Non-ptotic ocular myasthenia gravis: a common presentation of an uncommon disease

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Background: Myasthenia gravis (MG) is an acquired autoimmune disease of the neuromuscular junction which causes rapid muscle fatigue and weakness. Two thirds of all cases of myasthenia gravis (MG) initially manifest ptosis. In the absence of the characteristic variable ptosis, MG can present a challenge to the clinician. This article will review the current diagnostic and management strategies for MG.

Case Reports: Five cases will be presented that did not initially present with ptosis. Each of these cases was previously misdiagnosed as a result of presentation of atypical myasthenia gravis signs and symptoms. The first two cases had signs and symptoms of a typical accommodative/vergence anomaly. The others manifested diplopia not normally associated with MG: one had a noncomitant vertical deviation; another had a stable 6th nerve palsy; and the third had a basic esotropia.

Conclusion: Although the hallmark findings of MG are ptosis and eye muscle palsy with variability, MG may present without ptosis, affect nonstriated muscles, and/or manifest either as a nonstrabismic vergence anomaly or as comitant nonvariable strabismic deviation.

Key Words: Accommodative insufficiency, convergence insufficiency, diplopia, myasthenia gravis, oculomotor paresis, strabismus

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The name *myasthenia gravis* (MG) is derived from the Greek, meaning "gravely weak muscles," and was first described by Sir Thomas Willis in 1672.[1] It was later considered in detail by three German physicians—Goldflam, Erb, and Jolly—in 1890. Twenty years ago, an animal model was developed that led to a better physiologically based understanding of the disease, and which resulted in new treatment options.[1]

The pathophysiology of the disorder requires an understanding of the neuromuscular junction (NMJ), which is the point at which the nerve fiber either synapses with or terminates on a muscle fiber. When a nerve impulse is initiated, it travels to the NMJ. Here the neurotransmitter acetylcholine (Ach) is then released, passes through the NMJ, and ultimately attaches to receptors on the muscle surface, thereby resulting in muscular contraction. In MG, antibodies erroneously destroy Ach receptor sites, which are located at the postsynaptic membrane of the NMJ. This prevents Ach from binding to muscle cells, and hence inhibiting muscle contraction. (Current thinking is that T cells derived from the thymus stimulate B cells to produce the antibodies that react at the Ach sites.)[2] The result is a progressive muscle weakness that worsens with sustained activity.[3,4]

MG occurs in approximately 14 of every 100,000 people, resulting in a prevalence of 36,000 cases in the U.S. It can occur at any age, but has a bimodal distribution that affects women below age 40 years and men more than 60 years of age.[5-7] MG is characterized by ptosis, facial weakness, dysarthria, dysphagia, and dyspnea.[2] Among patients who manifest ocular myasthenia gravis (OMG), generalized myasthenic

symptoms will develop in more than 50% within two years.[8] Two thirds of all cases of MG initially manifest ptosis and/or diplopia. A history of a variable ptosis makes MG the most likely differential diagnosis. However, when the patient manifests diplopia, or with an accommodative/vergence insufficiency, the diagnosis of MG becomes more elusive.

The exact cause of this auto-immune disease is unknown; it is thought there might be a genetic and/or viral etiology. Thymus abnormalities are associated with MG, but the exact relationship is uncertain. The thymus produces cells involved in immune responses. Approximately 10% of patients with MG have a thymoma or tumor of the thymus, and 70% have hyperplasia of the thymus, which is usually associated with active auto-immune disease. Since the thymus is the central organ for immunological self-tolerance, it has been suggested that abnormalities of the thymus may cause an immune-mediated attack on the Ach receptor in MG.[9]

Patients with MG also have an increased prevalence of other auto-immune diseases, such as rheumatoid arthritis, thyroid disease, and vitamin B-12 deficiency. Symptoms of MG, which vary day-to-day, may be exacerbated by stress, systemic illness, thyroid disease, pregnancy, menstruation, and certain drugs.[3]

Diagnosis

The diagnosis of OMG is usually made by a combination of patient history, clinical findings, and other diagnostic procedures. The first suspicion of OMG should come to mind during the case history if the patient manifests symptoms of ptosis, diplopia, and/or blur, which increases with use of the ocular muscles, or as the day progresses. Patients with generalized systemic MG may also manifest fatigue of the face, neck, and limbs, worsening with activity. Brushing one's teeth or combing hair may become problematic. Head droop and down-sloping of a smile may be noted. Variability of symptoms should further trigger suspicion. The gold standard for diagnosis of OMG is the Tensilon test. However, there are a number of non-invasive tests that can also be used to make the diagnosis; all are simple, inexpensive, and highly sensitive.

The first test involves "fatiguing" the extraocular muscles in upgaze. The patient attempts to sustain extreme upgaze for 30 seconds, then quickly returns to primary position. Patients with OMG often demonstrate either a lid-lag or an increase in ptosis (Darple's sign). This is repeated five times, to initiate fatigue. Second, the patient is told close his or her eyes, and then there is an attempt to pry open the eyelids. In a non-OMG patient, this will be difficult to perform. However, in the OMG patient, minimal resistance will be found. Third, the eyebrow is lifted over the more ptotic eye. If a patient has OMG, the contralateral eyelid will exhibit more ptosis, while in normal patients only a minimal change will occur. These three tests are specific to the patient who manifests a ptosis.

Similar tests of ocular fatigue can be conducted while version, vergence, and/or accommodative testing are performed. It may be necessary to place a red lens over one eye to disrupt fusion and to identify a suppressing eye. Accommodative fatigue may be determined with accommodative facility testing (i.e., behind the phoropter while binocularly alternating the sphere power by ± 1.50 D to produce large changes in accommodative demand). In patients with MG, the initial response is often one of clarity. With repeated changes, however, fatigue rapidly occurs. Increased blur or diplopia on repetition is suggestive of MG.[10] In addition, monocular accommodative amplitudes may be different between the eyes by at least a diopter, generally lower in the second eye tested.

