# DIPLOPIA: NEUROMUSCULAR JUNCTION

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## INTRODUCTION

Myasthenia gravis (MG) is the most common disease of the neuromuscular junction. Ocular motor dysfunction in MG can mimic virtually any pupil-sparing abnormal eye movement, from pupil-sparing third nerve palsies to fourth and sixth nerve palsies to brainstem supranuclear gaze palsies to internuclear ophthalmoplegia. The pupil is not involved in MG. Diagnostic confusion often arises when the eye movements of MG mimic another disorder and ptosis is not present to raise suspicion of MG. It is always appropriate to keep MG in the differential diagnosis for any unexplained eye movement abnormality and to have a low threshold for pursuing diagnostic testing.

Botulism from Clostridium botulinum neurotoxin blockade also affects neuromuscular junction transmission. The eye movements are similar to those seen in MG, with variable patterns of ophthalmoplegia. However, tonic pupillary involvement (with slow tonic reaction and re-dilation to light and light-near pupillary dissociation manifested as better reaction to a near stimulus than to a light stimulus) is typical of botulism, whereas the pupils are not affected in MG.

A third disorder of the neuromuscular junction is the Lambert-Eaton syndrome (LEMS), which is due to pre-synaptic neuromuscular junction failure (in contrast to MG, which is a post-synaptic disorder). The primary clinical manifestation is skeletal muscle weakness. Up to half of patients have ptosis.[1] However, eye movements are affected minimally, if at all and when affected are rarely the presenting clinical feature.

This talk and the remainder of this syllabus will focus on MG.

## OCULAR VERSUS GENERALIZED MG

Much is now known about the anatomy and physiology of extraocular muscles and their neuromuscular junctions and it is clear that structural organization and physiologic properties differ significantly from skeletal muscle and skeletal muscle neuromuscular junctions. Extraocular muscle neuromuscular junctions lack the dense post-synaptic junctional folding found in skeletal muscle but share the molecular structure of post-synaptic skeletal neuromuscular junctions.[2] These differences may explain, at least in part, why eye movements are susceptible to involvement in specific disease states, such as MG.[3]

Eye movements, the levator palpebrae superioris, and orbicularis oculi are eventually involved in the majority of patients with generalized MG. When they are affected in isolation, this mild or localized form of disease is termed ocular MG. Over 50% of ocular myasthenics will progress to generalized disease.[4] If a patient reaches one year after diagnosis of ocular MG without generalization of disease, the risk of generalization substantially decreases.[5]

## HISTORICAL FEATURES

Patients with ocular myasthenia may complain only of binocular diplopia. As with any diplopic patient, it should be determined if the diplopia is horizontal, vertical, or oblique. In addition, it should be determined if diplopia is persistent or episodic and, if episodic, if the episodes are stereotyped (for example, always horizontal diplopia while viewing distant objects) or variable (for example, sometimes horizontal and sometimes vertical). The latter would be suspicious for ocular MG. It is important to keep in mind that episodic diplopia does not equate to ocular myasthenia, as diplopia from any cause (eye muscle, myasthenia, cranial nerve, etc) may be noted by the patient only episodically in different gaze positions. An example of this is, with a right sixth nerve palsy, the patient will have diplopia upon right gaze and possibly when looking straight ahead – but often no diplopia is present in left gaze.

The diurnal course of diplopia may be helpful, as myasthenic diplopia is often worse late in the day or precipitated by fatigue or exercise and possibly by sunlight. Historical features of generalized myasthenia should also be

sought in any diplopic patient - shortness of breath, proximal muscle weakness, and fatigability with chewing or swallowing.

**EXAMINATION FEATURES**

Examination signs of ocular MG include those listed in table 1. See cases at the end of the syllabus for photo examples of some of the signs. The presence of these signs raises suspicion for myasthenia; however, they are not pathognomonic and confirmatory laboratory testing of diagnosis is important to obtain, if possible.

*Variability:* Although not always present, moment to moment or visit to visit variability are very helpful in diagnosing ocular MG. For example, if a patient who appears to have an eye movement problem consistent with an isolated fourth (trochlear) nerve palsy comes in weeks later with resolution of this deficit but interval development of a different motility problem, ocular MG should be highly suspect – even in the absence of ptosis. Similarly, ptosis that shifts sides or that recurs after surgical ptosis repair is highly suggestive of MG.

