

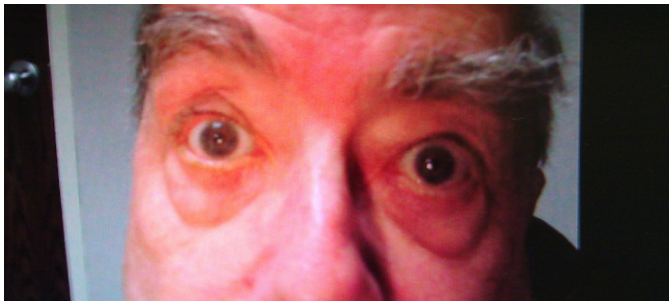


Figure 3
Case 1: Before Sustained Upgaze Test

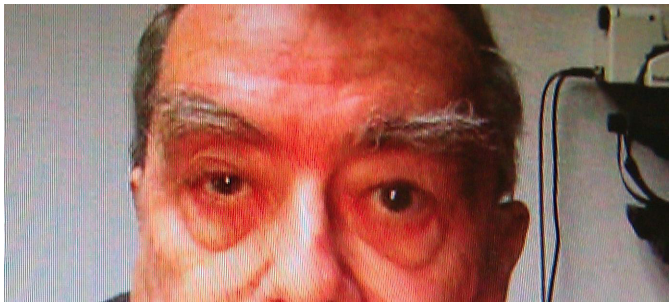
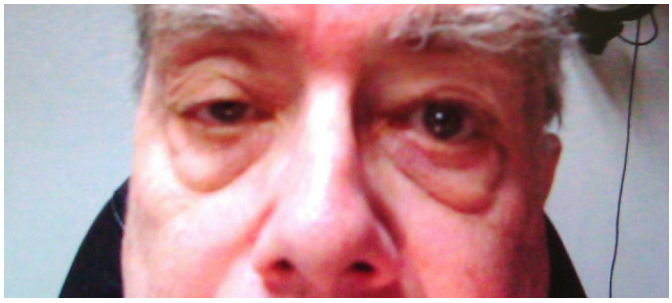


Figure 4
Case 1: After Sustained Upgaze Test



mine, which led to complete symptom resolution.

Case 2

A 34-year-old African American female presented with complaints of intermittent diplopia and ptosis, worse at the end of the day, for the last year. **(Table 2)** The diplopia fluctuated between horizontal, vertical and diagonal. She described her left eye as "lazy," and stated it had been getting progressively worse. She also reported foreign body sensation and tearing in her left eye for the last two months. Upon questioning, she complained of generalized muscle weakness, difficulty swallowing and breathing for the last three months. Her primary care physician had treated her for bronchitis without resolution of the symptoms. She was sent to an otolaryngologist, who treated her for postnasal drip with the same result. The patient's ocular history was remarkable for spectacle wear at distance and near. Her medical history included osteoarthritis, herpes simplex type two, depression, keloidosis and seasonal allergies. She was taking Benadryl for seasonal allergies and naproxen for osteoarthritis. She was a non-smoker and was oriented to time, place and person.

Due to the variable and fatigable ophthalmoplegia, ptosis, positive Cogan's lid twitch and systemic symptoms, the patient was diagnosed with presumed generalized myasthenia gravis with ocular involvement. The left eye was also diagnosed with exposure keratopathy secondary to incomplete blink. Both eyes were treated with one drop of artificial tears four times per day and lubricating ointment applied to the lower cul-de-sac before bedtime due to weakness observed with the orbicularis oculi muscles (OS>OD). The patient was immediately sent to the emergency room because of symptoms of dyspnea, dysphagia, and concern for immediate risk of mortality in myasthenic crisis. The patient was given a referral letter reporting concern for myasthenic crisis with documentation of her ophthalmological findings and systemic complaints to present to the emergency room when she arrived. The patient was told to follow up in the eye clinic in one month.

The patient was admitted to the hospital the same day. Generalized myasthenia gravis with myasthenic crisis was confirmed. Sixty milligrams of Mestinon and 50 mg of prednisone were initiated, and the patient was observed in the hospital for three days.

