Myasthenia gravis

Five new things

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Summary

Myasthenia gravis (MG) is the most common autoimmune disease affecting neuromuscular junction transmission. MG is characterized by muscle weakness that worsens with activity and fluctuates over the course of the day. Involvement of respiratory musculature can lead to life-threatening crisis requiring intensive care unit care. Antibody testing is positive in most patients with MG. Treatment of MG includes short-term symptomatic treatment, chronic immunosuppression, surgical intervention, and immunomodulatory therapies for severe disease or crisis. We review advances in 5 areas relevant to diagnosis and management of MG: the role of IV immunoglobulin vs plasmapheresis in myasthenic crisis and severe disease; the clinical characterization of patients with antibodies to muscle-specific tyrosine kinase receptors; old and new investigational treatments; management of MG in pregnancy; and new confirmatory diagnostic tests.

Myasthenia gravis (MG) is the most commonly encountered autoimmune disease of the neuromuscular junction with an estimated worldwide prevalence between 15 and 179 per million people. MG causes fluctuating weakness that worsens with activity and as the day progresses, and ocular weakness, causing ptosis and diplopia.¹ In 15% of patients, life-threatening respiratory weakness can occur, called myasthenic crisis. Ocular symptoms are the most common presenting symptoms, with around two-thirds of patients progressing to generalized disease, usually within the first 2 years. The diagnosis is based on clinical history and neurologic examination and confirmed by electrodiagnostic testing and the presence of serum autoantibodies directed at proteins in the neuromuscular junction. The vast majority of patients with generalized MG (~85%) and pure ocular MG (~50%) will have antibodies to the skeletal muscle nicotinic acetylcholine receptor (AChR). An additional 8%–10% of patients with generalized disease have antibodies to muscle-specific tyrosine kinase receptor (MuSK), an enzyme involved in acetylcholine receptor clustering in the synaptic cleft.

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Most patients respond well to immunosuppressive therapies, including prednisone and immunosuppressants such as azathioprine, cyclosporine, and mycophenolate mofetil. Cholinesterase inhibiting agents provide temporary relief from symptoms but do not alter the disease course. Approximately 10%–15% of patients will have evidence for thymoma on chest CT and benefit from thymectomy, but the role of thymectomy in nonthymomatous MG is currently under investigation. For patients in myasthenic crisis, with severe disease not responding to immunosuppressive therapy, or preparing for thymectomy, plasmapheresis (PLEX) and IV immunoglobulin (IVIg) are used to achieve rapid improvement.

In this review, we discuss 5 important topics in the diagnosis and management of MG: the relative effectiveness of PLEX vs IVIg for myasthenic crises or disease exacerbations; phenotypic characterization of patients with MuSK antibodies; old and new investigational therapies for MG including thymectomy and rituximab; management of MG in pregnancy; and finally, newly discovered antibodies and their future role in the diagnosis of MG.

Plasmapheresis vs IVIg

Mortality in patients with MG crisis or severe exacerbations has declined significantly in the past few decades due to intensive care unit (ICU) support and use of PLEX and IVIg. However, there is little information about which treatment strategy is better. There are 2 prospective parallel trials comparing PLEX to IVIg.^{2,3} Both studies found no difference between PLEX and IVIg, and both treatments improved symptoms from baseline, meeting predefined clinical response targets in 55%–65% of participants. One study found a trend toward shorter time to symptom improvement with PLEX vs IVIg, but fewer adverse events with IVIg.³ Limitations to the studies include different inclusion criteria, different dosing regimens for IVIg (0.4 g/kg for 3 or 5 days, or 1 g/kg for 2 days), and definitions of response (quantitative MG score vs myasthenic muscular score). Recent revised consensus guidelines for outcome measures for future clinical trials may help for cross-study interpretation of MG trials.⁴ A retrospective case series of patients in acute MG crisis (defined as respiratory weakness and forced vital capacity ≤ 1.0 L) found that for patients on a ventilator at randomization there was a higher frequency of extubation in patients receiving PLEX compared to IVIg at 2 weeks, which corresponded with improved clinical severity at 1 week.⁵ However, they were unable to conclude whether this represented a shorter time to response for PLEX or true benefit of PLEX over IVIg for myasthenic crisis.