If MG is still suspected, three simple tests may be performed at home by the patient: photo review, the ice test,[11,12] and the sleep test.[13] The photo review test requires looking at previous pictures, then taking early morning and late evening full-face pictures for three days. Lid position and ocular alignment are noted. If a patient has OMG, there will be an increase in the ptosis and/or ocular deviation in the evening pictures, when greater fatigue would be expected to be present. The picture review process may be combined with the sleep and ice test described here.

The ice-pack test has been shown to be both highly sensitive and specific for OMG in more than 90% of the cases.[12] The palpebral fissure is measured, and then an ice-pack is applied to the

ptotic lid for a minimum of 3 minutes. An increase in the palpebral fissure of 2 mm is considered a positive response. Non-myasthenic patients do not demonstrate such a change. The ice-pack test can also be performed to look for a decrease in diplopia; however, the results may be less dramatic.[14]

The sleep test is also sensitive and specific for MG. The patient sleeps for 30 minutes in the middle of the day or evening to ascertain if the ptosis and/or diplopia decrease with rest. In our practice, all three tests are combined at home. On one of the days the MG suspect performs a photo review, a 30-minutes nap is taken in the evening with an ice bag placed on one eye. Pictures are taken immediately on awakening. The patient then brings the pictures to the doctor, who reviews them with magnification (a 20 D condensing lens), looking for signs of reduction of ptosis and/or strabismus.

In addition, the patient with suspected MG should have a blood test performed to measure the level of serum anti-acetycholine receptor antibodies. The caveat to this test is that 20% of patients with general MG and 50% with ocular MG will be sero-negative. Another more-specific blood test can detect the presence of anti-striated muscle antibodies, which is positive in about 84% of patients with thymoma who are younger than 40 years of age. In individuals more than 40 years, anti-striated muscle antibodies can be found in MG without thymoma.[15,16]

If the diagnosis of MG is still suspected but unconfirmed, a Tensilon Test may be performed. Tensilon (edrophonium chloride), an anti-cholinesterase drug, inactivates the enzyme that breaks down acetylcholine. This results in an excess of acetylcholine in the neuromuscular junction, thus producing transiently improved muscle function. Tensilon is injected at a rate of 2 cc every two minutes for 10 minutes, until 10 cc are injected. Immediately following the injection, either the patient's ptosis or eye-muscle function will improve in a myasthenic patient. It should be noted that some patients with MG will have a negative Tensilon result. However, more than 90% of patients with OMG will have a positive Tensilon test. (Atropine should be readily available in case of a hypersensitivity reaction.)[17]

If Tensilon testing is contraindicated or negative in highly suspected cases, there are several electrodiagnostic tests that can be performed to support a diagnosis of MG. Repetitive nerve stimulation (RNS)—as the name suggests—involves repetitive electrical stimulation of the nerve while recording the muscle response.[18] A decrease in the fourth or fifth response by 10% of the initial value is a positive finding. While this test is highly specific for disorders of neuromuscular transmission (such as MG), it is not very sensitive. A negative result does not exclude the diagnosis of MG. Additionally, it is much more sensitive for general MG (60% to 85%) than for OMG (18% to 35%).

Single-fiber electromyography (SFEMG) is the most-sensitive clinical test of neuromuscular transmission.[19,20] SFEMG shows an increased activity in some muscles in almost all patients with MG. Its sensitivity is 91% to 100% for generalized MG, and 80% to 88% in patients with OMG. Though the SFEMG is very sensitive for MG and OMG, it is not very specific. The SFEMG requires specialized equipment and relies heavily on the skill of the examiner, so is not as easily performed as the RNS test.

A CT or MRI of the thymus is necessary for patients in whom OMG is diagnosed to rule out the presence of a thymoma. Lastly, all cases that manifest neurological signs such as ptosis and/or diplopia should have a threshold visual fields performed. (In the following cases presented, Humphrey threshold 24–2 visual fields were performed and were normal.)

Treatment

Treatment of OMG consists of one or more of the following options: cholinesterase inhibitors, thymectomy, plasmapheresis, corticosteroids, and/or other immunosuppressive drugs. Treatment goals are individualized according to the severity of the disease and the patient's predicted tolerance to specific therapies. Untreated MG has a mortality rate of 25% to 31%, usually due to respiratory muscle paralysis; however, with current treatment, the mortality rate has decreased to 4%.[21]

Oral cholinesterase inhibitors such as pyridostigmine bromide (Mestinon) are the first line of treatment. They slow down the enzymatic destruction

of Ach at the neuromuscular junction.[22,23] This allows the concentration of Ach to accumulate, which, in turn, prolongs muscle contraction. Cholinesterase inhibitors, the first line of treatment for OMG, may result in considerable improvement in some patients, but little to no improvement in others. Generally speaking, cholinesterase inhibitors work better in systemic MG. In some cases, they are ineffective because they may only reduce but not eliminate ocular misalignment, thereby causing diplopia to be more bothersome, or they may improve a severely ptotic eyelid, which can unmask diplopia. Because of their high incidence of gastrointestinal side effects, they are not well-tolerated in the elderly population. Rarely, cholinergic medications may result in a cholinergic crisis.

A thymectomy is the surgical removal of the thymus gland. It is often performed on young people early in the course of the disease.[24] The surgery is performed in young patients with or without a tumor. Unfortunately, patients more than 60 years of age rarely show substantial improvement from thymectomy.

Plasmapheresis, or plasma exchange, is used as a temporary treatment for patients with sudden worsening of symptoms.[23] Several liters of blood are removed, the plasma cells are filtered out, and then the red blood cells are returned with artificial plasma, in an attempt to remove the offending antibodies. Patients feel better for a few days after the procedure, but symptomatic improvement only lasts several weeks.

Immunosuppressive therapy improves muscle strength by suppressing the production of abnormal antibodies. Oral corticosteroid therapy (Prednisone) is typically prescribed in moderate-to-severe cases that do not respond to cholinesterase inhibitors and thymectomy.[25] Significant improvement occurs in more than 75% of the cases. The patient is started on a high daily dose of Prednisone (60 to 80 mg), which is then systematically reduced until the minimal effective dosage is reached. Long-term treatment may cause either remission or significant improvement in most patients in 1 to 4 months. However, long-term use may predispose patients to significant problems such as hyperglycemia, osteoporosis, gastric ulcer disease, weight gain, and Cushing's syndrome. Ocularly, intraocular pressure and cataract formation should be monitored.

