Ocular Myasthenia

Diagnosis, Treatment, and Pathogenesis

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Background: Although myasthenia gravis (MG) is often considered the best-understood autoimmune disorder and effective treatments have controlled life-threatening complications, the pathogenesis of ocular myasthenia (OM) remains enigmatic, and its clinical consequences offer therapeutic challenges.

Review Summary: About half of patients with MG present with visual complaints of droopy eyelids or double vision, and many will remain with purely ocular muscle weakness without generalized weakness, defined as OM. OM may be confused with disorders of the brainstem, ocular motor nerves, and eye muscles. Frustrating for the clinician, confirmatory tests such as the edrophonium test, serum acetylcholine receptor antibodies, and standard electrodiagnostic evaluations may fail to positively identify the clinical suspicion of OM. Patients may derive relief from nonpharmacologic interventions and cholinesterase inhibitors, but most will desire better symptom control with corticosteroids or need other immunosuppression. Early corticosteroid therapy may reduce the probability of generalization of the disease. The reasons for ocular muscle involvement by OM include physiologic and cellular properties of the ocular motor system and the unique immunology of OM, which, when better understood, will lead to novel treatments.

Conclusions: OM is a challenging disorder for the clinician and scientist, with both learning from the other for the betterment of the patient. The future requires answers to why the ocular muscles are so frequently involved by MG, whether the generalization of the disease may be limited by early corticosteroid treatment, and what treatment options may be developed which will improve symptoms without long-term complications.

Key Words: myasthenia gravis, ocular myasthenia, extraocular muscle

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Myasthenia gravis (MG) is a chronic disorder of neuromuscular junction function (Fig. 1), which produces fatigue of skeletal muscles. Although weakness may affect any striated muscle, the ocular muscles, the extraocular muscles (EOM), which move the globe, and the levator palpebrae that elevates the eyelid demonstrate a predilection for initial or isolated involvement. Close to all patients will have ocular manifestations at some time during the disease, and a large subset of patients will have manifestations restricted to the ocular muscles, so-called ocular myasthenia (OM). This review will emphasize diagnostic challenges, therapeutic options, and the enigmatic question of why the eye muscles are so frequently involved by MG.

Clinical Features and Differential Diagnosis

Patient Characteristics

MG affects all ages and sexes, with prevalence estimates ranging from 20–400 per million, with OM accounting for upwards of 20% of all patients.[1–5] The age distribution is bimodal, with incidence peaks in young women in the mid 20s and older men with a mean peak age after 40.[6,7] The overall prevalence of MG appears to be on the increase as a function of the aging population,[4,8] and importantly the diagnosis appears to be frequently overlooked in the elderly. One study identified individuals seropositive for serum acetylcholine receptors (AChR), a highly specific test for MG, but found that several individuals had not been diagnosed with MG but did have neurologic complaints that were consistent with MG.[9] Since many OM patients are seronegative, the number of elderly patients with OM may be significantly underestimated.

The epidemiology of MG demonstrates racial variation. A relatively higher onset in the first decade and before puberty is reported among the Chinese,[10–12] and OM occurs in greater than 50% of patients. In Virginia, the incidence and prevalence was found to be higher in the African-American population than in the corresponding Caucasian population. OM comprised 25% of this group of patients,[3] which was higher than found in previous series.

Ocular Manifestations of Myasthenia Gravis

Droopy eyelids or double vision occurs as the presenting symptom of MG in excess of 75% of patients and occurs in nearly all patients at some time in the course of generalized MG.[13–15] About half of patients who present with ocular manifestation develop generalized weakness disease within 6 months, and up to 80% will generalize within 2 years.[14,16,17]