Table 2
Case 2 Initial Presentation

	OD	OS
Best-corrected visual acuity	20/20	20/25
External exam	Ptosis (variable); + orbicularis oculi weakness; + Cogan's lid twitch	Ptosis (variable, but consistently worse than OD); + orbicularis oculi weakness; + Cogan's lid twitch
Pupils	ERRL, -APD	ERRL, -APD
Color vision (Ishihara)	normal	normal
Extraocular motility	Restriction 360; see Figure 5	Minimal infraduction only; see Figure 5
Exophthalmometry	24 mm	24 mm
Forced duction	negative	negative
Confrontation visual field	FTFC	FTFC
Prolonged upgaze test	Worsening of ptosis	Worsening of ptosis
Ice pack test	Improvement of ptosis	Improvement of ptosis
Biomicroscopy	Normal	2+ interpalpebral PEE
Intraocular pressure (GAT)	21 mmHg	21 mmHg
Dilated fundus exam	Pink, flat, optic nerve distinct borders; 0.3 c/d; flat, intact retina 360	Pink, flat, optic nerve distinct borders; 0.3 c/d; flat, intact retina 360

FTFC = full to finger count; ERRL = equal, round and reactive to light; APD = afferent pupil defect; GAT = Goldmann applanation tonometry; PEE = punctate epithelial erosions.

Table 3
Case 2 Follow-Up #1

	OD	OS
Best-corrected visual acuity	20/20	20/20
External exam	Ptosis variable and orbicularis oculi weakness but improved from last exam; see Figure 6	Ptosis variable and orbicularis oculi weakness but improved from last exam; see Figure 6
Pupils	ERRL, -APD	ERRL, -APD
Extraocular motility	Minimal restriction 360; see Figure 6	Moderate restriction primarily in adduction; see Figure 6
Confrontation visual field	FTFC	FTFC
Biomicroscopy	Normal	Normal
Intraocular pressure (GAT)	18 mmHg	18 mmHg

FTFC = full to finger count; ERRL = equal, round and reactive to light; APD = afferent pupil defect; GAT = Goldmann applanation tonometry.

Case 2: Follow-Up #1

The patient returned to the eye clinic one month later. **(Table 3)** She reported the diplopia and ptosis had improved since initiation of treatment. She also noted improvement of the dyspnea and dysphagia without complete resolution, and was under the care of a neurologist whom she was seeing every two weeks. The patient's ocular medication included artificial tears, one drop instilled two times per day in both eyes. The patient

Figure 5
Case 2: Initial Visit, Nine Cardinal Fields of Gaze

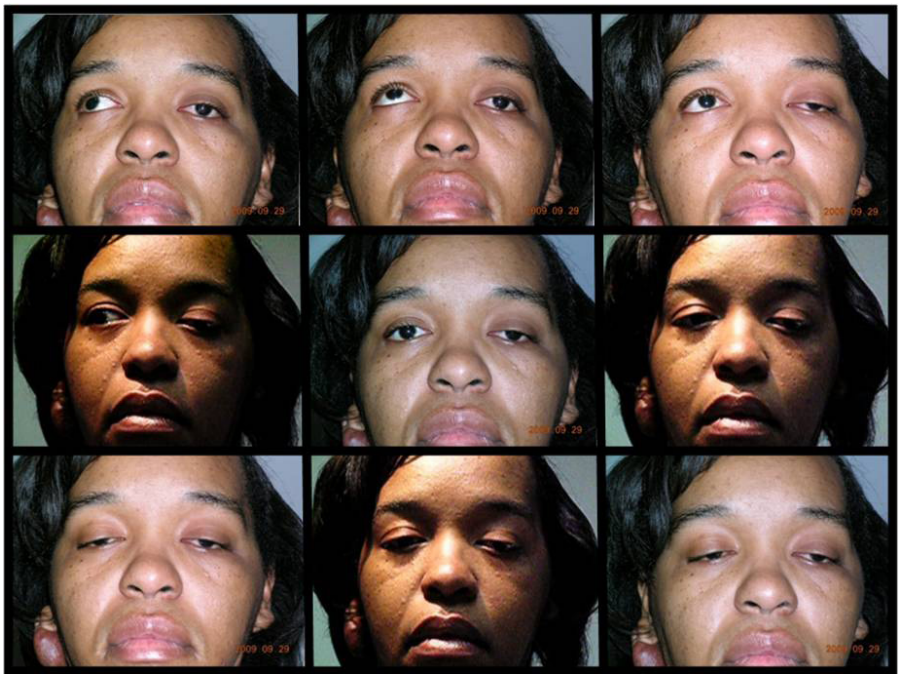
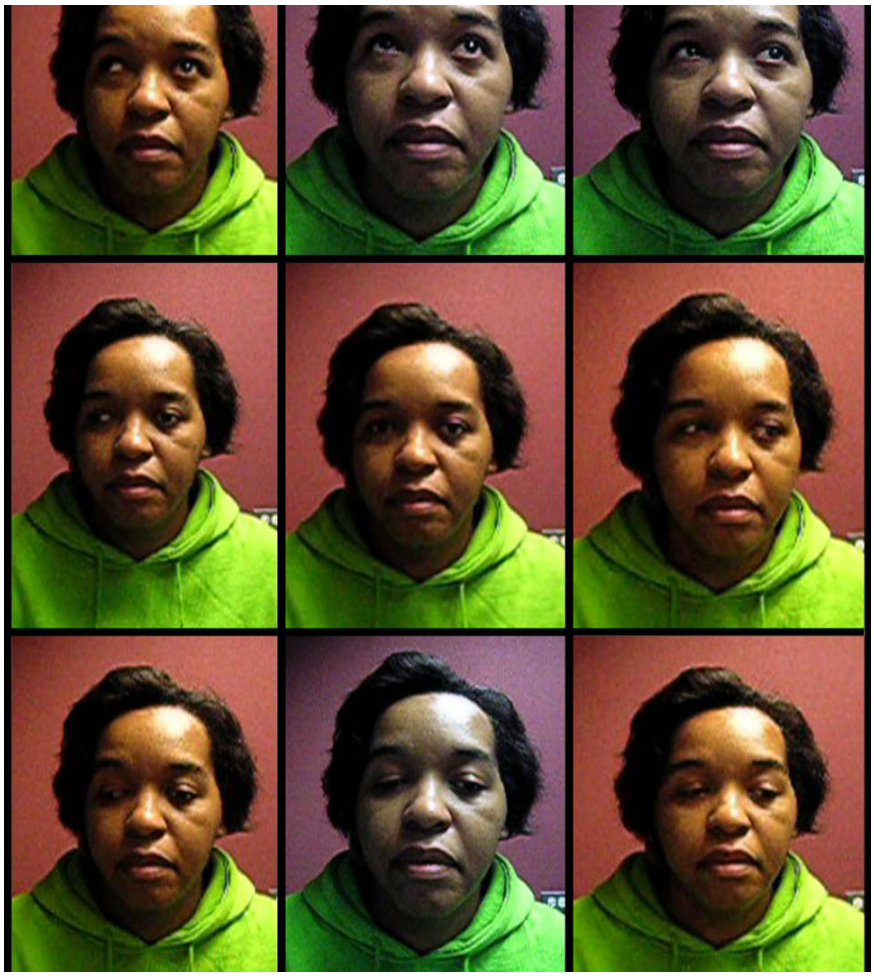


