Acquired Myasthenia Gravis:

Clinical Presentation and Diagnosis

Janice M. Massey, M.D.

Duke University Medical Center
Durham, North Carolina

Introduction

Myasthenia gravis (MG) is an acquired, autoimmune neuromuscular junction disorder characterized by fluctuating, fatigable, painless weakness of skeletal muscle. The symptoms and signs of MG arise from weakness of ocular, limb and oropharyngeal muscle groups in recognizable patterns. Fluctuating and fatigable weakness with periocular muscle involvement are hallmarks of the disease. The mechanism for muscle weakness in most cases is an antibody-mediated, T cell-dependent immunologic attack on the endplate region of the postsynaptic membrane. Other non-AChR components of the neuromuscular junction, such as the muscle-specific receptor tyrosine kinase (MuSK) [1,2] or low density lipoprotein receptor-related protein (LRP4) are targets in some patients[46, 47].

Clinical Features

Historical features and physical examination findings are key elements for diagnosis. Ocular weakness with fluctuating, asymmetric ptosis and binocular diplopia combine in the most typical initial presentation; however, early or isolated oropharyngeal or limb weakness occurs infrequently. Fatigue without specific weakness is rare. The course is variable and, without treatment, often progressive. Most patients with initial ocular weakness develop weakness elsewhere (limb and/or bulbar muscles) within three years of initial symptom onset. Weakness can be mild, even for many years, or fulminant and life threatening over a few weeks. In patients with mild, fluctuating weakness, the diagnosis may be challenging. The clinical diagnosis is supported or confirmed by diagnostic testing including the following:

- electrophysiologic testing with repetitive nerve stimulation (RNS) studies and/or single-fiber electromyography (SFEMG) that demonstrates a primary postsynaptic neuromuscular junctional disorder;
- serologic demonstration of acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) antibodies, LRP-4 antibodies;

- pharmacologic testing with edrophonium chloride that elicits unequivocal objective improvement of observable deficits in strength on examination (e.g. resolution of ptosis or extraocular muscle dysfunction).

. Other tests of possible utility include the Ice Pack test and ocular vestibular evoked myogenic potentials (51)

Classification:

Although a formal clinical classification system and research standards have been established for MG, [6] there are yet no widely accepted formal diagnostic criteria. MG is termed ocular MG when weakness is exclusive to the eyelids and extraocular muscles, and generalized MG when weakness extends beyond these ocular muscles. Seropositive (SP) MG defines disease with circulating antibodies to the AChR, while seronegative (SN) patients lack these antibodies. Antibodies to MuSK have been demonstrated in over 40% of patients with generalized, SN MG [1, 2, 3, 4, 5] and LRP4 is positive in another 5-10%..

Epidemiology

MG is rare. Prevalence rates for MG have increased over time and now approach 20/100,000 [7]. This increase is likely due to improvements in diagnosis and treatment. A wide range of incidence is reported with an estimate of about 2.0 to 10.4/million/year in Virginia [8] to 21.27/million/year in Barcelona, Spain [9]. Although onset of MG may occur throughout all ages from early childhood to the aged, the onset is bimodal with peaks in younger women and older men. Women predominate with a ratio of 7:3 in patients younger than 40 while after age 50 new cases of MG are slightly more common in men with a ratio of 3:2 [10, 11]. In the fifth decade, new cases of MG are evenly distributed between men and women.

Pediatric MG is very rare. Juvenile MG is an acquired, autoimmune disorder, while congenital MG results from genetic mutations that impair neuromuscular transmission. Occasionally, it

may be difficult to distinguish acquired juvenile MG from congenital MG, particularly in the absence of AChR or MuSK antibodies, or when a clear history of ptosis and other manifestations of hypotonia from the time of birth might suggest genetic disease[12].