*Fatigability:* For adequate assessment of fatigability, it is important to maintain upgaze for at least one minute and to assess for development or worsening of symptomatic diplopia, ptosis or eye muscle downward drift (Figs. 1 and 4). Patients with ocular MG may appear to develop upward beating nystagmus with prolonged upgaze due to downward drifts of the eyes from fatigue, followed by the patient's re-exerted effort to maintain the eyes in upgaze. While fatigable ptosis is highly suggestive of MG, it is not pathognomonic and has been rarely reported with central structural brainstem lesions.[6]

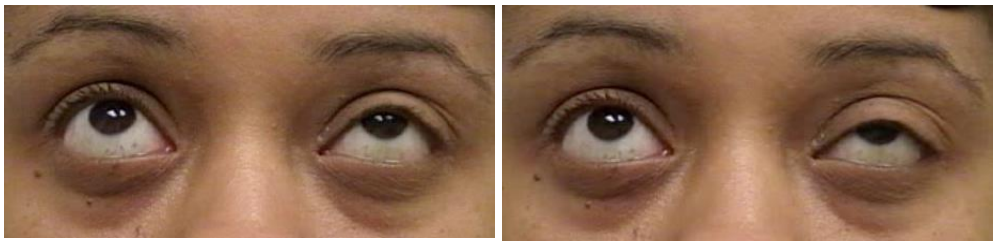


**Figure 1.** Fatigability with worsening of mild left ptosis (left picture) after 2 seconds of upgaze (right picture).

*Cogan's lid twitch:* Cogan's lid twitch is an excessive twitch of the upper lid upon return of the eyes to central position after 10 seconds of sustained downgaze. Cogan's lid twitch increases suspicion for a defect of neuromuscular transmission, but it is not pathognomonic, as it has been reported with central structural brainstem lesions and extraocular muscle disease.[7-9] Sensitivity (50%) and positive predictive value (25%) were poor in one prospective study of the sign in subjects with isolated, symptomatic ptosis.[9] Sensitivity may be higher in the presence of both ptosis and diplopia.

*Peek sign:* The peek sign is positive when attempts at sustained active eye closure result in exercise-induced orbicularis oculi weakness and lid separation ('peeking') after initial complete eye closure.[10]

*Enhanced ptosis or curtaining:* Hering's law of equal neural innervation to each eyelid is the basis for this sign.[11] The sign consists of development of increased ptosis in a less or non-ptotic eyelid upon manual elevation of the more ptotic lid (Figs. 3 and 6).[12] When ptosis is present, maximal neural innervation is supplied in an effort to overcome the ptosis. When this excess neural output is alleviated via manual elevation of the ptotic lid, contralateral ptosis may become more prominent.

| Table 1. Examination signs of ocular myasthenia gravis |
|---|
| Moment to moment or visit to visit variability in ocular motor range or eye alignment |
| Fatigue of lids or eye elevation with prolonged upgaze |
| Cogan's lid twitch |
| Peek sign |
| Orbicularis oculi weakness |
| Ptosis and enhanced ptosis |
| Faster than normal or 'twitchy' eye movements (lightening saccades) |

## DIAGNOSTIC BEDSIDE TESTING

*Ice and rest tests:* The fact that cold temperatures improve neuromuscular transmission is the premise for the ice test. To perform this test, an ice pack is placed over a closed ptotic eye for 2 minutes, followed by observation for resolution of ptosis. Sensitivity and specificity are reportedly 92-94% and 79-97%, respectively.[13,14] Enhanced neuromuscular transmission also occurs with rest in MG, thus, the rest test. Improvement in ophthalmoplegia or ptosis are observed following a period of rest or sleep in a positive test (Fig. 2).[15]

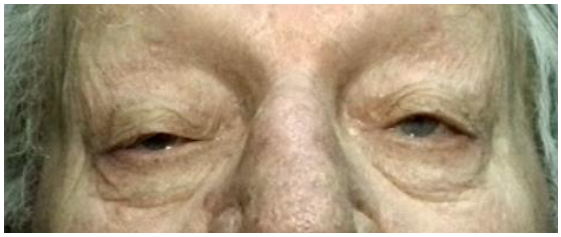
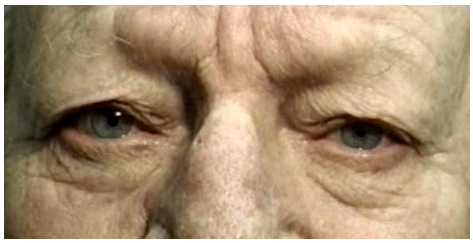
A.  B. 