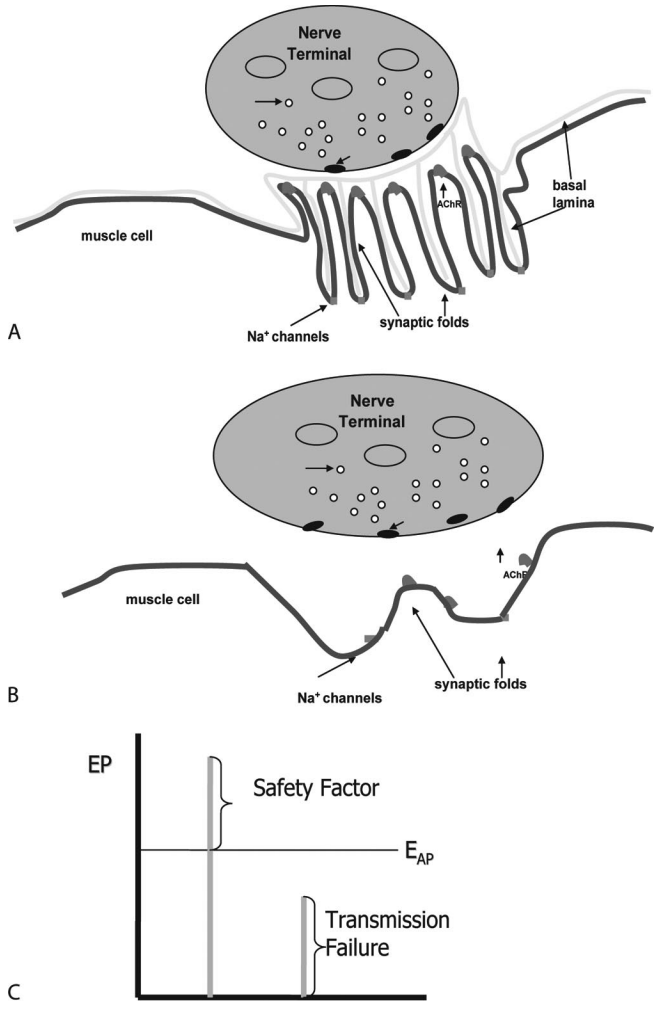

FIGURE 1. Pathophysiology of myasthenia gravis. A, An illustration of a normal neuromuscular junction (NMJ). The muscle membrane across from the nerve terminal has multiple invaginations, termed *synaptic folds*. AChR are concentrated the tops of the folds, while sodium channels are found at high density in the depths of the folds. The concentration of ion channels and the architecture of the synaptic folds enhance the endplate potential achieved when acetylcholine is released. As illustrated in B, AChR and Na channel coupled with a compromise in synaptic structure occurs in MG. C, The physiological consequences of MG. Normally, an endplate potential is well above that required to generate an action potential to signal muscle contraction. The difference between that endplate potential and the action potential threshold is termed the *safety factor*. In MG, the safety factor is reduced, and with a stress, such as repetitive stimulation, the endplate potential becomes inadequate to generate an action potential.

In studies with long follow-up, about 30% of the patients have restricted ocular symptoms.[7,17,18] Therefore, it is likely that patients who remain with symptoms localized to the ocular muscles for more than 2 years will not generalize.

Ptosis may be unilateral or bilateral (Fig. 2) but is usually asymmetric and occurs in association with diplopia.[19]

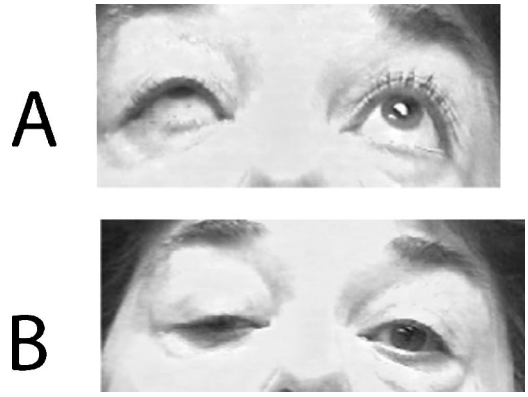

FIGURE 2. Patient with bilateral asymmetric ptosis in primary position (A) and in upgaze (B).

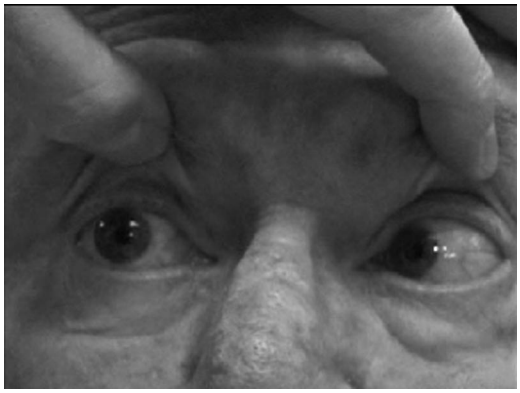

FIGURE 3. Patient instructed to follow a target to the right. Note the abduction abnormality of the right eye, which mimics a sixth-nerve palsy.

Variation in its severity is the hallmark of MG. Patients may have a primary complaint of blurred vision as the lid begins to cover the pupil and not immediately appreciate eyelid droop. If hyperretraction of the less-affected lid occurs, then the chief complaint may be ocular irritation because of exposure (see below). Although the classic symptom complaint is that of double vision, patients complain of dizziness, gait instability, visual blurring, or visual "confusion," which may be the dominant symptoms. These complaints should improve with closure of one eye.