Clinical Description

Patients present with fluctuating and fatigable weakness of specific muscle groups. The weakness is not to be confused with generalized fatigue or pain. Weakness varies from day to day and perhaps from hour to hour, but is generally worse later in the day. Sustained exercise and increased body temperature may increase weakness in some patients. Ocular weakness with asymmetric ptosis and binocular diplopia is the most common initial presentation, while early or isolated oropharyngeal or limb weakness is atypical.

Ocular weakness presents as fluctuating, fatigable, and sometimes alternating ptosis and binocular diplopia that resolves with closing or covering one eye. Many patients report difficulties with driving, reading, or watching television. Bright lights may be quite bothersome. Retrospectively, some patients report periods of intermittent blurred vision before they were able to discern dual visual images. In keeping with the symptoms, examination typically demonstrates asymmetrical weakness of multiple extraocular muscles that cannot be attributed to a single cranial neuropathy or brainstem lesion. Pupillary function is normal. Ptosis may be elicited or exaggerated with sustained upgaze. It is generally asymmetrical, and may be associated with ipsilateral frontalis muscle contraction to help compensate for the weak levator palpebrae. Excessive lid elevation or Cogan's lid twitch sign may be present when gaze is directed from down to upward.

Jaw closure muscles can be affected in MG, but strength is usually normal in jaw opening muscles. Patients may report difficulty chewing candy or tough meats, and some compensate by modifying their diet. Patients with jaw weakness may assume a thoughtful resting posture by

placing the thumb beneath the chin in order to hold the jaw closed. The jaw closure muscles can be examined by exerting sustained downward pressure on the chin while the patient attempts to hold the jaw closed.

Patients with facial weakness may appear depressed or expressionless owing to hypomimetic face muscles. They may have difficulty forming a lip seal, which impairs actions such as whistling, using straws, or inflating balloons. A “myasthenic snarl” may be observed when the patient attempts to smile due to weakness of the zygomaticus muscles. Many patients exhibit weak forced eye closure that can easily be overcome by the examiner. The presence of a Bell’s phenomenon with upward and lateral rotation of the eyes on attempted forced eyelid closure distinguishes effort versus weakness of the orbicularis oculi muscles. A patient with overt lower facial weakness cannot maintain cheek puff and air readily escapes through the lips when the cheeks are squeezed. In severe lower facial weakness, the lips cannot be voluntarily opposed.

Oropharyngeal muscle weakness produces dysarthria and dysphagia. With weakness of palatal muscles, air or liquid can escape through the nose. With air escape, speech has a nasal quality and may become worse with prolonged speaking. Liquid may escape through the nose during attempted swallowing with nasal regurgitation. Incomplete glottic closure during swallowing may produce aspiration. Myasthenic weakness of laryngeal muscles is uncommon but when present yields a hoarse, breathy voice. Examination of the pharynx may reveal reduced or absent palate elevation. Tongue weakness also may be present as demonstrated when the patient attempts to protrude either cheek with the tongue against resistance. With marked tongue weakness, the patient may not even be able to protrude the cheek in the absence of applied resistance by the examiner. With severe lingual weakness, the tongue may not protrude beyond the lips. When myasthenic tongue weakness is chronic, tongue atrophy and triple furrowing may develop with accentuated median and lateral lingual furrows.

Neck flexor and extensor muscles are often weak in MG. Though the neck flexors are usually weaker, a “dropped head syndrome” due to neck extensor muscle weakness infrequently occurs. Although painless weakness is the rule in MG, patients with neck extensor weakness may experience posterior neck myalgias.

Limb weakness in MG may be associated with complaints of difficulty performing overhead tasks with the arms, and there may be difficulty climbing stairs due to lower extremity weakness. Examination reveals asymmetrical weakness involving any muscle group in the limbs, though the deltoids, triceps brachii, wrist and finger extensors, and foot dorsiflexors are often involved.