Figure 6
Case 2: One Month Follow-Up After Treatment



was not applying the lubricating ointment before bed as instructed at the last exam. The patient's systemic medications now included Mestinon 50 mg per day and 60 mg of prednisone per day. A CT of the chest was performed and no thymus gland abnormality was observed. The patient was scheduled to follow up with neurology in one month.

The patient was assessed with generalized myasthenia gravis with ocular involvement with significant improvement of ocular signs with systemic therapy. Both eyes were assessed for exposure keratopathy. The patient was instructed to continue using artificial tears four times per day OU, and instructions for the lubricating ointment at bedtime OU were reinforced. The patient was instructed to continue follow-up with neurology for systemic treatment of the generalized myasthenia gravis and to follow up in the eye clinic in three months.

Learning Objectives

At the conclusion of the case discussion, participants should be able to:

1. Understand the pathophysiology of myasthenia gravis
2. Take an appropriate ocular and systemic history for patients presenting with diplopia
3. List and differentiate key ocular and systemic signs and symptoms associated with myasthenia gravis
4. Perform in-office diagnostic testing to help diagnose myasthenia gravis
5. Differentiate myasthenia gravis from other ophthalmoplegias
6. Correlate clinical findings with the patient history to determine diagnosis
7. Understand ocular and systemic treatment options for myasthenia gravis

Key Concepts

1. Understand the neuromuscular anatomy and physiology in myasthenia gravis
2. A history of variable and fatigable muscle weakness suggests myasthenia gravis

3. Recognize clinical findings of myasthenia gravis
4. Understand the risks and benefits of various diagnostic testing for myasthenia gravis
5. Differentiate between emergent and non-emergent referrals for patients presenting with signs and symptoms of myasthenia gravis
6. Understand the significance of a multidisciplinary approach when managing individuals with myasthenia gravis
7. Understand how to select clinically appropriate problem-based testing

Discussion Points

A. Knowledge of Potential Clinical Findings
   1. Describe the classic signs and symptoms of ocular myasthenia gravis.
   2. Describe the classic symptoms of systemic myasthenia gravis.
   3. Describe the mechanism of action of the pharmaceutical agents involved in the diagnosis and treatment of myasthenia gravis.
   4. What in-office tests can optometrists perform to aid in the diagnosis of myasthenia gravis?
   5. What history questions should one ask every patient suspected of having myasthenia gravis?
   6. What is the definition of myasthenic crisis?
   7. What medications should be avoided in patients with myasthenia gravis?