Recently, other immunosuppresive drugs have been used effectively to treat MG, such as Cyclosporine and Azathioprine. Cyclosporine is a fungal peptide with potent immunosuppressive activity.[26] It inhibits the T-lymphocyte-dependent immune response in MG. Its maximum effectiveness occurs in six months, after which time the drug is tapered to achieve the minimal effective dosage. Two of the most-serious side effects of cyclosporine are hypertension and nephrotoxicity. Azathioprine (Imuran™) may be effective in those patients who do not respond to either Prednisone or cyclosporine.[27] The effect of this drug, however, may take 6 to 8 months; therefore, the two drugs might be used simultaneously. While the Prednisone is tapered, the Azathioprine effect begins.

A new short-term treatment currently under investigation uses intravenous human immune globulin (IVIG).[28] It saturates the body with pooled gamma globulin antibodies derived from many donors, which is thought to have a nonspecific suppressive effect on the immune system. Improvement starts within a few days and peaks in a few weeks.

Recent studies by both Kupersmith et al.[29] and Mee et al.[30] strongly suggest that immunomodulatory therapy (e.g., corticosteroids, azathioprine, thymectomy), significantly delays—or even prevents—generalization of the disease.

Case Reports

Case 1

The pathognomonic pattern of accommodative fatigue in ocular myasthenia gravis.[10] A 25-year-old female reported asthenopia after 5 minutes of near work; i.e., blurred vision, pulling sensations, and headaches. The symptoms had been occurring for 12 years prior to the initial examination. Her hyperopia was corrected to 20/20 OU with spectacles. Extraocular muscle movements were full and concomitant. Cover testing revealed orthophoria at distance and 4Δ exophoria at near. The near point of convergence was 2/4″. Suppression was noted on first- and second-degree targets, thus suggesting an oculomotor anomaly of long duration. Vergence amplitudes were reduced and without elicitation

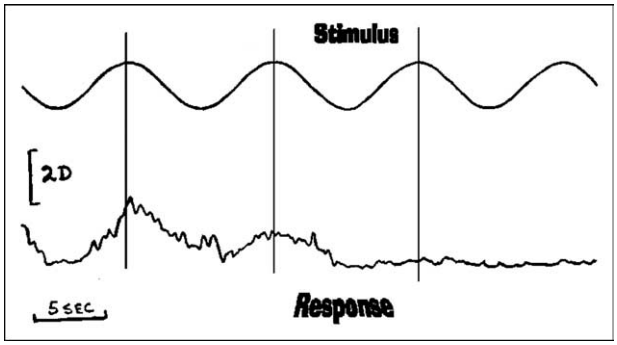

Figure 1 Accommodative findings of a patient with ocular myasthenia gravis are presented. The top tracing depicts the sinusoidal stimulus and the bottom the response. Note, the initial responses were reasonability robust with a delayed latency. After a complete response, accommodative fatigue is evident, becoming flat over a short period of time. (Reprinted with permission of *Binocul Vis Eye Muscle Surg Q.* 1988:3 p.145).

of blur (BO X/9/4 and BI X/8/5), but with asthenopia induced on testing. Accommodative facility was initially normal, with ± 1.50 flippers performed both monocularly and binocularly at 40 cm, but rapidly showed fatigue with repetition.[31]

These findings suggested an overall accommodative and fusional-vergence insufficiency with associated asthenopia. Vision therapy was begun, which included activities to improve smooth fusional capabilities, step or jump ductions, and accommodative facility and amplitude training. Paradoxically, training increased her signs and symptoms. Two months after the initial examination, a re-evaluation was performed that demonstrated a variable extraocular muscle paresis and mild ptosis with repeated eye movement testing.

A Tensilon test was performed, which was equivocal. However, single-fiber electomyography tests were positive for MG. To document the presence of an accommodative deficit objectively, a high-speed infra-red optometer was used to measure accommodative responses dynamically to sinusoidally moving accommodative targets. Figure 1 presents the recording. Initially, accommodation was robust and accurate. With repetition, effects of fatigue were evident. Accommodation initially displayed a lag, and eventually showed fatigue to the point that no change in accommodation occurred in response to the blur stimulation.

Case 2

Ocular myasthenia gravis masquerading as accommodative and convergence insufficiency.[32]

A 25-year-old female optometry student came to us with a history of ocular fatigue, associated with near work, occurring over the preceding two years. She had a childhood diagnosis of asthma for which she was taking salmeterol xinafoate (Serevent, GlaxoWellcome, Reasearch Triangle Park, North Carolina), triamcinolone acetonide (Asmacort, Rhone–Poulenc Rorer, Collegeville, Pennsylvania), and metaproterenol sulfate (Alupent, Boehringer Ingelheim, Ridgefield, Connecticut). Non-cycloplegic and cycloplegic refractions were identical (–0.75 sph 20/20 O.D.; –0.75 sph 20/20 O.S.).

At her initial vision examination, as a first-year student, she reported difficulty focusing while reading. This was verified with an abnormal monocular and binocular ± 1.50 accommodative flipper test result and reduced accommodative amplitudes of 2 D sphere right eye and 0.5 D sphere left eye. The age-related clinical norm was 11 D. (By chance, this patient also participated in a study in which dynamic accommodative measurements were performed and were found to be normal.) Phorometric findings revealed 2Δ of left hyperphoria. Random-dot stereopsis was present, but reduced (660 sec arc), thus indicating bifoveal fixation. All other ocular findings were normal. The record did not suggest any treatment or further testing based on these abnormal findings.