Etiology

Autoimmune MG results from antibody-mediated, T cell-dependent immunologic attack on the postsynaptic membrane of the neuromuscular junction. Abnormal neuromuscular transmission and clinical weakness in MG result from the effects of antibodies that bind to various epitopes of the skeletal muscle endplate region. In most cases, antibodies bind to the main immunogenic region of the α-subunit of the AChR, though MG patients with antibodies to MuSK exhibit clinical weakness and electrophysiologic findings that are quite similar to MG patients with AChR antibodies. MuSK initiates aggregation of AChRs at the muscle endplate during development, but the function of MuSK in mature skeletal muscle and the pathophysiology of MG related to MuSK antibodies are currently unknown.

In SP MG, binding of antibody to the AChR initiates autoimmune attack on the endplate region. Subsequent damage to the postsynaptic membrane results in simplification of the normal, highly-infolded surface that is accompanied by reduced number and density of AChR [13]. The functional loss of AChRs reduces the integrity of successful neuromuscular transmission following quantal release of acetylcholine by the motor nerve terminal, resulting in clinical weakness in striated muscles.

MG and other autoimmune disorders result from the loss of tolerance to self-antigens. T-lymphocyte tolerance to self-antigens is established in the thymus, and thymic abnormalities are often present in MG. Thymic hyperplasia is found in about 65% of MG patients, and thymomas are present in about 10% of MG patients [14]. MG patients with thymoma have more severe and generalized weakness, higher AChR antibody titers[49], and more severe electrophysiologic abnormalities. Accordingly, patients with SN and ocular MG are less likely to have thymomas. Most thymic tumors are benign, well differentiated, and encapsulated. While thymoma resection is necessary to prevent compromise of mediastinal structures, the benefit of thymectomy for patients with non-thymomatous MG has recently been studied by a MGFA-sponsored international randomized trial with pending results.

http://myasthenia.org/docs/MGFA_MedicationsandMG.pdf.

Diagnostic Methods

Pharmacologic Testing

Edrophonium testing. Edrophonium chloride is an acetylcholinesterase inhibitor with rapid onset (approximately 30 seconds) and short duration (approximately 5 minutes) of pharmacologic action. Edrophonium chloride temporarily improves the safety factor of neuromuscular transmission and may produce improved strength in patients with abnormal neuromuscular transmission. The test is considered positive when *unequivocal*, objective improvement in strength follows intravenous administration of edrophonium. Development of increased weakness may also suggest abnormal neuromuscular transmission. The primary limitation of edrophonium testing relates to selection of an objective muscle strength parameter for assessment. Therefore, edrophonium testing is most useful in patients who have significant ptosis or restricted extraocular movements that can be graded objectively. In other muscles, volition and the muscarinic effects of edrophonium may complicate strength measurement and render the test uninterruptable.

The sensitivity of edrophonium testing has been estimated to be about 86% for ocular MG and 95% for generalized MG [15]. False positive edrophonium testing may occur in other neurological conditions including lower motor neuron disorders and brainstem tumors [16, 17, 18, 19].

During testing, up to 10 mg of intravenous edrophonium chloride may be administered. Because of the potential for serious muscarinic side effects including bronchospasm and bradycardia, atropine should be readily available. Typical muscarinic side effects include increased sweating, lacrimation, salivation, nausea, and diarrhea. An incremental dosing schedule should be utilized with one minute observation periods following each dose of edrophonium. An initial 2 mg dose and subsequent doses of 2 mg, 3 mg, and 3 mg are given if needed. If muscle strength improves clearly within one minute following any dose increment, the test is considered to be positive and the procedure is concluded. This strategy reduces the risk of giving excessive edrophonium and producing untoward muscarinic side effects.