**Figure 2.** A. Right greater than left ptosis in a patient with myasthenia gravis. B. Signficant improvement in ptosis following a period of sleep (in other words, a positive rest test). Photos courtesy of Dr. Eric Eggenberger.

*Edrophonium chloride test:* Edrophonium chloride is a reversible acetylcholinesterase inhibitor that slows breakdown of acetylcholine in the neuromuscular junction synaptic cleft, thereby improving neuromuscular transmission. Bedside testing is most useful when there is a defined deficit, such as significant ptosis or a fixed ocular motor deficit, that may be monitored for an unequivocal test response (Fig. 5). Sensitivity and specificity in ocular MG are 80-90% and 86-88%, respectively.[16,17] Some clinicians no longer perform this test, or do so only in an environment with cardiac monitoring, due to the potential test risks of cardiac arrhythmias, syncope, and respiratory failure. However, the risk of serious side effects is approximately 0.16% and incremental administration of the edrophonium lowers the risk, as a small dose (mean 3.3 mg) will often result in a positive test (See case 1 at end of syllabus).[18,19]

## DIAGNOSTIC LABORATORY TESTING

*Serum antibody testing:* Three acetylcholine receptor antibodies are available: binding, blocking, and modulating. Binding antibodies are the most sensitive. The literature reports a sensitivity of 96% for acetylcholine receptor antibodies in generalized MG; however the reported sensitivity in ocular MG is lower and variably reported to be between 38-71%.[20] Therefore, the antibodies are only helpful if present (specificity is very high) but their absence does not exclude ocular MG.[16,21] Anti-MUSK (muscle specific kinase) antibodies are found in a high percentage of generalized myasthenics seronegative for acetycholine receptor antibodies. Eye movements are frequently affected in these patients and may be the initial presenting feature in up to 36%, with subsequent generalization. Anti-MUSK antibodies are rarely found in isolated, chronic ocular MG; however several cases have been reported.[22-24]

*Electrophysiology:* Detection of a decremental repetitive stimulation response on EMG has a specificity of over 97% in ocular MG, but a sensitivity of only 24%.[25] Orbicularis oculi single fiber EMG has high specificity (97%) and sensitivity (92%) in ocular MG.[26] A small study (n=27) of a new technique, oVEMP (ocular vestibular evoked myogenic potentials), that may be useful in diagnosis of MG was reported last year.[27,28] This technique is akin to repetitive stimulation of the inferior oblique muscle. A decremental response of 15% was shown to have a sensitivity of 89% and a specificity of 64%, with equal sensitivity in isolated ocular MG and generalized MG with ocular involvement. Certainly further study is required to determine its clinical utility, however preliminary data shows promise.

## TREATMENT

Optimal treatment for isolated ocular MG is unclear. If manifested as a stable ocular motility defect with stable eye alignment, optical prism therapy may be quite effective. Pyridostigmine often helps ptosis, but is less effective for diplopia.[29] Corticosteroids may help both ptosis and diplopia, as well as decrease the risk of progression from ocular to generalized MG.[29]

**CASE EXAMPLES**

***Case 1: Classic ocular myasthenia gravis – You can know it's myasthenia, and it is.***

A 68 year old woman with a history of Sjogren syndrome, hypothyroidism, hyperlipidemia, and hypertension presented with double vision and a 'drooping left lid'. Three months prior, she had an episode of painless binocular horizontal diplopia upon getting up to the bathroom in the middle of the night. Over the next few weeks, she had diplopia only with lying down to watch television. One month prior, she developed painless left ptosis, which gradually increased over time and was worse at night. She denied proximal muscle weakness or difficulty swallowing.