On examination, MG is suggested by several signs (Fig. 3). Because of Hering's law of equal innervation, the brain may attempt to compensate for a unilateral ptosis with additional neuronal stimulation; therefore, the lid less affected by MG may become hyperretracted. When the ptotic lid is manually elevated, the retracted lid droops; this sign is commonly considered specific for MG. Similarly, enhanced ptosis is identified when, with passive elevation of a ptotic lid, the contralateral lid droops.[20] The Cogan lid twitch sign is identified by the examiner requesting the patient to look down for 15 seconds, then rapidly look up to an examiner's visual target. The ptotic eyelid overshoots and is transiently higher than the contralateral lid and then slowly drops to its previous ptotic position. The phenomenon is caused by transient im-

provement in lid strength after resting of the levator muscle in downgaze. MG is the only diagnosis to consider with a history of alternating or recurrent painless ptosis.[21]

Ophthalmoparesis is the second most common manifestation of OM. Nearly 90% of patients who present with diplopia have associated ptosis, and this combination should immediately bring the diagnosis of MG to the forefront.[21,20] Any pattern of EOM weakness may occur and mimic central and peripheral nervous system eye movement abnormalities (Fig. 2). The severity of weakness varies from complete paralysis to subtle weakness, which may produce isolated nystagmus. Dissociated gaze-evoked nystagmus contralateral to a paretic eye may be observed in OM and represents adaptive responses of increases in the pulse of innervation. On dynamic testing, saccadic velocity may be preserved or increased in a limited range of movement (highly suggestive of MG) or intrasaccadic fatigue may be identified when a fast eye movement suddenly slows in midflight.

Orbicularis oculi weakness in combination with ptosis or ophthalmoparesis is a strong indicator of MG. "Afternoon ectropion" of the lower lid from fatigability of orbicularis oculi can be found in OM.[13,20] "Peek-a-boo sign" is observed by the gradual appearance of lagophthalmos after forceful lid closure over a minute. Initially, the orbicularis oculi is able to produce tight lid closure, followed by fatigue, which leads to separation of lid closure, showing a rim of sclera, with the patient appearing to peek at the examiner. However, this sign is not specific for OM and is also seen in seventh-nerve disorders.[13] By routine clinical examination, pupil responses are always normal in MG, which allows immediate differentiation from botulism and third nerve palsy that commonly compromise the pupil.[13,21]

Differential Diagnosis

OM may mimic any pupil-sparing ocular motility disorder, including fourth, sixth, and partial third nerve palsies and central gaze disorders, such as internuclear ophthalmoplegia, the one-and-a-half syndrome, and chronic progressive external ophthalmoplegia.[20–22] Horner syndrome should be easily distinguished based on pupillary involvement and elevation of the lower lid, while intrinsic brainstem pathologies will usually have associated central nervous system signs and symptoms. Graves ophthalmopathy can mimic OM by restrictive EOM weakness, but ptosis should be absent, and if the patient is thyrotoxic, lid retraction may be present. Ptosis in a patient with Graves disease suggests the coexistence MG. Chronic progressive external ophthalmoplegia caused by a mitochondrial disorder produces symmetric ptosis and ophthalmoparesis, but slow saccades usually differentiate it from OM.[22–24] Oculopharyngeal dystrophy should be differentiated from OM by its chronic progressive history, familial occurrence, and prominent involvement of nonocular, bulbar musculature. Other neuromuscular junction disorders may mimic OM such as Lambert-Eaton syndrome, congenital myasthenic syndromes, botulism, or organophosphate poisoning, although purely ocular presentations of these disorders are rare. Appropriate history, physical examination, and ancillary testing should distinguish these conditions from MG.

Additional Evaluation

Despite thymomas only rarely being present in patients with OM, chest imaging should be performed to exclude their presence. Since about 10% of patients with MG have thyroid hormone abnormalities, thyroid function tests should be done, and correction of hypo- or hyperthyroid states may improve MG symptoms. If clinically indicated, the coexistence of other autoimmune disorders should be assessed, including rheumatoid arthritis, pernicious anemia, and systemic lupus erythematosus. Tuberculin testing is indicated at initial evaluation of MG patients because of the expected treatment with immunosuppressant therapies, which may lead to reactivation of tuberculosis.