Electrophysiologic Testing

Repetitive Nerve Stimulation (RNS) Studies. With low rates of motor nerve stimulation (2-5 Hz), RNS depletes the immediate stores of acetylcholine at the neuromuscular junction. This reduces the safety factor and probability of successful neuromuscular transmission. In neuromuscular junction disorders, the safety factor is reduced, and further reduction by RNS causes some endplate potentials to fail to reach depolarization threshold. This results in a failure to elicit muscle fiber action potentials. With a reduced number of individual muscle fiber action potentials, the compound muscle action potential (CMAP) becomes reduced in both amplitude and area with a resulting decremental response.

In MG, RNS study findings are abnormal when the amplitude of the fourth CMAP is reduced more than 10% from the baseline value. This may not be present in stimulus trains recorded following rest, but it may only develop in trains collected subsequent to an exercise period as a consequence of post-activation exhaustion. The sensitivity of RNS is increased when recordings

are made from clinically weak muscles. Careful attention to proper technique is important to avoid erroneous results. There must be adequate immobilization of the stimulating and recording electrodes, delivery of supramaximal stimuli, muscle warming to 35ºC, and withholding of acetylcholinesterase inhibitors for at least 12 hours prior to testing [20, 21].

In general, proximal muscles including facial muscles, trapezius, deltoid, and biceps brachii are more likely to exhibit abnormal findings. In MG, when RNS studies are performed in a hand and in a shoulder muscle, the overall sensitivity is approximately 60%. RNS studies are relatively more sensitive in generalized MG and relatively less sensitive in ocular MG [21].

Single Fiber EMG (SFEMG). SFEMG is the most sensitive diagnostic test for detecting abnormal neuromuscular transmission. In SFEMG, individual muscle fiber action potentials generated by the same motor neuron are recorded by a specialized concentric needle with a 25 μm diameter recording surface and a 500 Hz high-frequency filter. In most normal muscles, this arrangement facilitates recordings from two individual muscle fiber action potentials. The variability in time interval between the firing of one muscle fiber potential with relation to the other is termed the neuromuscular jitter [22].

SFEMG should be performed in a clinically weak muscle whenever possible. In many laboratories, the extensor digitorum (EDC) is studied initially. If the findings are normal in the EDC, a facial muscle should be studied [23]. When a facial and a limb muscle are studied, SFEMG is over 97% sensitive for detecting MG [24]. A finding of normal jitter in a clinically weak muscle virtually excludes MG as a cause of weakness in that muscle. Rarely in mild disease recent pyridostigmine may mask an abnormality and testing should be performed or repeated after withholding of acetylcholinesterase inhibitors for at least 24 hours prior to testing [20]. SFEMG also demonstrates abnormal neuromuscular transmission related to other motor unit disorders including motor neuropathic and myopathic disorders. Normal SFEMG fiber density measurements can aid in distinguishing primary disorders of neuromuscular transmission from

other motor unit disorders such as motor neuropathic or myopathic processes. In light of its reduced specificity, SFEMG must be performed and interpreted in the appropriate clinical context to avoid false positive results due to diseases other than those primarily affecting the neuromuscular junction. It is a test that requires special expertise and equipment that are not available in all centers. Concentric needle jitter (CN-jitter) measurement is a similar but not identical technique to SFEMG. Measurements of neuromuscular junction transmission by this technique may underestimate jitter as compared to SFEMG measurements.

Serological Testing

AChR Antibodies. The AChR binding antibody assay utilizes purified human skeletal AChRs incubated with patient serum immunoglobulin. The assay is very specific, and positive antibody studies confirm MG in a patient with appropriate symptoms and clinical findings. AChR binding antibodies are present in approximately 80% of patients with generalized MG, but in only 55% of patients with ocular MG [25, 26]. About one-half of prepubertal children with MG are SN [27]. Though relatively less sensitive than SFEMG, AChR binding antibodies are highly specific for autoimmune MG. Although very useful in the diagnosis of autoimmune MG, they are less useful in predicting disease course[48,50]. Rarely, false positive results in AChR binding antibody assays have been observed in patients with other autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and inflammatory neuropathy. False positive results have also been reported in motor neuron disease, patients with thymoma without MG, and relatives of patients with MG [28]. Some initially SN patients may seroconvert within the first several months of disease. Seroconversion may be identified in these patients by repeating the AChR binding antibody studies after six months of symptoms [31].