The American Academy of Neurology (AAN) published guidelines for the use of IVIg in the treatment of neuromuscular disorders, and recommended IVIg should be considered in the treatment of MG (level B).⁶ More controversially, consensus guidelines on the use of PLEX in neurologic disease published by the AAN in 2011 suggested there is insufficient evidence for the use of PLEX in acute MG crisis, due to the lack of randomized, placebo-controlled trials.⁷ However, many neuromuscular specialists disagree with this assessment, which led to an editorial in response to the guidelines. The editorial outlined a number of what we believe are valid concerns: insufficient evidence might be misinterpreted as a “negative recommendation”; randomized controlled trials may not be feasible in rare diseases; and a trial with a placebo group may not be seen as ethical for a treatment widely accepted as a standard of care.⁸

Based on the evidence available and our personal experience, IVIg and PLEX are equally effective for treatment of severe MG or MG exacerbations, but PLEX seems superior in true crisis requiring ventilator support. IVIg is easy to administer and generally well-tolerated, but may require longer for a clinically meaningful effect than PLEX. PLEX generally requires 10 days of therapy if treatments are given every other day, and it is not universally available. Finally, a cost-benefit analysis of IVIg vs PLEX concluded that IVIg was associated with lower hospital costs and fewer complications; however, the disease severity at initiation of treatment was not available for their analysis.⁹ It is possible that patients receiving PLEX were more severely affected, resulting in longer ICU stays and increased costs.

MuSK phenotype

Antibodies to MuSK make up about 40% of AChR-negative patients with MG. MuSK plays an important role in AChR clustering at the postsynaptic neuromuscular junction. Many case series have begun to elucidate key clinical features, and important distinctions in response to therapy in patients with MuSK vs patients with other generalized MG. One of the more striking differences is the female predominance of patients with MuSK, ranging between series from 78% to 100% women.^{10–12} Three relatively distinct clinical patterns have emerged: oropharyngeal weakness, with occasional profound tongue and facial atrophy; neck, shoulder, and respiratory weakness without ocular weakness; and a phenotype indistinguishable from AChR-positive MG. One large series of 53 MuSK-positive patients from 9 US neuromuscular centers found facial and bulbar weakness in 96%, neck weakness in 92%, limb weakness in 81%, ocular weakness in 72%, and breathing difficulties in 60% of patients.¹⁰ The high prevalence of respiratory involvement is important when considering diagnosis and therapeutic options. Unlike generalized AChR-positive MG, the majority of case series report poor response to cholinesterase inhibitor medications in MuSK-positive patients, and the response to thymectomy in these patients has ranged from no response to 50%. Many patients require PLEX for stabilization, and one case series found 98% on 2 or more forms of immunotherapy. Despite this, long-term outcomes are still quite good, with approximately three-fourths of patients eventually achieving pharmacologic, clinical, or minimal manifestation remission.

MuSK-antibody-positive MG should be considered in the differential diagnosis of patients with unexplained restrictive respiratory failure, or in mechanically ventilated ICU patients who cannot be extubated with no clear underlying etiology.

New (and old) treatment strategies

Thymectomy The first thymectomy for thymomatous MG occurred over 70 years ago. While thymectomy is considered standard treatment for the 10%–20% of MG cases with thymoma, the role of thymectomy in nonthymomatous MG is not as clear, and it is generally not considered appropriate for purely ocular MG. The AAN published guidelines in 2000 for the role of thymectomy in MG, and concluded that thymectomy is an option for treatment in MG.¹³ They based this recommendation on an apparent association with better outcome in patients receiving thymectomy in 28 case series between 1953 and 1998: using median response rates, patients undergoing thymectomy were 2.0 times as likely to achieve a medication-free remission, 1.6 times as likely to become asymptomatic, and 1.7 times as likely to improve. The benefit was modest and appeared to be most pronounced for moderate or severe MG. Limitations included differences in baseline characteristics between those receiving surgery and medical management alone, lack of blinding, and different methods of assessment.

Noninvasive video-assisted thoracotomy, transcervical, and transsternal thoracotomy are routinely performed. Comparisons among the techniques are largely retrospective. In general, the benefit of less-invasive techniques with shorter recovery times needs to be weighed against the ability to obtain a maximal resection of tissue. Long-term (>5 year) response rates for minimally invasive techniques approach 40% for complete symptomatic remission, with procedure-related morbidity rates (~20%) comparable to more invasive techniques. That said, a meta-analysis comparing VATS to median sternotomy in 6 studies for