Two years later, the patient returned with similar symptoms of ocular fatigue, but now with the additional symptom of occasional diplopia. Findings again suggested an accommodative insufficiency now associated with convergence insufficiency. Both near point of convergence and fusional amplitudes were reduced. Interestingly, the initially measured hyperphoria of two years earlier was not present. On the basis of these findings, weekly vision therapy was initiated to improve both accommodative and fusional vergence function. The therapy was designed to improve static and dynamic accommodation, vergence, and their interactions. Normally, vision therapy is successful in improving accommodative and vergence function with concurrent elimination of symptoms in more than 90%

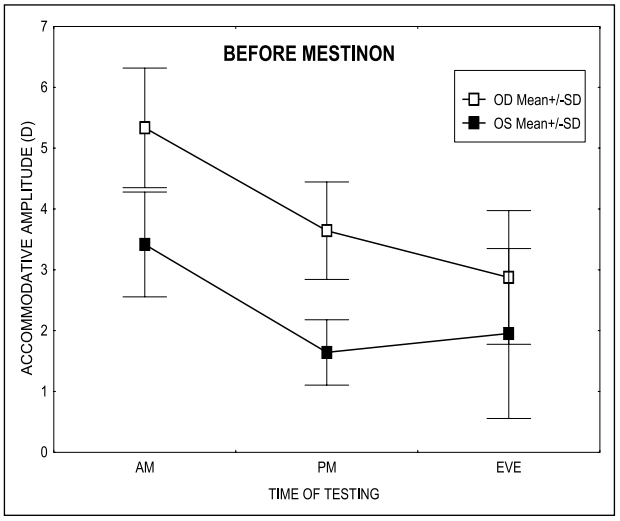

Figure 2 Accommodative amplitudes were measured using pushup methods on the right and left eye in the morning, afternoon, and early evening. It is readily apparent that amplitude decreases from morning to evening. Also, note the discrepancy between the right and left eyes. (Reprinted with permission of *Neuro-Ophthalmol* 2000;20:p8)

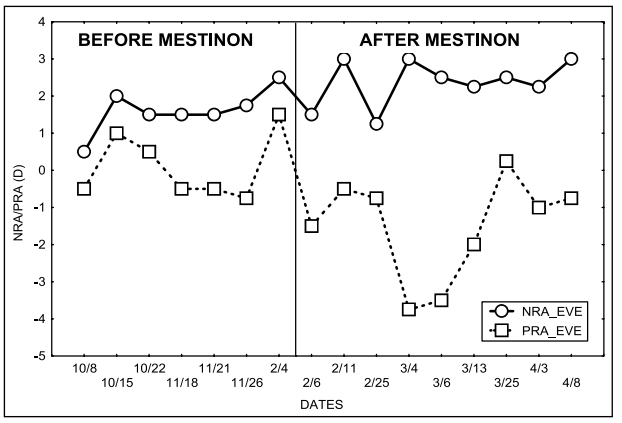

Figure 3 NRA and PRA measurements were performed morning, afternoon, and early evening. This figure depicts NRA and PRA over time. The NRA is normal and unchanged with Mestinon. However, the PRA is reduced (normal for age -2.50) to zero before Mestinon, but improves with Mestinon. (Reprinted with permission of *Neuro-Ophthalmol* 2000;20:p8)

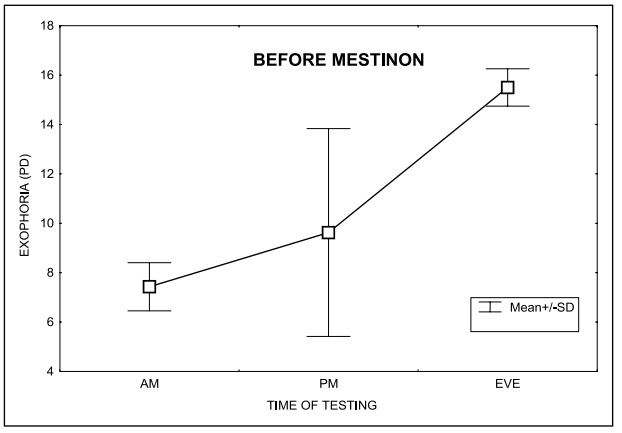

Figure 4 Phorias were measured with the VonGraffe technique in the morning, afternoon, and early evening. The phoria increases dramatically during the course of testing from 8Δ to 16Δ. The phoria decreased after administration of Mestinon. (Reprinted with permission of *Neuro-Ophthalmol* 2000;20:p9)

of patients with either convergence insufficiency or various accommodative anomalies.[34]

In this case, however—and as in Case 2—vision therapy produced a transient reduction in accommodative and vergence function. The student at this point contacted one of the authors (JC), since her symptoms had not abated from therapy. A review of her record by JC noted that her pattern of fatigue occurring during therapy was suggestive of MG. Ocular fatigue testing and the sleep test were equivocal, and the ice test was negative. Approximately two months later, a 3-mm ptosis of the left eye developed. She then had a comprehensive neurological examination, including magnetic resonance testing. The patient refused to have a Tensilon test because of her history of asthma. On initial testing, her accommodative and convergence findings were initially normal, but showed fatigue on repetition. There was also a subtle oculomotor noncomitancy of 4Δ on extreme levoduction.

We measured accommodation (positive relative accommodation, negative relative accommodation and accommodative amplitudes); vergence (positive fusional amplitudes and their respected recoveries); and cover tests in the morning, afternoon, and evening (*see* Figures 2 through 6).

On the basis of these findings, the consulting neurologist agreed with our suggestion of placing the patient on a diagnostic trial of Mestinon (Zeneca, Wilmington, Delaware) in an attempt to mimic the results of Tensilon testing. We continued to measure accommodative and vergence after the administration of Mestinon. It is clear from the results that all accommodative/vergence measurements exhibited significant reduction from morning to evening. In addition, Mestinon clearly improved both accommodative and vergence amplitudes and facility. These findings are diagnostic for MG—since Mestinon is similar to Tensilon—except for having a longer duration of action.