On exam, she had 4 mm of left ptosis, with enhanced ptosis of the right lid (Fig. 3). Cogan's lid twitch was equivocal. There was no orbicularis oculi weakness. There was fatigability of the ptotic left lid with 2 minutes of prolonged upgaze (Fig. 4). Pupils were normal. Motility was normal other than 90% of normal elevation of the right eye in an adducted position (action of the right inferior oblique muscle).

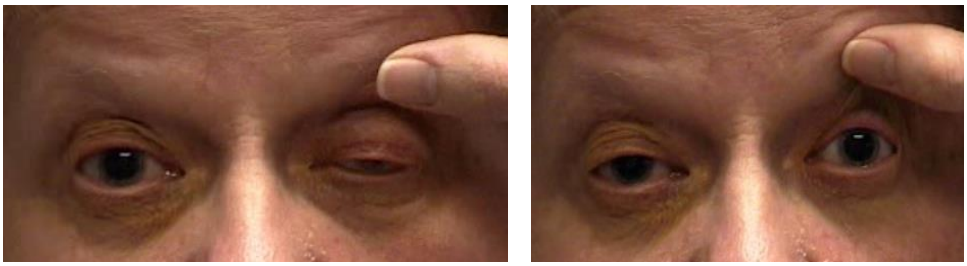


**Figure 3.** Eye appearance at rest (left photo) with prominent, nearly complete left ptosis. Demonstration of enhanced ptosis (right photo) shows development of right ptosis with manual elevation of the left lid. The pupils are pharmacologically dilated in this patient in Figures 3-5.

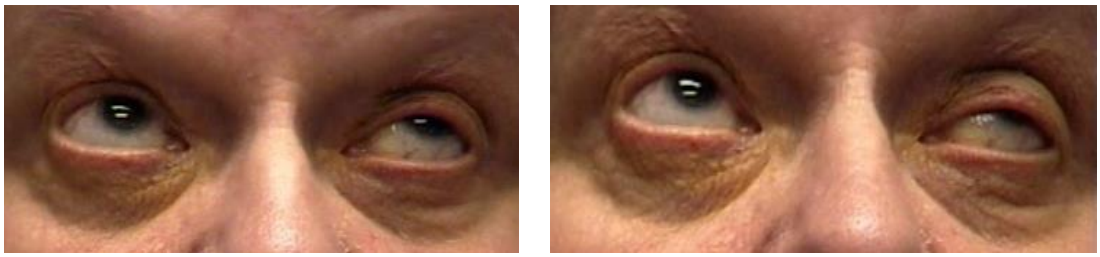


**Figure 4.** Eye appearance after a few seconds of upgaze (left photo) shows left ptosis. Note that the inferior third of the pupil and iris are visible. Eye appearance after 120 seconds of upgaze (right photo) shows increased left ptosis with nearly complete coverage of the pupil and iris. This fatigability would have been missed if upgaze had been maintained for less than one minute, as it took it over one minute to develop.

Edrophonium hydrochloride testing was done in the office. Following administration of 1 mg, there was complete resolution of ptosis (Fig. 5). Acetylcholine receptor antibodies were positive: binding 6.2 nmol/L (normal 0.0-0.4), blocking 55 (0-15), and modulating 44 (0-20).

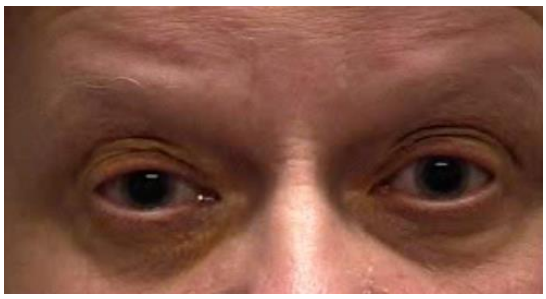


**Figure 5.** Positive edrophonium test. Resolution of left ptosis 15 seconds after administration of 1 mg of edrophonium. Compare with baseline left photo in Figure 3.