Diagnostic Evaluation

Once OM is suspected, clinical tests, serum AChR antibodies, and electrodiagnostic studies may be used to confirm the diagnosis. Clinical tests, such as the edrophonium, ice, or rest tests, are easy to perform and specific but of variable sensitivity. The AChR antibodies are often not found in patients with OM. Electrodiagnosis testing often then needs to be used, but repetitive nerve stimulation (RNS) also has poor sensitivity for OM and is operator dependent. Single fiber electromyography (SFEMG) is the most sensitive test but is available only at specialized centers and is time-consuming for patient and physician. SFEMG should be strongly considered to confirm the diagnosis of OM to justify use of immunotherapies with serious adverse effects.

Clinical Tests

Intravenous infusion of edrophonium chloride inhibits the action of acetylcholinesterase (AChE), which increases the acetylcholine concentration at the synaptic cleft, thereby increasing the endplate potential. Unequivocal improvement in strength of a ocular muscle after administration of edrophonium forms the basis of a positive test for MG.[25] Exact procedures for edrophonium administration vary, but in general, an initial 1-mg dose is given and the patient monitored, followed after 1 minute by another 3–4 mg. If improvement in a weak muscle does not occur, then additional edrophonium may be administered every minute until the full 10-mg dose is given. If no improvement occurs within a few minutes after a total dose of 10 mg is administered over 3 minutes, the test is negative. The test is most useful if improvement in ptosis or the strength of an EOM may be demonstrated because of the objective nature of this response.[25] In one study, all patients who had a positive test required at most 7 mg to achieve a response, with a mean dose of about 4 mg.[16] Administration of edrophonium after a definitive positive response only increases the chance of cholinergic adverse effects, such as stomach cramps, diarrhea, or syncope. The sensitivity of the edrophonium test as assessed by improvement in ptosis may approach 95%; however, EOM weakness does not respond as well in most studies.[16,18,26] Equivocal improvement should not be interpreted as a positive test. False-positive edrophonium tests are described in Lambert-Eaton syndrome, botulism, Guillain-Barre syndrome, compressive cranial neuropathies, and brain stem lesions.[21,26] Blinded performance of the edrophonium test is not advo-

cated for 2 reasons. (1) Because of the characteristic muscarinic side effects that are obvious to the patient and clinician, true blinding cannot be performed. (2) An *unequivocal* response is sought as determined by the clinician evaluator, not a subjective improvement in symptoms by the patient.

The edrophonium test is safe, with a serious complication rate, primarily bradycardia and syncope, of 0.16%, as assessed by survey of over 23,000 tests.[27] As expected, muscarinic effects of tearing, salivation, sweating, abdominal cramps, and nausea are common, which serve to confirm the activity of the drug. Atropine should be available to reverse bradycardia associated with syncopal symptoms. Relative contraindications to edrophonium testing are cardiac dysrhythmias and bronchial asthma.[21,26] It is the authors' opinion that routine cardiac monitoring is not necessary for the majority of patients. Neostigmine methylsulfate is a longer-acting anticholinesterase, which is administered by intramuscular injection, with an onset of action in 15 minutes and a peak at 30 minutes. The neostigmine may be used as an alternative to edrophonium, particularly in children; however, a selected end point may be more difficult to interpret, given the slower onset of improvement.

The ice pack, sleep, and rest tests are other clinical tests that may substitute for the edrophonium evaluations. These tests are simple and can be done quickly in the office without serious complications, but their drawback lies in the lack of extensive data evaluating their sensitivity, specificity, and interobserver reliability in comparison to a gold standard, such as single-fiber evaluations. The ice test is performed by placement of an ice pack on a ptotic eyelid for 2 to 5 minutes, followed by evaluation of ptosis[28] or eye movement deficit.[29] A sensitivity of 80% to 100% and 100% specificity may be achieved, but these case series are small. Some patients may have difficulty tolerating the ice pack. For the sleep test, the patient is asked to lie with eyes closed in a quiet, dark room for 30 minutes and then be evaluated for improvement in ptosis and ophthalmoparesis. Among 42 edrophonium-positive patients, all had positive sleep tests, and OM was identified in 2 patients with negative edrophonium tests.[30] The rest test requests the patients close their eyelids for 2 to 5 minutes, and improvement in ptosis is assessed. A small, randomized trial compared the ice test to the rest test and found that the median improvement of ptosis with the rest test was 2 mm, and with the ice test, 4.5 mm; no improvement was found in nonmyasthenic patients.[31] These tests may be performed in patients in whom pharmacologic testing may be contraindicated.