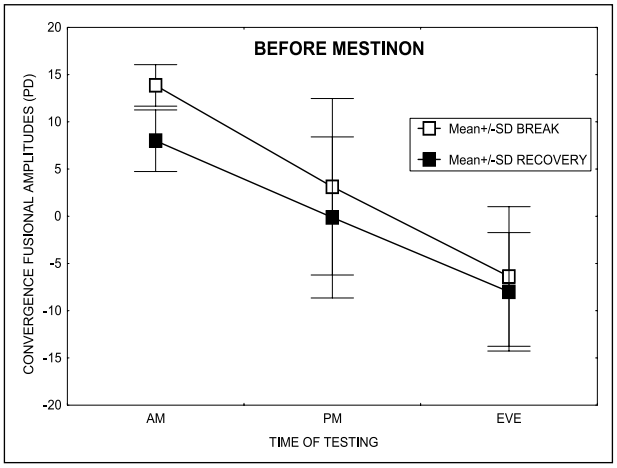

Figure 5 Convergence amplitudes (break) and recovery were measured with the Risley prisms in the morning, afternoon, and early evening. The convergence amplitude decreased dramatically from morning to evening from 15 to -8Δ. One third of the decrease may be attributed to a change in phoria. Improvement occurred with the administration of Mestinon. (Reprinted with permission of *Neuro-Ophthalmol* 2000;20:p9)

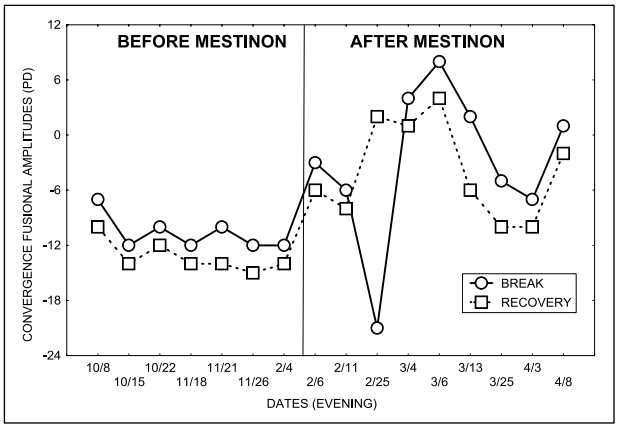

Figure 6 Convergence amplitudes (break and recovery) in the evening are presented by date. It is apparent that the amplitude varies daily, but is improved with the administration of Mestinon. (Reprinted with permission of *Neuro-Ophthalmol* 2000;20:5-11)

Prior to taking Mestinon, the patient experienced significant ocular and systemic fatigue by 7:00 PM. After taking Mestinon (60 mg daily), there was an immediate improvement in both accommodative and vergence findings, as well as a decrease in the ptosis. In addition, she reported elimination of her general fatigue. Follow-up examination one and a half years later substantiated these findings. During a short interval in which she ran out of her medication, the ptosis and ocular and systemic fatigue all reappeared. She has since remained stable with a regimen of 60-mg Mestinon twice a day.

Case 3

Ocular myasthenia gravis masquerading as a non-comitant vertical muscle palsy. A 50-year-old man was referred to author JC for evaluation of his recent-onset diplopia. The patient had a history of vertical diplopia for the previous two months. The diplopia worsened as the day progressed, and improved when he tilted his head to the left. He had been seen previously for this symptom of the diplopia without resolution. Other than Crohn's disease, all other history was unremarkable. He mentioned he was going through a stressful time in his personal life.

Best-corrected vision with a low hyperopic correction was 20/20 in each eye. Distance cover testing revealed a 3Δ left hypertropia in primary gaze, orthophoria in right gaze, and a 9Δ left hypertopia in left gaze. Diplopia was worse on right head tilt. A Park's 3-Step Test indicated a left inferior rectus (IR) palsy. (It should be noted that isolated nontraumatic, noncongenital palsy of the IR is very rare.)[35] The patient's left supraduction was 5/3, and left infraduction was –1/–3. This is consistent with a recent-onset deviation, since there was no evidence of prism adaptation. No ptosis was present. All other findings were unremarkable. Due to the recent onset of his symptoms, as well as the presentation of a non-comitant vertical muscle deviation, a blood work-up was ordered, which included Acetylcholine Receptor Antibody Titers, TSH, T3,T4 ESR, RPR, Lyme serology, and a fasting blood sugar test. The patient was instructed to perform a home sleep/ice pack test with picture review. He was also prescribed a 3Δ Fresnel press-on prism base-down over the left eye, to alleviate his diplopia.

On a follow-up examination, the blood test results were abnormal for the acetylcholine-receptor antibody level (i.e., 1.4 nmol/L—reference range is less than 0.7 nmol/L); Striated Muscle Antibody Titers (i.e., 1:160—reference range is 1:40); and TSH (i.e., 6.94 mIU/L—reference range, 0.40 to 5.50 mIU/L). All other blood findings were normal. The patient reported improvement of his diplopia after performing an ice-pack test at home on two separate occasions. These findings were consistent with acquired autoimmune MG and thyroiditis. A CT scan of the thymus was ordered, and the patient was re-

ferred to a neurologist who specialized in neuromuscular disease, and to an endocrinologist.

There was no evidence of a thymoma or thymic hyperplasia on a chest CT scan. A Tensilon test was performed, which was positive. The patient was placed on a regimen of 40-mg Prednisone every other day, later tapered by 5 mg per day. After two weeks of treatment, the patient reported a decrease in the frequency and magnitude of his diplopia. Subsequently, the patient moved out of state and was lost to followup.

Case 4

Ocular myasthenia gravis masquerading as a stable, longstanding 6th nerve palsy. A 66-year-old woman came to us with a history of horizontal diplopia for the previous 5 years. She noted that the diplopia was worse when looking into the distance than at near. The patient was taking hormone replacement therapy. She had a history of a surgical ptosis repair of her left eyelid two years earlier for cosmetic reasons. The etiology of the ptosis was not investigated at the time, nor was the diplopia, despite numerous previous visits to eye doctors.

With a slight hyperopic prescription, best corrected visual acuities were 20/25 in each eye. Distance cover test measured 10Δ left esotropia with 2Δ left hyperphoria, and the near cover test measured 12Δ esophoria with 4Δ left hyperphoria. Vertical vergence ranges were normal at distance and near. Near vergence ranges were BI x/–4/–14 and BO x/25/12. All other findings were within normal limits.