Discussion: This is a patient with classic isolated ocular MG suggested by history (painless intermittent diplopia followed 2 months later by fatigable ptosis) and examination (ptosis with enhanced ptosis of opposite lid and a combination of elevation defect in adduction in the right eye and left ptosis not easily explained by single cranial nerve process) in a patient predisposed to autoimmune disease (history of Sjogren and hypothyroidism). Diagnosis was confirmed by edrophonium and acetylcholine receptor antibodies. This patient would be a good candidate for pyridostigmine, since she was primarily bothered by ptosis.

***Case 2: The pseudo-INO – You can wonder if it's an INO – but keep myasthenia in differential diagnosis, and it is myasthenia.***

A 58 year old man with a history of right Bell's palsy 10 years ago presented with complaints of double vision and a droopy left eyelid with onset two weeks ago. He denied proximal muscle weakness, shortness of breath, or difficulty swallowing or chewing. The symptoms were painless and he had no other neurologic complaints.

On exam, he had left ptosis and questionable, very subtle enhanced ptosis (Fig. 6). There was no fatigability of the ptosis or eyes with prolonged upgaze for 2 minutes. There was no Cogan's lid twitch, orbicularis oculi weakness, or proximal muscle weakness. Motility exam revealed full motility in all directions. Smooth pursuit appeared normal. Dynamic evaluation of horizontal saccades (fast eye jumps between two targets) disclosed very subtle slowing of adduction in the right eye with saccades from right gaze to left gaze (suggestive of a partial adduction deficit of the right eye for saccade velocity only) and 1-2 beats of abducting nystagmus of the left eye. Ocular alignment testing revealed a small exophoria that increased in size upon left gaze.

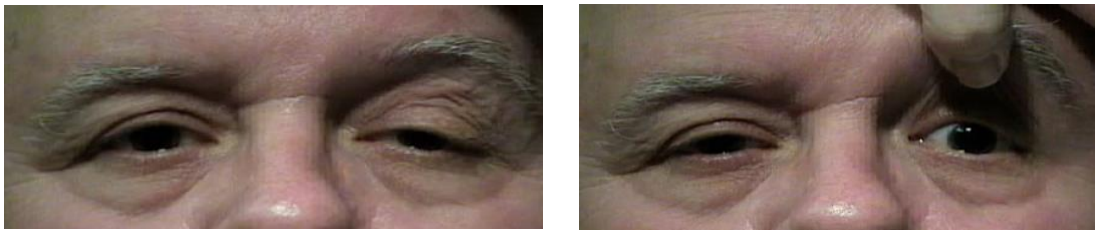


**Figure 6.** Eye appearance at baseline (left photo) with excessive lid skin (dermatochalasis) and prominent left ptosis with probable milder right ptosis. Manual elevation of the ptotic left lid results in a very subtle narrowing of the right palpebral fissure (right photo).

Slowing of adduction in the right eye, an exophoria larger in left gaze suggesting an adduction defect of the right medial rectus, and abducting nystagmus of the left eye all suggested a mild right internuclear ophthalmoplegia. However, lid findings raised the possibility of MG. Acetylcholine receptor antibodies were positive.

Discussion: This is a patient with isolated ocular myasthenia with left ptosis and a right pseudo-internuclear ophthalmoplegia. Ocular motility range was normal and, other than for very subtle possible enhanced ptosis, there were no examination features to specifically suggest MG.

***Case 3: Myasthenia after third nerve palsy – You can think it's not myasthenia, and it turns out to be.***

A 64 year old man with a history of hypertension and hyperlipidemia presented with complaints of double vision and ptosis. Two months prior, he had the onset of a headache over his left eye. Three days after headache onset, he developed binocular oblique diplopia and partial left ptosis. The next day, ptosis was complete. According to his ophthalmologist, his pupils were normal. Brain MRI with contrast and MRA were normal. He was diagnosed with a microvascular ischemic left third nerve palsy. On neuro-ophthalmologic exam, he had normal pupils, 5 mm of left ptosis, and impaired elevation, depression, and adduction of the left eye with a left eye positioned "down and out" (right hypertropia and exotropia).

At 2 month follow-up, consistent with the expected temporal course of a microvascular ocular motor cranial mononeuropathy, his pain, diplopia, and ptosis had resolved. The prior examination findings had resolved, but he had mild abduction impairments bilaterally with an inward deviation (esotropia) of the eyes that increased on right and left gaze. He also developed diplopia in right and left gaze. There was no ptosis, fatigability, Cogan's lid twitch, or orbicularis oculi weakness.