Acetylcholine Receptors and Other Autoantibodies

The clinician may order 3 types of AChR antibody tests: binding, blocking, or modulating.[32] The binding antibody is the most sensitive test, with 90% of patients with generalized MG and 50% of OM patients having positive tests. If the test yields a negative result, then an AChR modulating antibody increases the diagnostic yield slightly; however, the test suffers higher rates of false positives. AChR blocking antibodies do not help in MG diagnosis, because they are found in only 1% of MG patients without AChR binding antibodies, making them of limited diagnostic utility. It is important to appreciate that for many OM patients, the diagnosis cannot be confirmed by autoantibody testing.

Several other points are important to appreciate. (1) There is no correlation between the antibody titer and the severity of the disease in general, although in the individual patient, fluctuations in disease severity correlate with antibody titer. (2) Among OM patients with detectable AChR antibodies, the risk of generalization may be higher, but their detection does not have value in predicting whether an individual patient will generalize. (3) AChR antibodies are found in other conditions when there is no clinical or electrodiagnostic evidence of MG. False-positive detection of AChR antibodies may be in autoimmune liver disease, systemic lupus erythematosus, inflammatory neuropathies, amyotrophic lateral sclerosis, Lambert-Eaton syndrome, thyroid ophthalmopathy, first-degree relatives of MG patients, thymoma patients, rheumatoid arthritis, and in patients taking D-penicillamine.[32]

Antibodies to striated muscle were the first autoantibodies discovered in MG.[32] They are elevated in 30% of all adult-onset MG patients and are associated with thymoma, being positive in 80% of thymomatous MG. They are also found about a quarter of thymoma patients without MG. Striational antibodies are clinically useful as a marker of thymoma in patients with MG onset before 40, but thymoma in OM patients is rare. False positives are found in Lambert-Eaton syndrome, rheumatoid arthritis that is treated with penicillamine, in recipients of bone marrow allografts, graft-versus-host disease, and paraneoplastic disease.[33]

About a third to a half of generalized MG patients without antibodies against the AChR have been found to have antibodies against muscle specific kinase (MuSK), a neuromuscular junction protein that plays an important role in the clustering of AChR.[34–38] One patient with OM and MuSK antibodies has been described,[39] but MuSK antibody is not recommended as an initial, routine investigation in patients with OM, since the MuSK examination is about 40 times the cost of the AChR binding test.

Electrodiagnosis

Since clinical assessments may be equivocal and AChR antibodies negative, it is common for the patient with suspected OM to need electrodiagnostic evaluations. The 2 principal studies are RNS performed in concert with nerve conduction studies and needle muscle examination and the SFEMG.[40,41] A complete electrodiagnostic evaluation also will assist in assurance that the patient does not have other disorders of nerve and muscle. The needle EMG is usually normal in MG but may show nonspecific findings such as short duration, low amplitude, and polyphasic motor unit action potentials. The diagnostic yield of RNS for OM is increased by evaluation of the orbicularis oculi, orbicularis oris, or nasalis, although patients find these studies more difficult to tolerate than extremity evaluations. It is also important for AChE inhibitors to be discontinued at least 12 hours prior to evaluation. A decremental response may be identified in at least 75% of generalized MG patients, but less than 50% of OM will have such an abnormality. Therefore,

even after standard electrodiagnostic studies, the diagnosis of OM may not have been confirmed. Also, the identification of a decremental response in an extremity muscle does not predict or define progression to generalization.

SFEMG is the most sensitive test of neuromuscular transmission, with a sensitivity from 80%–100% in detecting MG.[42] SFEMG involves repeated measures of the temporal relationship between the action potentials of 2 different fibers in a single muscle during contraction. In MG, abnormalities occur because of the failure of one muscle fiber to transmit an action potential because of failure of the endplate potential to reach threshold, and sometimes one of the muscles may even fail to be activated, resulting in a neuromuscular block. A study is considered abnormal if the mean jitter (defined as the difference in muscle potentials from a single motor unit) of all fiber pairs (or end plates) exceeds the upper limit of normal for that muscle or if more than 10% of pairs have jitter that exceeds the upper limit of jitter during voluntary activation. Normal SFEMG in a weak muscle indicates the weakness is not due to a defect of neuromuscular, transmission and MG can be excluded.[43,44] Some studies suggest that an abnormal single-fiber examination may be associated with progression to generalization.[45] With normal nerve conduction studies and needle examination, abnormal jitter is highly specific for a neuromuscular transmission disorder.[40,41,43,44] SFEMG has limitations due to the requirement for specialized training of the examiner, time-intensiveness, and the difficulty that some patients have in tolerating the evaluation.