The diagnosis of a longstanding 6th nerve palsy was made, and the patient was given prism with her prescription of +2.25 D –0.75 D × 85 = $1\frac{1}{4}$ Δ BU = $3\frac{1}{2}$ Δ BO right eye and +1.25 D sph = $1\frac{1}{4}$ Δ BD = $3\frac{1}{2}$ Δ BO left eye with an add of +2.75 D in a progressive addition lens design. Blood tests were ordered, including thyroid function tests (T3,T4, TSH) sed-rate (ESR), and Acetylcholine receptor antibody titers. Given the length of time the patient was experiencing symptoms, an MRI was not immediately indicated.

On follow-up examination two weeks later, the patient stated that the diplopia was eliminated with the prism spectacles. Cover testing with correction revealed 3Δ esophoria at distance and 3Δ exophoria at near. The ice pack test was equivocal in reducing the patient's diplopia. Blood tests were negative. Due to the unexplained hyperphoric deviation associated with the horizontal deviation, the patient was referred to a neuro-ophthalmologist for evaluation. The neuro-ophthalmologist wanted to rule out MG by performing a Tensilon test. A diagnosis of OMG was made on the basis of a positive Tensilon test, and a diagnosis of hypothyroidism as indicated by a repeated blood test. The patient was placed on a regimen of 60-mg Mestinon q.i.d. for the OMG and Synthroid for the hypothyroidism. On follow-up examination 3 months later, the patient stated that her diplopia was no longer present with her current spectacles and that she was doing well with current medications. Cover testing with correction revealed orthophoria at distance and near. The patient was instructed to continue with her current spectacles and medication regimen to maintain her positive status.

Case 5

Ocular myasthenia gravis masquerading as a concomitant esotropia. A 22-year-old man with best-corrected visual acuities of 20/20 OU was referred to author JC for vision therapy. The referring optometrist noted a basic esotropia of recent onset. She had ordered an MRI, which was negative. At the initial examination, a 16Δ constant esotropia with 2Δ of hypertropia was found at distance and near. Since the patient was leaving for college, he was prescribed a prismatic correction and was referred for vision therapy in the city in which he attended college. A few months later, he returned from college and returned to JC for a followup. He stated that the prism correction initially eliminated the diplopia, which lasted for only a short period of time. After the patient returned to college, the optometrist—who initially provided the vision therapy—advised the patient that the initial prismatic correction was incorrect.

On the patient's return to JC, the variability of his measured deviation led us to suspect the possibility of MG. We performed an ice/sleep test and ordered an Ach Receptor Antibody blood test. The ice/sleep test was positive for MG (*see* Figure 7, *A* and *B*), while the antibody level was negative. A subsequent cover testing revealed a concomitant 20Δ left esotropia at dis-

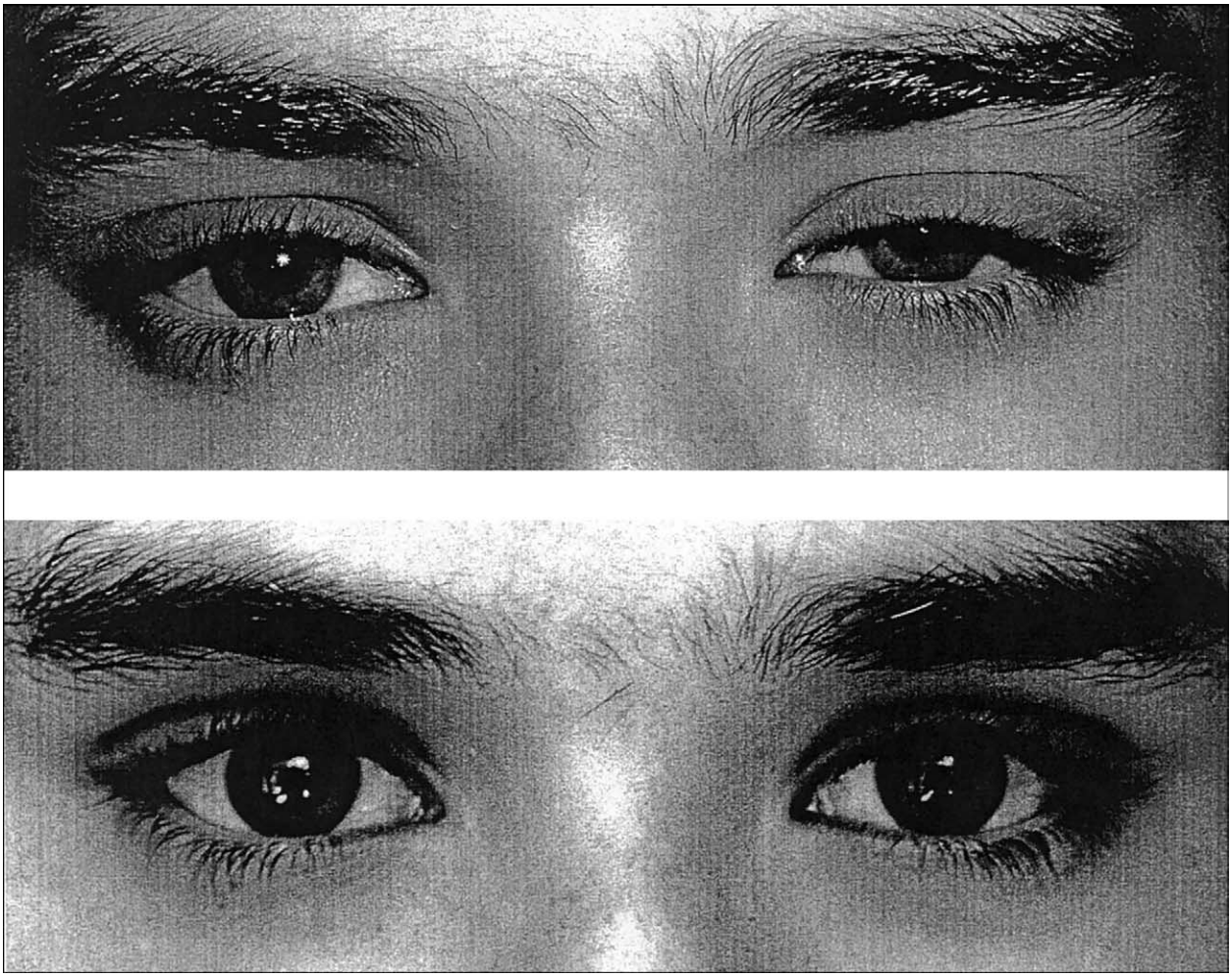

Figure 7 Patient with unequal ptosis secondary to ocular myasthenia gravis. Ice was applied for five minutes over both eyes after which a dramatic elevation of his lids was noted.

tance and 10Δ of esophoria at near. Versions were concomitant.