Differential localization included bilateral sixth nerve palsies and myasthenia gravis. Repeat MRI brain with contrast was normal, as was lumbar puncture (including opening pressure). Acetylcholine receptor antibodies were negative. Repeat exam after 3 more months was unchanged. The patient reported having been sent to physical therapy for "difficulty hauling himself out of chairs". He had mild lower extremity proximal muscle weakness. EMG with repetitive stimulation revealed a decrement and the patient was diagnosed with generalized MG.

Discussion: This is a patient with generalized myasthenia diagnosed following spontaneous resolution of a microvascular third nerve palsy. While the initial ptosis and motility examination in light of the normal pupil examination could have been myasthenic in origin, the exam was classic for third nerve dysfunction and the presence of pain strongly favored microvascular palsy over ocular MG. After resolution of the third nerve palsy, his ocular motor exam did not reveal any particular features of MG – but MG may mimic any ocular motor disorder even in the absence of specific MG signs. Ocular MG was the likely explanation for the bilateral abduction deficits, with subsequent generalization of disease.

***Case 4: Don't be fooled – You can think it's myasthenia, and it's not!***

A 43 year old man who was given a diagnosis of MG 15 years ago presented with two weeks of painless double vision and ptosis. Fifteen years ago, he had the onset of binocular oblique diplopia, ptosis, and generalized weakness. He recalls having been given "an IV medication" that helped his arms move better, having blood tests for MG that were negative, and being discharged on pyridostigmine with a diagnosis of MG. His illness resolved completely over 3 months and he discontinued pyridostigmine over 14 years ago with no recurrent symptoms until 2 weeks ago.

Acetylcholine receptor antibodies and EMG, as ordered by his neurologist, were unremarkable and he was told he had recurrent MG and was placed on pyridostigmine.

On neuro-ophthalmologic examination, he had impaired bilateral abduction, adduction, and elevation of both eyes (horizontal eye movements are shown in figure 7) and mild bilateral ptosis. There was no Cogan's lid twitch, fatigability on prolonged upgaze, or orbicularis oculi weakness. His pupils had decreased reactivity to light bilaterally, with normal reaction to a near stimulus and general neurological exam revealed complete areflexia.

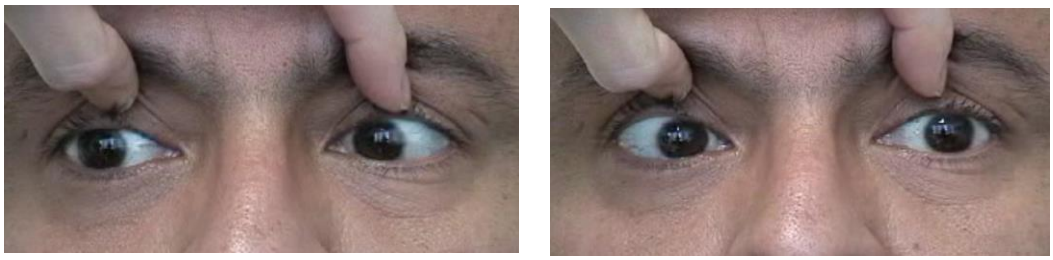


**Figure 7.** Impaired abduction and adduction on attempted right gaze (left photo) and left gaze (right photo).

Anti-GQ1b antibodies were significantly elevated. Examination spontaneously normalized without treatment 2 months after symptom onset.

Discussion: This is a patient with Miller-Fisher syndrome (MFS), likely recurrent after 15 years. The presence of tonic bilateral pupils and areflexia are characteristic for MFS and are not associated with MG. Miller-Fisher syndrome consists of a classic triad of ophthalmoplegia (from multiple cranial nerve involvement), areflexia, and ataxia.[30] This patient lacked ataxia, but an incomplete triad is reported with the syndrome. Recurrent MFS is also reported and it is probable that the illness 15 years prior was also MFS.[31,32]

***Take home message: Keep myasthenia in differential for any patient with diplopia!***

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