B. Comprehension of Clinical Data
   1. What diagnostic tests were done in this case to help diagnose myasthenia gravis?
   2. How does one differentiate between myasthenia gravis and other ophthalmoplegias?
   3. What blood work and other diagnostic tests should be ordered in patients suspected to have myasthenia gravis?

C. Management
   1. What are the classes of medication used to treat myasthenia gravis?
   2. What are the goals of treatment for myasthenia gravis patients?
   3. How do you determine what warrants an emergent vs. non-emergent referral?
   4. What other physicians should co-manage a patient with myasthenia gravis?
   5. How do you manage the patient's ocular symptoms?
   6. What surgical treatment options are available?

D. Patient Education
   1. What are potential consequences associated with non-compliance to the treatment plan?
   2. What pertinent information should be used to educate patients on the condition?
   3. Discuss appropriate responses to a patient's anxiety about the ocular and/or systemic condition, and long-term disease consequences associated with the condition.

Educator's Guide

The educator's guide includes the necessary information to discuss the case.

Literature Review

Myasthenia gravis (MG) is an autoimmune disease targeting nicotinic acetylcholine (Ach) receptors in post-synaptic connections of skeletal muscle.[1,2,3] It affects voluntary skeletal muscle either only in the eye (ocular) and/or the entire body (generalized). The process by which muscular weakness manifests is a result of competitive inhibition. Anti-acetylcholine receptor antibodies block or destroy Ach receptors, thus decreasing the number of sites available for Ach binding;[2] therefore, the initial weakness observed is transient and improves with rest.[1]

It is estimated that 85-90% of MG cases present with ocular symptoms; 20-50% of cases have been reported as purely ocular. Ocular myasthenia gravis (OMG) is considered a separate diagnosis from generalized MG; yet, most cases of generalized MG have ocular symptoms.[1]

Epidemiology

The prevalence of MG is approximately 20/100,000/year in the United States.[2] MG has no racial or geographic predilection and can affect any age group, although it is rarer in the first or after the sixth decade of life.[2,4] Onset tends to occur at an earlier age in women than in men. In patients with onset prior to age 40, women tend to predominate, whereas over the age of 50 men predominate. In generalized MG the female to male ratio is 3:2; however, in OMG men are more frequently affected, especially after age 40.[2,4] MG in the North American and European pediatric population comprises 10-15% of MG cases. However, in Asian countries, up to half have an onset before 15 years of age, and most are purely ocular MG.[3]

Pathophysiology

Acetylcholine is a neurotransmitter that stimulates nicotinic Ach receptors at the postsynaptic muscular junction resulting in muscle contraction.[2] Neuromuscular synapses are initiated by action potentials that depolarize motor nerve axons and cause an increase in calcium permeability. This increase in permeability elicits the release of acetylcholine into the synaptic cleft. Ach diffuses across the synaptic space and binds to the Ach receptors on the crests of the convoluted folds located on the post-synaptic membrane. This opens the receptor's ion channels and depolarizes the post-synaptic membrane causing the muscle to contract. Upon completion of each synapse, Ach is removed from synaptic space by diffusion and acetylcholinesterase enzyme activity.[4]

In MG, autoantibodies are directed against the Ach receptors at the endplates of neuromuscular junctions. They prevent neuromuscular synapses, characterizing the muscle weakness in MG.[4,5] The pupillary sphincter muscle does not have nicotinic Ach receptors; therefore, the pupils are not affected.[2]

The production of autoantibodies against Ach receptors in MG is a T-cell dependent process due to a breakdown in the immune system's recognition of self-antigens. It is not understood why this occurs, but several factors indicate

that thymus gland abnormalities (thymus hyperplasia or thymoma) are important. First, this theory is supported by the fact that thymectomy alters the course of the disease. Second, there are histopathologic changes to the thymus in up to 85% of patients. Third, Ach receptor antibody producing cells can be found in the thymus, bone marrow and peripheral blood. The latter two explain why thymectomy changes the course of the disease but is not curative.[5]

Clinical Presentation and Diagnostic Testing

Fifty to eighty percent of MG patients present with visual complaints of diplopia or ptosis. Half of the patients that present with ocular signs progress to generalized MG weakness in six months and 80% will generalize within two years. The disease will likely be limited to ocular MG if there are no generalized symptoms past three years.[1]