The patient had a neuro-ophthalmological examination; nerve-conduction studies, and EMG results, all of which were normal. The neuro-ophthalmologist concluded that OMG was not present. However, a Tensilon test—which we requested—was not performed at that time. We saw him again and noted the variable esotropia. We conferred with a second neuro-ophthalmologist, who agreed with our tentative diagnosis of MG. We referred the patient back to the neuro-ophthalmologist located in his college town who subsequently noted a new ptosis and performed a Tensilon test, which was positive. The patient was started on a regimen of 30-mg Mestinon q.i.d. p.o. and advised to have a chest CT scan.

The patient returned to us six months later, taking 60-mg Mestinon q.i.d. p.o. He reported less ptosis with the medication; however, the abdominal side effects forced him to discontinue the medication. Cover testing revealed a concomitant 16Δ esotropia at distance and orthophoria at near. Accommodative amplitudes were 6.5 diopters in each eye. A thymectomectomy was performed; the patient discontinued Mestinon and was treated with 60-mg Prednisone, with some improvement. His deviation stabilized and he was advised to wear a distance prism correction.

Discussion

MG usually manifests a recently acquired, variable ptosis, greater in one eye than the other. When this occurs, the diagnosis is straightforward and is readily confirmed by the gold stan-

dard—the Tensilon test. Previous studies have suggested that 90% of all patients with myasthenia gravis manifest a ptosis, and that a generalized MG will eventually develop (within two years) in 50% of those who manifest an ocular sign.[8] In dealing with relatively stable acquired ptosis is more difficult to ascertain the origin; however, even in those cases, MG must be considered. We believe that patients manifest nonptotic signs of MG more frequently than previously reported. When the presenting sign is other than ptosis—such as an accommodative/vergence insufficiency, or a concomitant or noncomitant oculomotor paresis—then diagnosis of MG is much more elusive. For the patient with myasthenia gravis who manifests nonclassical symptoms, MG may be overlooked by the neuro-ophthalmolgists, ophthalmologists, optometrists, and primary care practitioners.

Perhaps the primary reason that patients who initially manifest MG-induced accommodative and vergence deficits are not appropriately diagnosed is that the ophthalmic community is not sensitive to the subtle initial signs and symptoms of MG—i.e., asthenopia, blur, diplopia, and visual fatigue. The most-common finding of MG is fatigability of either striated or non-striated ocular motor muscles—accommodation, vergence, and levator palpebrae. This fatigability may occur with minimal usage: within minutes, from morning to evening, and/or from day to day. No other condition manifests such variable findings. Thus, any patient suspected of having MG should have morning baseline testing to establish lid position and accommodative/vergence functioning. Measurement should be repeated in the evening to assess fatigability.

There are a variety of non-invasive, simple office and home tests that we have discussed previously to support the diagnosis of MG (*see* Figure 8). If ptosis is present, the clinician should attempt to fatigue the orbicularis muscles. Also, 2.5% neosynephrine may be used to differentiate senile ptosis from other forms of ptosis. The patient should be instructed to perform the photo test at home. If a patient has diplopia, atypical oculomotor fatigue, and/or demonstrates a decrement of findings during or immediately after vision therapy, MG should be suspected.

It has been assumed that MG only affects striated muscles. As early as 1900, however, Campbell and Bramwell[36] demonstrated that accommodation may be involved in the MG syndrome. We have presented and published two case studies that objectively demonstrate accommodative insufficiency as the presenting sign.[10,33] We believe that the paucity in reporting of accommodative anomalies is related to the lack of testing of accommodative amplitude, and/or facility of accommodation. It is important that those providing vision therapy recognize the pattern of accommodative findings associated with MG. There are a few caveats in making the diagnosis of accommodative insufficiency secondary to MG, since these accommodative findings are unique. *First*, asymmetrical accommodative amplitudes between the eyes are present. *Second*, the amplitudes are usually reduced and will decrease further on repeated testing. *Third*, accommodative facility as measured with ± 1.50 D lenses in the phoropter demonstrates fatigue with repeated testing. *Fourth*, the general accommodative (and related vergence) findings fatigue by the end of the day, and thus their respective amplitudes and/or facility will be less in the evening, as compared to the morning. *Fifth*, the findings will vary from day to day. And *sixth*, Tensilon or Tensilon equivalent medications (such as Mestinon) will have a positive effect on accommodative functioning.

After the classical sign of ptosis, the most commonly described sign of MG is variable diplopia. The classical myasthenic patient will manifest a non-comitant, oculo-motor paresis varying as the day progresses. This myasthenic patient will have motor fields that are not indicative of a specific oculomotor paresis; variability is the hallmark of MG. Like accommodation, increased variability is usually noted with repeated testing or time of day. The patient may manifest a subtle ptosis, so the external examination must be carefully performed. Fatigue, induced by repeated versions or vergence testing with a prism bar, will result in increased diplopia and/or a change in the cover test value. Version and vergence testing may be enhanced with the use of a red lens. The red lens serves three functions: to disrupt binocularity, to eliminate suppression, and to determine the diplopia direction. The sleep/ice test usually results in improvement of the diplopia, as noted in two of the cases.