Treatment

The objective of treatment is to minimize the patient's symptoms, the adverse effects of therapy, monitor and prevent progression to generalized MG, and ultimately achieve disease remission. Unfortunately, relatively little evidence-based data exist to guide treatment of OM patients, and recommendations in this review are based largely on retrospective studies and clinical experience. The clinician should present both nonpharmacologic and pharmacologic treatment options to the patient and a joint care plan should be devised.

Nondrug Therapy

Nonpharmacologic treatments include eyelid tapes and crutches for ptosis and prisms, while various forms of occlusive devices may be tried for double vision. Some patients will achieve adequate symptomatic relief with such approaches and prefer them to drug therapies. Eye muscle surgery or botulinum toxin is generally not indicated in OM except in rare cases when a fixed strabismus occurs and nonfatiguing ptosis is documented.[46,47] Botulinum toxin should only be used with extreme caution since the agent can have systemic effects on neuromuscular transmission.

Cholesterase Inhibitors

AChE inhibitors, usually pyridostigmine bromide, are commonly the first step in treatment of OM patients. Pyridostigmine can be started at 30–60 mg 3 times per day and titrated up to 90 to 120 mg every 3–4 hours a day, as determined by its efficacy and side effects. Symptoms of dose-related muscarinic excess, such as abdominal cramps, nausea, vomiting, and diarrhea, are the major side effects, which occurred in 34 of 100 MG patients in one study.[15] Coadministration of atropine or glycopyrrolate may limit these adverse effects. Relative contraindications include bradycardia, asthma, and prostatic hypertrophy. Weakness produced by cholinergic excess is a frequently referred to phenomenon, which probably does not exist. However, the cholinesterase inhibitor dose may be reduced and the patient's response assessed to eliminate any such concern. Many will derive some benefit, particularly improving ptosis[48,49]; however, improvement in ptosis may have the undesired side effect of unmasking double vision, which may be more debilitating.[21] Kupersmith and Ying's[50] experience suggests patients do well with cholinesterase inhibitor treatment early on, but a drop in long-term follow-up suggests patients ultimately move to other treatment options. These medications do not alter development of generalization in OM patients.[16,51]

Corticosteroids

If a patient has not had an adequate response to Cholinesterase (ChE) inhibition and nonpharmacologic therapy, the next step is usually corticosteroid therapy. Treatment regimens vary, but usually prednisone 10–20 mg once a day is started and increased by 5–10 mg every 3 days until symptoms are controlled or a 60- to 80-mg/day dose is achieved.[16,52,53] Improvement usually begins within 2 weeks. Maintenance dose after titration varies from 60 mg per day or switching to alternate-day dosing. Therefore, begin tapering by only 5–10 mg per day every 2 weeks as the prednisone dose is decreased to 20 mg every other day; taper even more slowly until the patient is successfully tapered off the medication. Too rapid a taper may lead to symptom recurrence, but even with slow tapers most patients will have recurrence of symptoms. Retrospective studies show significant clinical improvement by subjective measures, with "good" results in 72%–96% of patients.[18,49,50,54] Most patients will need to be maintained on low doses for years and many require intermittent increases in corticosteroids for exacerbations.

Whether early treatment with prednisone may prevent OM patients from developing generalized MG is debated.[51,55,56] Retrospective studies suggest reduced rates of generalization in patients treated with corticosteroids.[16,52,57,58] However, there is no conclusive evidence from prospective, randomized, controlled studies that corticosteroids prevent generalization. In addition, the balance of the adverse effects of corticosteroids may be severe and outweigh their benefit. Patients need to be monitored for development of diabetes, osteoporosis, hypertension, sleep disorders, emotional alterations, and other adverse effects. Every patient needs to be made aware of complications prior to institution of corticosteroid treatment.

Other Immunotherapy

Some patients will neither improve nor tolerate cholinesterase inhibitors or corticosteroids, yet will have significant visual disability.[54] At this point, the clinician will need to consider immunosuppressant therapy and be guided by experience in treatment of generalized MG. Azathioprine, cyclosporine, tacrolimus, and mycophenolate mofetil are agents that may be considered. Azathioprine was been shown

in a randomized, placebo-controlled trial to reduce corticosteroid requirements,[59] and retrospective studies show improvement in OM patients.[60–63] Cyclosporine and mycophenolate mofetil are steroid-sparing agents that have shown benefit in small, double-blind, placebo-controlled, and retrospective studies of severe generalized, treatment-resistant MG patients.[64–68] Tacrolimus (FK-506) has been used widely in Japan for treatment-resistant generalized MG patients, with good results, but again the retrospective studies do not address use in OM.[69] Intravenous immunoglobulin therapy is used for management of acute exacerbations and chronic management, but no evidence base exists to guide intravenous immunoglobulin treatment of OM. Most clinicians do not recommend thymectomy in OM, because of its potential for significant morbidity, albeit rare; however, there are reports of the efficacy of thymus removal for OM.[70,71] Patients with a thymoma should have the tumor removed, along with coincidental removal of the remainder of the thymus.