Table Rituximab in MG: Case series summarized in this review

Study	Patients	Response rates	Dosing regimen	Adverse events
15	11 AChR, 3 MuSK (nonresponsive or contraindication to IS therapy)	11 improved by MGFA Clinical Research Standards (3 MuSK patients achieved clinical remission)	1 g infusion, independent of body weight, in 2 divided doses, 2 weeks apart	2 immediate side effect (flu-like symptoms, warm sensation, hypertension), 1 alteration in sweet taste, 1 reactivation of oral herpes zoster
17	6 AChR, 8 MuSK (nonresponsive, could not lower therapy without relapse, or contraindication to IS therapy)	13 patients on corticosteroids showed dose reduction (8 completely off prednisone after 3 cycles); 11/12 patients who received PLEX in prior 12 months PLEX-free at 12 months; clinical improvement by chart review in 11	375 mg/m ² (× 4 infusions, 1 week apart), cycles repeated at 6 months, up to 4 cycles	Out of 132 infusion notes available: 6 reactions during infusion (pruritus, flushing, dyspnea, chills/rigors, hot sensation); 1 patient with chills/rigors in 2 subsequent infusions
16	11 AChR, 6 MuSK (resistant to prior therapies, prednisone, and at least 3 second-line IS, MGFA class III to V)	16 improved at mean 31 months follow-up by MGFA Clinical Research Standards (including 6 MuSK patients who remained in minimal manifestations or remission)	375 mg/m ² (×4 infusions, 1 week apart, then monthly ×2 months)	2 patients facial flushing and generalized skin rash that responded to parenteral hydrocortisone

Abbreviations: AChR = acetylcholine receptor antibody positive; IS = immunosuppressive; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MuSK = muscle specific tyrosine kinase receptor antibody positive; PLEX = plasmapheresis.

nonthymomatous MG found shorter hospital stays for VATS, lower blood loss, and similar mass of thymic tissue resection.¹⁴ Indeed, minimally invasive techniques are increasingly recommended by surgeons, and will be an option commonly presented to patients.

For the clinician trying to decide on the role of thymectomy vs best medical treatment in MG, an ongoing NIH-sponsored international trial of thymectomy in nonthymomatous MG is currently nearing completion and will hopefully answer this important question.

Rituximab The mainstay of immunosuppressive treatment for MG is prednisone. In addition, many steroid-sparing immunosuppressive drugs (e.g., azathioprine or cyclosporine) have also been shown to be effective. Despite this, some patients with MG remain refractory to treatment.

Rituximab is a monoclonal antibody to CD20, which leads to B-lymphocyte depletion, which has shown to be effective in other antibody-mediated autoimmune disorders. A number of retrospective case series have examined use of rituximab in treatment of refractory myasthenic patients (table). Response rates between 78% and 100% for clinical improvement have been reported over time frames typically >6 months, often with repeated cycles of treatment; in addition, concomitant reductions in corticosteroid or immunosuppressive doses were reported.^{15–17} Similar response rates have been seen in non-treatment-refractory MG. Complication rates varied between studies, with the most common adverse events directly related to infusions (flushing, pruritus, chills, or rigors). A dramatic response is seen in MuSK-positive patients, with improvement seen in nearly all patients. The effect on circulating antibody levels has been inconsistent, but there appears to be a trend toward a direct

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reduction in antibody levels following infusions. One study noted clinical improvement which corresponded to B-cell depletion, and worsening of symptoms corresponding to B-cell recovery, making this a possible indicator of need for repeat infusion. Complicating interpretation of the case series are varied regimens for infusions of rituximab—some studies using dosing per meter squared of body area, others using fixed doses—and different number of repeat infusion cycles, with differing periods of time between infusions.

A multicenter randomized control trial of rituximab for MG is currently being planned.

Myasthenia gravis and pregnancy

MG poses particular challenges in the management of women during pregnancy. Approximately one-third of women will experience an exacerbation of symptoms, most commonly in the first trimester or postpartum. Sudden and occasionally severe exacerbations, including respiratory insufficiency, can occur in the first weeks puerperium; therefore, closer monitoring is recommended during this time. Interestingly, improvement in symptoms of MG or even complete remission may occur in some women in the second or third trimester, thought to be related to the physiologic immunosuppression that occurs during those phases of gestation.¹⁸

The incidence of spontaneous abortions does not appear to be increased in women with MG, although some studies reported increased frequency of premature rupture of membranes. A study examining adverse pregnancy outcomes in 163 women with MG between 2001 and 2003 in Taiwan found no significant increase in adverse pregnancy outcomes in MG, although a trend toward lower birthweight, small for gestational age newborns, and cesarean deliveries was noted.¹⁹