The muscle weakness seen (generalized or ocular) is variable in nature, often increased at the end of the day or after sustained, repetitive muscle contraction, and improves with rest.[8] Weakness is worsened with exposure to heat, infection and stress.[3] The weakness typically involves specific skeletal muscle groups. The distribution is generally: ocular (extraocular muscles, levator palpebrae superioris, orbicularis oculi), bulbar (speech, swallowing chewing muscles), limb extremities (arms more affected than legs), neck muscles, and respiratory muscles in the chest.[2,3]

Generalized MG can present in a variety of additional ways. Bulbar muscle involvement can be seen in 60% of patients, presenting as fatigable chewing, painless dysarthria (impaired speech) and dysphagia (difficulty swallowing).[3,9] These signs occur due to weakness of palatal, facial and oro-pharyngeal muscles. Changes in facial expressions and flattened nasolabial fold may be seen, giving the patient an "expressionless" appearance. Weakness may also occur in axial and limb muscles. When these are involved, the patient may present with unsteady gait and weakness of arms, hands, legs and neck.[4] Neck muscles are commonly affected, with the weight of the head overtaking the extensor muscles, producing a "dropped head syndrome."[3]

Respiratory muscle weakness can lead to myasthenic crisis, which can be life-threatening. Myasthenic crisis is defined as acute respiratory failure due to worsening MG, requiring mechanical ventilation.[10] Symptoms of respiratory failure include dyspnea (shortness of breath), dysphagia, tachypnea (rapid breathing), or bradypnea (slowed breathing). It can be precipitated by infections and certain medications such as aminoglycosides, telithromycin, neuromuscular blocking agents, magnesium sulfate, beta blockers, and fluoroquinolone antibiotics.[3] Not every patient with an exacerbation of MG requires mechanical ventilation, but all need close monitoring and immediate access to resuscitation facilities.[10]

Ptosis is the most frequent initial symptom of ocular and generalized MG. Ptosis may be unilateral or bilateral and is often asymmetric between the two eyes. Ptosis in MG has clinically distinct characteristics that are absent from other causes: it is variable and fatigable. A fatigue test may be performed several ways. One includes having the patient perform any physical activity, such as climbing a flight of stairs. It is followed by re-evaluation of signs and symptoms of ocular MG. The most common sign is worsening of the ptosis.[1] Another fatigue test has the patient look up for 30 seconds and then return to primary gaze to fatigue the levator. The examiner looks for lid lag or an increase in ptosis, known as Pseudo Von Graphe's sign.[1,8] Some examiners look for levator fatigue by having the patient look in extreme upgaze for 1-2 minutes. A positive prolonged upgaze test result is an increase in ptosis while the eyes are in upgaze.[1]

If one eyelid is manually elevated, the contralateral upper eyelid becomes more ptotic due to Hering's law of equal innervation. This has been labeled "see-saw ptosis." Cogan's lid twitch is frequently seen in MG and occurs when the eyes are rapidly moved from down gaze to primary gaze. This is generally tested by having the patient look down for 15 seconds and then look at a target in primary gaze.[7] Upon returning to primary gaze, the upper eyelid overshoots and elevates excessively before returning to its ptotic state. This is attributed to the fatigability and rapid recovery of a myasthenic muscle.[8]

Diplopia, secondary to paresis of extraocular muscles, is the second most frequent initial symptom of ocular and generalized MG. Like ptosis, the ophthalmoplegia worsens at the end of the day or upon exertion. It may mimic any disorder of eye movements or exhibit complete external ophthalmoplegia. Reduced accommodative amplitudes, facility, and near point of convergence stamina may also be associated in MG patients.[1,8]

Orbicularis oculi weakness is also a common finding and can be assessed by having the patient tightly squeeze the eyelids shut while the examiner uses finger pressure to attempt to pry open the eyelids. A positive result is a successful attempt to overcome the blepharospasm. In a normally functioning orbicularis oculi muscle, the examiner should not be able to overcome the tight lid closure by finger pressure alone.[1]

Corneal exposure is rarely a problem, but punctate keratitis can occur due to incomplete closure of the lids during blinking. Bell's phenomenon (protective measure of eyes rolling up and laterally during forced eyelid closure against resistance) may also be diminished or absent, usually consistent with the amount of upgaze restriction.