The AChR modulating antibody assay measures the degradation rate of labeled AChRs from cultured human myotubes. AChR blocking antibodies compete for the acetylcholine binding site or allosterically inhibit binding of radiolabelled α-bungarotoxin to the AChR [28]. The AChR modulating and blocking antibody assays are probably useful only when the AChR binding

antibody assay is negative, since they increase diagnostic sensitivity only slightly. Approximately 4% of patients with negative AChR binding antibodies have an elevated AChR modulating antibody assay, and approximately 1% of patients with negative AChR binding antibodies demonstrate increased AChR blocking antibodies [29].

Anti-Striated Muscle Antibodies. Anti-striated muscle or anti-striational antibodies react with contractile elements of skeletal muscle. They are found in 30% of patients with adult-onset MG, and they appear to be more common in patients with later disease onset [30]. These antibodies may be useful as a serological marker for thymoma in younger patients. Anti-striated muscle antibodies have been demonstrated in 80% of patients with thymoma in the absence of MG[49]. Following thymoma resection, a rise in anti-striated muscle antibody titer may suggest recurrent tumor [30]. In one series, thymomas were demonstrated in 60% of patients with anti-striated muscle antibodies and MG beginning before age 50, and in less than 2% of patients without these antibodies [31].

Muscle Specific Kinase (MuSK) Antibodies. MuSK appears to facilitate clustering of AChR at the neuromuscular junction. Antibodies to MuSK have been demonstrated recently in about one third of patients with generalized SN MG [1, 2, 4], although the role of MuSK antibodies in producing neuromuscular junctional disease has not yet been defined. The recent demonstration of MuSK antibodies in many SN patients with generalized MG suggests an alternate pathophysiology for autoimmune MG that awaits further characterization.

Other antibodies. Antibodies against the intracellular skeletal muscle protein titin may be present in patients with thymoma, but they are also present in about half of patients with late-onset MG without thymoma [32, 33]. Ryanodine antibodies are also associated with late-onset MG. Patients with ryanodine antibodies may exhibit severe, treatment-resistant MG associated with malignant thymomas [34]. Although the role for these antibodies in the diagnosis of MG has yet to be determined, they may have prognostic value and expedite chest imaging studies for

detection of thymoma. Low-density lipoprotein receptor-related protein (LRP4) has been identified as the agrin receptor and as such it interacts with agrin binding, which activates MuSK. There is increasing evidence that many double sero-negative patients have LRP4 antibodies[46, 47].

Other Testing

Chest computerized tomography (CT) should be performed in patients with AChR binding antibodies [49] to exclude the presence of thymoma. Chest CT is more sensitive than plain chest radiographs for delineating anterior mediastinal masses, and chest MRI does not improve diagnostic sensitivity. Iodinated contrast agents have rarely precipitated significant worsening of myasthenic weakness [35, 36]. Though this is an uncommon phenomenon [37], we do not routinely use iodinated contrast agents during chest CT studies performed to assess for thymoma. Since MG often co-exists with other autoimmune disorders, particularly autoimmune thyroid disease, patients should undergo thyroid function testing along with testing for other autoimmune disorders when clinically appropriate.

Diagnostic Testing--Summary

All diagnostic testing must be interpreted in the context of the clinical setting. Pharmacologic testing with intravenous edrophonium is sensitive when performed in patients with significant ptosis or external ophthalmoparesis.