Treatment for MG during pregnancy should be individualized based on severity of underlying weakness. For mild disease, symptomatic cholinesterase inhibitors can be used alone, which at usual oral therapeutic doses (<600 mg/day) are safe for the fetus. Corticosteroid use poses little if any teratogenic risk to the fetus and can be continued for pregnant women requiring immunosuppression. Other immunosuppressive agents should not be initiated; in particular, mycophenolate should be avoided in women of childbearing age planning to have children due to its teratogenic risk, and risk of spontaneous abortion. However, the most common steroid-sparing immunosuppressant used in MG, azathioprine, has been reported to be safe in pregnancy in other autoimmune diseases and a large transplantation database. If required, both IVIg and PLEX are generally safe to use to manage severe worsening of symptoms. Thymectomy should be considered prior to planning for pregnancy.

New antibody testing

Antibody testing for AChR and MuSK are confirmatory in MG; despite this, around 10% of patients will remain antibody-negative. A protein recently discovered to play a role in retrograde signaling from muscle to the presynaptic nerve terminal has generated a lot of interest, as antibodies to this protein, low-density lipoprotein receptor-related protein 4 (Lrp4), are believed

to be found in a proportion of double-seronegative patients with MG (negative for both AChR and MuSK antibodies). Lrp4 is required for agrin-induced activation of MuSK and is thought to induce clustering of synaptic-vesicle and active-zone proteins in the neuromuscular junction.²⁰ Antibodies to Lrp4 were first identified in 2011, and 3%–50% of double-seronegative patients meeting diagnostic criteria for MG have been found to have detectable Lrp4 antibodies.^{20,21} In addition to patients with double-seronegative MG, Lrp4 antibodies can be detected at low frequency in MuSK-positive patients and rarely in patients with other neurologic diseases (including patients with neuromyelitis optica), but have not yet been found in AChR-positive patients or healthy controls. Furthermore, a portion of sera from Lrp4 antibody-positive patients disrupted the agrin-Lrp4 interaction and inhibited agrin-induced AChR aggregation in cultured myotubes, suggesting a possible pathogenic role for the antibodies.^{20,21}

Indeed, the term seronegative may be a misnomer in MG, a disease where it seems increasingly likely that patients with negative antibody testing may simply reflect our inability to test for the proper antibody. Supporting this are 2 studies that tested patient sera against clustered AChRs and found so-called clustered AChR antibodies in 60% of previously seronegative patients with generalized MG, and 50% of seronegative ocular MG. They were able to show that transfer of these IgG1 antibodies into mice reduced miniature endplate potentials to an extent similar to AChR antibodies.²²

While testing for AChR and MuSK antibodies remains the mainstay of diagnostic testing in MG and detects antibodies in around 90% of patients with generalized MG, testing for Lrp4 or clustered AChR antibodies may increase the sensitivity of MG antibody testing to >95% in the near future.

DISCUSSION

Advancement in our understanding and treatment of MG has transformed this once debilitating disease into one of the most treatable neuromuscular disorders. The majority of patients can achieve symptomatic remission with immunosuppressive drugs and cholinesterase inhibitors. Immunomodulatory therapies like PLEX and IVIg have reduced morbidity and mortality during myasthenic crisis, shortening time on ventilator support and hospital stays. The role of thymectomy is still being elucidated, but is a first-line treatment for patients with thymoma-associated MG, and may be a viable option for nonthymomatous MG. New investigational drugs like rituximab hold promise for future treatment of refractory disease. As our understanding of the neuromuscular junction advances, so does our rational choice of targets for both therapy and diagnostic testing, making MG one of the best understood and treatable autoimmune neuromuscular disorders.

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- IVIg or plasmapheresis can be used in severe disease and exacerbations, but PLEX is probably better for true myasthenic crises. Plasmapheresis may produce a more rapid response, but IVIg is less expensive and may have fewer complications.
- Patients with MuSK antibodies are more often women, and can have distinctive clinical patterns of disease including an oculopharyngeal pattern and neck, shoulder, and respiratory weakness pattern.
- Case series suggest thymectomy is beneficial for nonthymomatous MG, and newer, less-invasive techniques show comparable efficacy, with shorter hospital stays. Rituximab may prove beneficial in patients with MG resistant to immunosuppressive therapy and patients with MuSK antibodies.
- An increase in symptoms of MG can be seen in pregnancy, but with proper multidisciplinary management, pregnancy is generally not associated with adverse pregnancy outcomes.
- As our ability to detect new target antibodies to proteins in the neuromuscular junction increases, the number of patients who remain “seronegative” decreases, and the sensitivity of antibody testing increases to ~95%.

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