Saccadic movements can be abnormal. A common observation in MG patients is hypometric (undershooting) large saccades and hypermetric (overshooting) small saccades. This is speculated to be the central nervous system's adaptation to muscle weakness. Nystagmus can also be seen in MG and may be unilateral, bilateral, horizontal or vertical in presentation.[8]

Optometrists may use simple, non-pharmacologic, screening tests to aid in the diagnosis of MG. The ice pack test is performed by placement of an ice pack across the patient's eyes for two to five minutes. The localized decrease in temperature slows the breakdown of acetylcholine, increasing its availability in the neuromuscular junction. The clinician then looks for improvement of ptosis or ophthalmoplegia after removing.[3] A positive result is an improvement in the ptosis of greater than 2 mm.[1]

The sleep test requires the patient to lie in a quiet dark room for 30 minutes with his/her eyes closed. Having

the patient rest reduces the demand for acetylcholine. Also, the 30-minute rest time allows for replenishing of available acetylcholine. A positive result is any improvement of ptosis and/or eye movement deficit.[1,3]

Some examiners may ask patients to take at-home, full-face, early morning and late evening pictures for three days. Lid position and ocular alignment are evaluated. If ocular signs of MG are present, there will be a worsening of the ptosis and/or ocular misalignment later in the day.[8]

Pharmacological testing using intravenous edrophonium chloride (Tensilon test) is considered the gold standard diagnostic test for MG. Edrophonium inhibits the enzyme acetylcholinesterase and results in an increase in acetylcholine at neuromuscular junctions. A positive test results is a decrease in muscle weakness usually observed in levator function or ocular motility. Onset of action begins in 30-60 seconds and effects usually subside in less than five minutes due to rapid hydrolyzation. During the test, blood pressure and electrocardiographic monitoring are sometimes recommended because of the rare risk of bradycardia, hypotension and cardiac arrest. Mild side effects of edrophonium include epiphora, perioral fasciculations, salivation, mild sweating, abdominal cramps, vomiting and flush.[3] Sensitivity of the test using ptosis measurement has been reported as high as 86-97% in OMG and 82-100% in generalized MG. Extraocular muscle movement did not respond well in most studies. False positives have been reported in Lambert-Eaton syndrome, botulism, Guillain-Barre syndrome and other cranial neuropathies.[4]

Serologic testing may also be used to confirm the diagnosis of MG. An elevated acetylcholine receptor (AchR) antibody titer confirms the diagnosis. However, obtaining a negative titer does not exclude the disease. 15% of generalized MG patients have no detectable antibodies to AchRs, meaning they are "seronegative." About half of ocular MG patients are seropositive. Titers in seropositive patients cannot be used to predict the severity of the disease as levels of the antibody correlate poorly with clinical status.[1,2] Recent studies have shown sensitivities of 98-99% in generalized MG and 40-77% in OMG. Rarely, a false positive titer is found in first-degree relatives of MG patients or other autoimmune diseases.[11]

Research has shown antibodies to muscle-specific kinase (MuSK) are found in 40-70% of seronegative AchR antibody patients. No positive MuSK titers were found in patients with positive AchR antibody titers. Reports also found no patients with strictly OMG to have positive MuSK titers. Clinicians are using this titer when AchR antibody testing is negative.[12] This subgroup of seronegative AchR antibody patients with MuSK-positive MG have a marked female predominance and frequent oculo-bulbar weakness leading to respiratory crisis.[2]

Electrophysiological testing such as single fiber electromyography (SFEMG) is the most sensitive diagnostic test for MG and can be helpful in confirming the diagnosis for seronegative patients.[2,3] It is done by using a special needle electrode that allows identification of action potentials from individual muscle fibers.[3] However, this test is not readily available in every community, and abnormalities are not specific for MG.[2,3]

Repetitive nerve stimulation is used to assess neuromuscular transmission. It is done by supra-maximally stimulating the nerve. A 10% decrease between the first and the fifth evoked muscle contraction is diagnostic for MG. However, this test lacks the sensitivity as compared to SFEMG. It is abnormal in 75% of patients with generalized MG and 50% of patients with OMG.[3]

A CT or MRI of the chest with attention to the thymus gland is also performed to rule out the presence of thymoma. MG also often coexists with thyroid disease, so thyroid function tests are also obtained in patients with MG.[3]

Differential Diagnoses

The diagnosis of myasthenia gravis may be a challenge because it mimics any pupil-sparing ophthalmoplegia. MG should be considered in any patient presenting with diplopia and/or ptosis. However, the keys to diagnosis are the variable and fatigable signs and symptoms and that they improve with rest. The pupils are not involved in patients with myasthenia gravis. Keeping that information in mind, other causes of diplopia and/or ptosis should be considered. Thorough case history and clinical exam may help rule out the differentials below as they will not demonstrate variability or fatigability and some may have pupil involvement, thus helping to differentiate from myasthenia gravis:[1]