Why Eye Muscles Are Preferentially Involved in Myasthenia Gravis

MG is caused by the failure of skeletal muscle to respond appropriately to nerve stimulation due to antibody-induced injury (Fig. 1).[72] The antibodies are produced by autosensitized B cells by a T-cell-dependent mechanism and induce neuromuscular transmission compromise by blocking the AChR, increasing its rate of internalization, or the predominant mechanism of complement-mediated injury. In OM patients, the concentration of antibody is lower or absent than in patients with generalized MG. Although absolute correlation of antibody concentration and severity of weakness is poor,[32,73] the low titers of antibody support the clinical impression that EOM is more susceptible to autoantibody injury. The properties that may mediate this susceptibility include antibody targets, the immune response, and the safety factor of the EOM neuromuscular junctions.

Antibody Target

What makes EOM more sensitive to MG in terms of antibody production and T-cell response has not been determined, although OM patients show defined differences from generalized MG patients. The lower levels or absence of AChR antibodies seen with OM,[32,73] suggests a greater sensitivity to the antibodies produced either through a higher exposure AChR target, an epitope that is specific to EOM,[74,75] or less of an ability to moderate complement attack due to lower levels of the complement regulator or decay accelerating factor (DAF), or some combination of all 3 factors.[76,77] The in vitro response of the T cells to AChR is lower in ocular patients than patients with generalized MG, and this activity fluctuates over time.[78] The end result is that the limited supply of antibody to AChR is insufficient to produce a generalized weakness.

In a fundamental look at the differences between EOM and other skeletal muscle, gene expression studies were performed on human, rat, and mice samples to assess specific markers that create divergence in a tissue type. Using microarray and serial analysis of gene expression, the results identified significant numbers of differentially expressed genes in EOM, ranging in number from approximately 100 to 350 genes.[77,79–81] The studies indicate expression differences compared with other skeletal muscle of genes involved in intermediary metabolism, excitation-contraction coupling, structural organization, transcriptional regulation, and myogenesis. Investigations of how these differences correspond to functional differences are under way; however, a few genes of interest have begun to emerge that may lead to a greater understanding of EOM disease susceptibilities.

A high number of embryonic isoforms have been identified in EOM. Khanna et al[82] have suggested the embryonic muscle traits persist due to continuous growth that exists in the EOM. The constant mechanical stretch experienced in the EOM may induce signaling cascades that trigger up-regulation of genes normally seen in embryonic or fetal development. The importance of embryonic isoforms to the susceptibility of EOM to MG is the expression of potential antigens, as in the case of the fetal isoform of AChR.

Structural and signaling proteins of the neuromuscular junction (NMJ) of the EOM are the same that have been identified in other skeletal muscle fiber types.[83] The majority of EOM fibers are singly innervated fibers (SIF) and share similar endplate morphology with other skeletal muscles having a single en plaque neuromuscular junction. These fibers have less prominent synaptic folds, and therefore one would predict fewer AChRs and sodium channels on the postsynaptic membrane.[84–86] However, EOM contains an elevated expression of AChR receptor subunits and AChE, which relates to a high innervation ratio.[77,80,81] The EOM miniature endplate potential amplitudes are similar to those of leg muscle junctions, indicating that AChR density is similar at these synapses. Therefore, the lower degree of invaginations of the synaptic folds and the higher number of endplates may allow for a greater number of exposed target sites for antibody interaction.

Molecular organization of 2 members of the dystrophin-glycoprotein complex, alpha-dystrobrevin and syntrophin beta1, maintain differences in EOM compared with other skeletal muscle in localization.[86] The potential difference in the expression pattern may contribute to the distinctive lack of junctional folds at the NMJ. For example, rapsyn has been shown to reduce disease severity in experimental MG by increasing the integrity of the NMJ.[87] The result has shown that tightly coupled neuromuscular junctions decrease membrane loss. Although no reduction in expression or changes in localization of rapsyn have been uncovered in EOM, the lack of junctional folds is one sign that the integrity of the neuromuscular junction in EOM may be uncertain and under duress due to the underlying molecular organization.