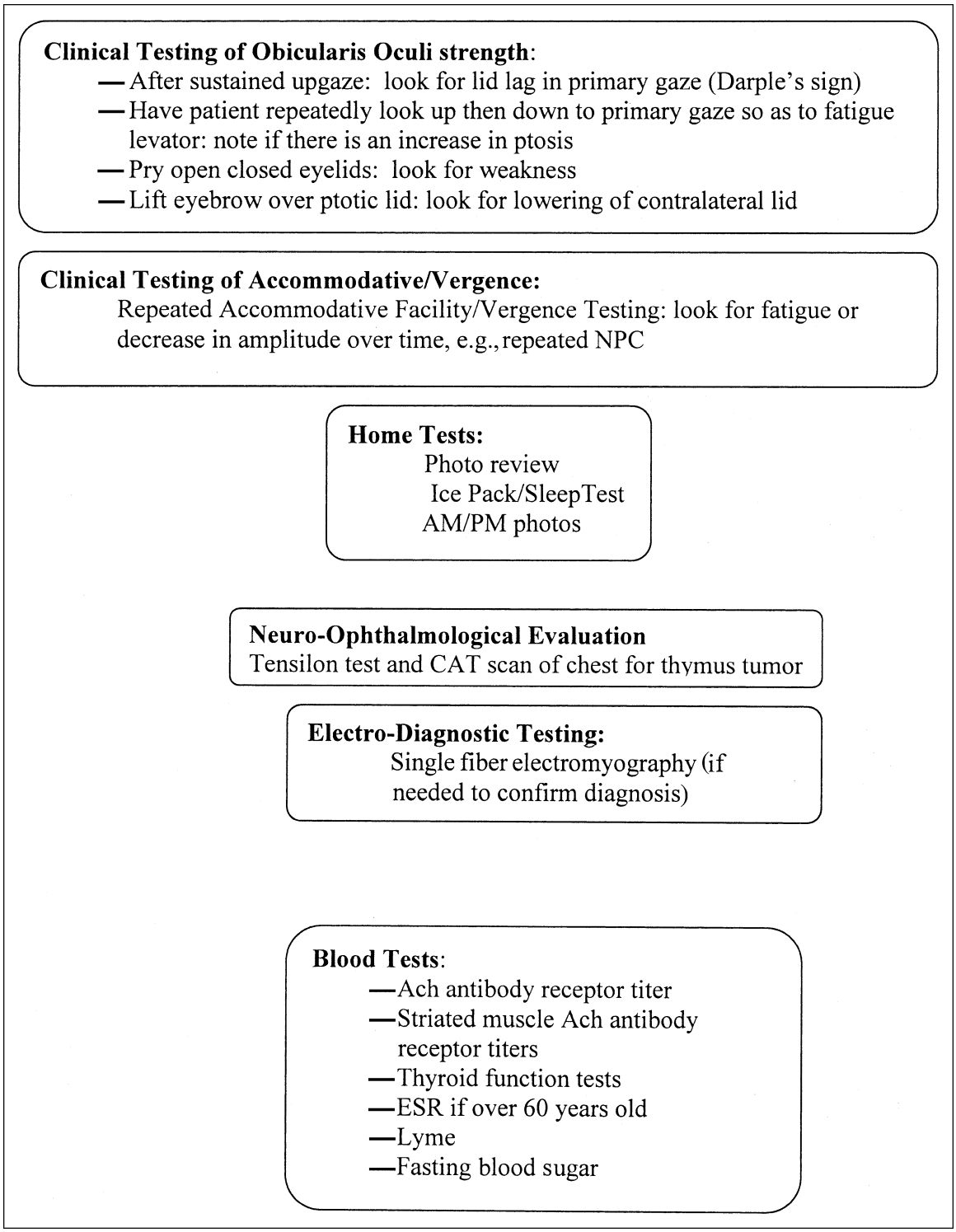

Figure 8 Testing sequence for suspected myasthenia gravis. Most testing can be easily performed in the office. Ice and sleep tests, which can be combined with a photo review, are sensitive and specific to myasthenia gravis.

Myasthenia may masquerade as a convergence insufficiency, a divergence insufficiency, or a concomitant hyperdeviation. Myasthenia both follows and breaks the rules. Thus, any unexplained diplopia—particularly under the age of 60 years—should include MG in the differential diagnosis, even if another health care practitioner has dismissed the diagnosis of MG. Although

four of the five cases had variable findings which lead to a more-detailed investigation of possible MG, one did not. This patient was particularly elusive, since the ptosis was previously eliminated by surgery, and her deviation was concomitant and unchanging over a course of several years.

If the patient is still not confirmed as having MG after simple, non-invasive office and home tests, further testing is warranted. A blood workup should include a MG antibody test, thyroid testing, fasting blood sugar, Lyme titer, and ESR in those over 60 years of age. If intracranial disease is suspected, an MRI with contrast should be performed. The radiologist should be advised to carefully examine the pathways of 3rd, 4th, or 6th N from the eye to the midbrain, and the higher neurological centers if a gaze palsy is noted. Lastly, a neuro-ophthalmological consult is in order with Tensilon testing and single-fiber myography to make the final differential diagnosis.

After stabilization with medication, patients with MG should have a re-evaluation of their accommodative and vergence functions. Stable MG patients who manifest accommodative and vergence defects may benefit from prismatic correction incorporated into a progressive lens. A progressive lens provides the advantage of compensating for the variable accommodative amplitudes noted during the day and from day to day. One must remember, for the young patient, that the add power should be determined monocularly before prism is determined (by relaxing accommodation, there is a relaxation of convergence; i.e., increase in exophoria). The add, which may be determined by conventional means (i.e., cross cylinder, balancing PRA/NRA, etc.) should be prescribed monocularly to eliminate asymmetry in accommodative findings.

In summary, MG should be considered when examining the patient with unexplained ocular and general fatigue, unexplained accommodative fatigue or vergence fatigue, unexplained ptosis, or diplopia. There are a multitude of simple clinical tests that help make the diagnosis of this often elusive disease. Early diagnosis and treatment of MG is beneficial, to eliminate costly neurological testing and to improve the quality of life of our patients.

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