- Mechanical: levator aponeurosis dehiscence, involutional, iatrogenic/ocular surgery, trauma, cicatrization, eyelid mass
- Myogenic: Chronic progressive external ophthalmoplegia, myotonic dystrophy, oculopharyngeal dystonia
- Neurogenic: multiple sclerosis, Horner's syndrome, cranial nerve palsies, internuclear ophthalmoplegia
- Mass: thyroid orbitopathy, idiopathic orbital inflammation, orbital neoplasia
- Pseudoptosis: enophthalmos, hypotropia, contralateral lid retraction

Treatment and Management

MG must be treated aggressively, and therapy is individualized to each patient. Treatment early in the course of the disease provides the best overall clinical response. Long-term medical and surgical treatments are used to manage the disease.[3]

Medical treatment includes palliative treatment in the form of acetylcholinesterase inhibitors and immunosuppressive therapy. Surgical treatment includes thymectomy. The goals of treatment are to prevent mortality with the fewest side effects and to improve the patient's quality of life by remission of symptoms and lowering the risk of transition from ocular to generalized MG.[3]

Palliative Treatment

Acetylcholinesterase inhibitors such as pyridostigmine bromide (Mestinon) and neostigmine bromide (Prostigmin) are used as first-line treatment to relieve muscle weakness in MG. The mechanism of action works to prevent the hydrolysis and breakdown of Ach in neuromuscular junctions. With more Ach available in the neuromuscular junctions, there is an improved efficiency activating the remaining viable Ach receptors. The onset of action for

pyridostigmine, the most commonly used acetylcholinesterase inhibitor, is within 15-30 minutes orally and two to five minutes intravenously. The duration of action is six to eight hours orally and two to three hours intravenously.[13] Side effects include gastrointestinal disturbance, pallor, cold sweats, epiphora, increased urinary urgency and muscle weakness. Most patients have symptomatic relief but do not have disease remission. Very seldom is this used as monotherapy. Immunosuppressive agents are needed to suppress the ongoing immune attack on the remaining Ach receptors.[14]

Long-Term Immunosuppressive Treatment

Corticosteroids such as prednisone are usually the first recommendation for immunosuppression in patients with moderate to severe generalized disease and have been shown to lower the risk of progression from OMG to generalized disease.[3,15] There is no established protocol for initiation of treatment. Some clinicians advocate starting the patient on high-dose steroid treatment until remission is reached, then tapering when symptoms are improved. Others recommend starting with alternate day treatment and gradually increasing the dosage until remission to limit corticosteroid complications. Fifty percent of patients develop worsening of weakness in the first month, usually within the first few days after initiation of corticosteroids. Certain high-risk generalized myasthenia gravis patients, such as those in myasthenic crisis, are required to remain hospitalized during initiation of treatment.[9] Side effects include obesity, hypertension, diabetes, opportunistic infections, osteoporosis, glaucoma, cataracts and corneal ulcer. Side effects are dependent on dosage and duration of treatment.[9]

Azathioprine (AZA) is a purine analogue that inhibits the synthesis of nucleic acids thereby interfering with T-cell and B-cell proliferation. AZA is used as monotherapy or as an adjunct to corticosteroids.[10] Improvement in symptoms is gradual and may continue for up to two years of treatment. AZA side effects include malignancy, leukopenia, thrombocytopenia, nausea, vomiting and hepatotoxicity.[3]

Cyclosporine A inhibits calcineurin. The mechanism blocks helper T-cell synthesis of interleukin-2 and prevents helper T-cell dependent function. It is mainly used when patients are intolerant of AZA or corticosteroids. Side effects include hypertension, renal failure, hirsutism, gingival hyperplasia, gastrointestinal disturbance, flu-like symptoms, paresthesias, myalgia and headache.[3]

Other long-term immune suppressive agents used in the treatment of MG include mycophenolate mofetil (used to prevent transplant rejection), cyclophosphamide, rituximab, tacrolimus, methotrexate and etanercept. All of these agents have been successfully used as second-line agents to treat MG. With all immunosuppressive agents, side effects must be monitored closely and the cost-benefit ratio must be weighed.[3]

Short-Term Immunosuppressive Agents

Plasmapheresis and intravenous immunoglobulin therapy (IVIg) have rapid onset and lead to improvement within days, but effects are transient. They are used in situations of severe exacerbations of MG, myasthenic crisis and before surgical procedures. They can also be used intermittently in patients whose disease is not well-controlled despite chronic immunomodulating therapies.[3] Plasmapheresis works by removing AchR antibodies from circulation. One exchange is done every other day, four to six times.[3]