The epitope differences may occur in OM sera. Most notably are sera that do not contain detectable levels of AChR antibody, seronegative MG. Studies have found that antibodies to a muscle-specific receptor tyrosine kinase were identified in some seronegative MG patients with ocular and bulbar muscle weakness.[38,39,88] However, other groups have expanded the patient profiles to include the seropostive MG and classify the patients into a generalized MG form. Of the OM patients that are seropositive, T cells recognize all AChR

subunits, although a greater number of peptides of the γ subunit were detectable in OM compared with generalized MG.[78] The fetal form of the AChR could be a specific antigenic target to OM development since the expression level remains high in adult EOM.

Complement and Immune Response

Blood flow is higher in mammalian EOM compared with skeletal muscle. The higher rate may be due to an increase in functional ocular motility, the dependence on aerobic metabolism, or the combination of the 2 factors.[89,90] The increase in blood flow would also include the increase in circulating T cells, B cells, and macrophages to the muscle and would increase antibody delivery to the EOM neuromuscular junctions.

The complement cascade is responsible for the destruction to the NMJ after antibody targeting. DAF is a regulator of the complement-mediated injury by blocking the cascade at the C3 level.[91] DAF has been found to be lower in expression level in the EOM, which potentially may allow for greater membrane attack complex deposition and greater lysis of the muscle membrane.[76,77] Studies on DAF knockout mice have shown an increase susceptibility to experimental MG than the control littermates.[92] DAF could be a target for therapeutic agents, as well as the down-regulation of the complement cascade system.

Production of anti-AChR $CD4^+$ cells is required for the development of MG due to their role in antibody synthesis.[93] The $CD4^+$ T cell responds to the entire molecule of AChR in MG and few differences occur between the response of T cells from generalized MG and OM. T cells from OM do have a wider range of activation from the γ subunit of the AChR and a limited response from the ε subunit. The other difference in the T cells' response is the variation that occurs over time, suggesting that the T cells are not stable as in generalized MG.[78] The instability of the response may indicate that the T cells themselves are not enough to initiate antibody production that results in generalized weakness.

Safety Factor

The ocular motor neuron firing frequency is directly related to eye position, both of which are in continuous action. Firing frequencies may reach peaks of 400–600 Hz during saccades. In contrast the rapid movement of a limb would be the result of a firing frequency of 150 Hz from the spinal motor neuron. The response of the muscle due to motor neuron firing differs as well between EOM and other skeletal muscles. In most skeletal muscles, a safety factor allows for a wide range of firing frequencies to produce an action potential.[94] However, in EOM the safety factor is low or absent, and any lowering in the summation would result in a lack of membrane depolarization. This difference is important to the understanding of the susceptibility of EOM to autoimmune attack.[86]

While most NMJ of skeletal muscle function as a slave to the firing of the motor neuron, the NMJ of EOM has its own unique response. Ocular motor neuron firing frequency correlates with eye position. As well, force appears be controlled by the motor neuron firing rates rather than having additional motor units recruited to generate additional force. Multi-innervated fibers (MIF) act in a tonic fashion, similar to slow or tonic fibers of amphibians, with no safety factor and no action potentials. Force generation is directly proportional to the membrane depolarization caused by the endplate potential, and action potentials are not generated. Therefore, a safety factor does not exist for MIF, and any reduction of endplate potential induced by a loss of AChRs would decrease contractile force of these fibers.

The contraction and relaxation properties of orbital fibers vary along their length. These fibers contract in a graded fashion in the region of the MIF endplates and in a twitch pattern around the SIF endplates. The motor neurons innervating the MIF lie in the periphery of ocular motor nuclei and are innervated by premotor neurons that control smooth pursuit, vergence, and gaze holding. This pattern of innervation suggests that these fibers are likely to serve a proprioceptive role, although their precise function in generation of eye movements has not been defined. Any changes in the response of the MIF would have a drastic change on the ability for eye movement to be maintained.

CONCLUSION

Although MG is often considered the best understood autoimmune disorder, this review has identified several clinical and basic questions that require study. Although generally effective for improving visual deficits, prednisone's long-term effects need be weighed when considering its use in patients, and no robust data exist specific to OM to guide patients or physicians. Of critical importance is the determination of whether generalization of disease may be limited if corticosteroids are used early. The benefit of steroid-sparing agents as primary therapy for MG also is not known. Data are accumulating regarding the unique immunologic environment of EOM, and this may lead to new therapeutic avenues.

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