RNS studies may demonstrate impaired neuromuscular transmission, especially when performed recording from clinically weak muscles, though they are relatively insensitive in ocular and in mild generalized MG. SFEMG is the most sensitive laboratory test for MG, although abnormal SFEMG findings may be seen in motor neuropathic and in myopathic disorders. Another cause for abnormal SFEMG finding is prior botulism or administration or Botulinum toxin

[52]. In the absence of cholinesterase inhibitors, normal SFEMG findings in a clinically weak muscle exclude a diagnosis of MG. CN-jitter measurements are less sensitive than SFEMG.

In the clinical context of fluctuating and fatigable weakness, AChR or MuSK antibodies provide confirmation of the diagnosis of MG, though nearly half of patients with ocular MG are SN.

Differential diagnosis

Differential diagnosis includes other disorders of the neuromuscular junction including Lambert Eaton syndrome, botulism, congenital myasthenic syndromes, and tick paralysis. Congenital ptosis or levator palpebral dehiscence may produce isolated ptosis. In addition, acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and variants of AIDP affecting cranial muscles such as the Miller-Fisher and cervical-brachial-pharyngeal variants may simulate MG, though the weakness does not have the same variability. EMG studies usually distinguish these disorders from MG. Mitochondrial neuromuscular disorders, particularly those featuring external ophthalmoplegia and ptosis, may simulate MG [53]. However, the onset of symptoms is gradual, and the weakness does not fluctuate greatly. Motor neuron disease involving oropharyngeal weakness may appear similar to MG, though the presence of corticobulbar features, denervation and reinnervation changes on EMG or increased fiber density measurements on SFEMG can assist in distinguishing these entities. Finally, brainstem ischemia may simulate the fluctuating character of MG, though unlike MG, consciousness, balance and coordination, and sensation are often impaired.

Prognosis

Most patients develop initial symptoms of extraocular muscle weakness with asymmetric ptosis and diplopia. The course is frequently variable, particularly within the first year of disease.

Nearly 85% of patients with initial ocular symptoms progress to develop weakness of bulbar and limb muscles within the first three years [10, 39]. Initial presentations with oropharyngeal and limb weakness are less common. Maximum disease severity is reached within the first year in almost two-thirds of patients [11]. Myasthenic crisis or respiratory failure due to myasthenic weakness occurs in about 20% of patients, usually within the first year of illness [40, 41]. Myasthenic symptoms and signs may worsen in the setting of systemic illness, particularly viral upper respiratory infections, thyroid disease, pregnancy, increased body temperature, and exposure to drugs that impair neuromuscular transmission (Table 1) [23, 42].

Early in the course of MG, symptoms may fluctuate and occasionally remit, although such remissions are rarely permanent [39, 43]. Three major stages of generalized MG have been proposed [44]. An active stage characterized by relapses and remissions lasting approximately seven years is followed by an inactive stage lasting about 10 years. The inactive stage is characterized by less disease volatility, though patients may experience exacerbations related to intercurrent illnesses, pregnancy, or exposure to medications that compromise neuromuscular transmission. In the ultimate stage of “burned-out” disease, untreated weakness may become fixed in association with muscle atrophy.

Prior to the widespread use of immunomodulators, prognosis for patients with MG was grim with about 30% mortality [39]. Along with advances in mechanical ventilation and intensive care, immunotherapy has been one of the major factors contributing to improved outcome in MG, and contemporary disease-specific mortality is less than 5% [45].

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Table 1 - Medications that may exacerbate weakness in myasthenia gravis and Lambert-Eaton Syndrome

- Selected antibiotics including
  - aminoglycosides (tobramycin, gentamycin, kanamycin, neomycin, streptomycin)
  - macrolides (erythromycin, azithromycin, telithromycin [Ketek®])
  - fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, pefloxacin, moxifloxacin)
- Beta-blockers
- Calcium channel blockers
- Magnesium salts (milk of magnesia, some antacids, tocolytics)
- Botulinum toxins (Botox®, Myobloc®, Dysport®, Xeomin®)
- D-penicillamine
- Curare and related drugs
- Quinine, quinidine or procainamide