The mechanism of IVIg on the autoimmune response is complex. It acts by suppressing antibody production and the immunoreactivity of autoantibodies via anti-idiotypic antibodies. In addition, it inhibits complement activation and the formation of membrane attack complexes.[16] Other mechanisms include preventing the binding of Fc receptors on macrophages, Ig receptors on B-cells, and antigen recognition by T-cells.[17] Plasmapheresis has been shown to be equally effective for exacerbations of MG, but IVIg is better tolerated by patients and thus used more frequently.[10]

Surgical Treatment

Thymectomy was the first immunemodulating treatment used in MG. It became a generally accepted treatment for generalized MG in the 1940s and 1950s. Approximately 85% of MG patients have thymic abnormalities, including hyperplasia and thymomas. Surgical thymectomies have shown therapeutic effect, but the benefit is controversial. Stable remission has been reported in the range of 15-64%.[9] Wide variability is likely due to differing surgical techniques. The benefits are sometimes delayed months to years after surgery.[13]

Myasthenic Crisis

Presentation of myasthenia gravis is a non-emergent referral with one exception: signs of dyspnea or dysphagia. Weaknesses to bulbar (speech, chewing, swallowing) muscles and respiratory muscles, including the diaphragm, produce symptoms that define myasthenic crisis. Myasthenic crisis requires immediate referral to the emergency room for prevention of respiratory arrest and ultimately death. Close observation, intubation and feeding support may be instituted. In addition to supportive therapy, the focus of action may be reducing circulating antibodies with plasmapheresis, or administration of autoimmune modifying drugs, such as corticosteroids and intravenous immunoglobin. While corticosteroid treatment is initiated, patients must be closely observed due to the risk of acute worsening of weakness.[18]

Approximately 15-20% of patients with generalized MG experience myasthenic crisis at some point during the course of the disease. Current statistics report a 3-8% mortality rate from MG. Seventy percent of myasthenic crisis cases are provoked by concurrent infections or fever that include the upper and lower respiratory tracts. Other risk factors include certain medications and surgical interventions. The remaining patients present in crisis because of inadequate control or delayed diagnosis and treatment of the disease.[18]

Ocular Management

Ocular management of MG is focused on relief of symptoms. The most elementary technique to relieve variable diplopia is teaching patients the use of head turn. Through the use of a head turn, the patient can find a position of gaze where fusion can be appreciated.

Occlusion therapy may be indicated

for persistent or non-tolerable diplopia. Occlusion patching or high-plus contact lenses can be used. When orbicularis oculi weakness is exhibited, incomplete blinking causing exposure keratopathy can be observed. This is usually successfully treated with topical lubrication. In extreme cases, eyelid taping may be used. Due to the fluctuation of the ophthalmoplegia, no prism is indicated in the setting of MG.

Surgical treatment options are mainly for symptomatic relief of persistent ptosis. They include ptosis repair surgery, blepharoplasty, frontalis suspension, external levator advancement and tarsomyectomy. Other non-surgical options to treat ptosis are botulinum toxin type A injections and the use of a ptosis crutch. The ptosis crutch is made of Teflon or plastic and is mounted onto a spectacle frame to pull back the eyelids. Topical lubrication may also be needed if eyelid taping or ptosis crutch is used due to the risk of exposure keratopathy.[1]

Medications that may Exacerbate Myasthenia Gravis

Many medications have been implicated in either inducing or worsening myasthenia gravis. The reasons for the exacerbation are likely multifactorial and may or may not be solely related to the medication. These medications include aminoglycosides, telithromycin, neuromuscular blocking agents, magnesium sulfate, beta blockers and many antibiotic therapies.[3] The Myasthenia Gravis Foundation has a report for healthcare professions on "Medications and Myasthenia Gravis," which can be found at: http://www.myasthenia.org/HealthProfessionals/EducationalMaterials.aspx. If a MG patient needs an oral medication for management of an unrelated ocular condition, a consultation with the patient's co-managing neurologist is warranted prior to initiation of treatment.

Conclusion

With diplopia and ptosis being the most common presenting symptoms of myasthenia gravis, optometrists may be the first to encounter an undiagnosed patient. The cases presented here demonstrate classic signs of purely ocular (case 1) and generalized myasthenia gravis with ocular involvement (case 2). Recognition of bulbar and respiratory signs and symptoms require emergent referral to prevent respiratory failure and ensuing death. These teaching cases exemplify the importance of optometric in-office history skills, diagnostic testing and clinical decision-making for effectively diagnosing and managing emergent and non-emergent cases of myasthenia gravis. Thorough history, prompt diagnosis, and referral may be life-saving for patients with myasthenia gravis.

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