Myasthenia Gravis and Congenital Myasthenic Syndromes

By Emma Ciafaloni, MD

REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: **Myasthenia gravis (MG) is an autoimmune neuromuscular disease that causes fluctuating weakness in ocular, bulbar, and limb muscles and can, in 15% of cases, cause myasthenic crisis, a neurologic emergency characterized by respiratory failure. Although infrequent, MG needs to be promptly recognized and treated because the potential for improvement and remission is very high. The diagnosis of MG can be challenging and delayed because of the fluctuating nature of muscle weakness and the overlap of signs and symptoms with other neuromuscular diseases.**

This article reviews the importance of prompt recognition of the typical signs and symptoms, best tests to confirm the diagnosis, currently available acute and chronic treatment modalities, the role of thymectomy, and the natural history of the disease. Special consideration related to the diagnosis and management in women during pregnancy and in children will also be reviewed. This article also includes an overview of congenital myasthenic syndromes.

RECENT FINDINGS: **Recent significant efforts in standardizing and improving the care of patients with MG have occurred, as well as new momentum in developing new drugs for patients with MG who do not adequately respond to currently available treatments. The number of clinical trials and drugs in development for MG is steadily increasing. Eculizumab has been recently approved by the US Food and Drug Administration (FDA) for adult patients with generalized MG who are acetylcholine receptor–antibody positive, based on the REGAIN (Safety and Efficacy of Eculizumab in Refractory Generalized Myasthenia Gravis) study, a phase 3, randomized, double-blind, placebo-controlled, multicenter trial. An international, multicenter, randomized trial comparing thymectomy plus prednisone with prednisone alone has demonstrated that thymectomy improves clinical outcome in patients with nonthymomatous MG. Clinical care guidelines have been published, and the recommendations for clinical research standards and the Myasthenia Gravis Foundation of America MGFA clinical classification published in 2000 have become widely accepted by the clinical and research community of MG experts.**

SUMMARY: **MG is a highly treatable disease with many effective treatment modalities available and with a natural history that continues to improve**

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Address correspondence to Dr Emma Ciafaloni, MD, 601 Elmwood Ave, PO Box 673, Rochester, NY 14642, *Emma_Ciafaloni@URMC.Rochester.edu*.

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thanks to better diagnostic tests and effective drugs. The diagnosis and management of patients affected by MG can be highly rewarding for any neurologist as most patients are able to live normal lives if treated appropriately. Nevertheless, future research is needed to address unresolved clinical issues, such as when and how to discontinue immunosuppressive medications in patients in remission, the role and timing of thymectomy in children, and better treatment options for refractory patients.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease affecting the neuromuscular junction and causing fatigable ocular, limb, and bulbar muscle weakness. It has a prevalence of approximately 1 in 5000. MG affects patients of all ages with a peak in younger women and older men. Antibodies against the acetylcholine receptor (AChR) or the muscle-specific tyrosine kinase (MuSK) are found in the majority of affected patients, but seronegative cases occur in approximately 50% of purely ocular cases and 20% of generalized cases. Severity varies from mild weakness limited to the ocular muscles causing ptosis and diplopia (purely ocular MG) to generalized limb and bulbar weakness causing mild to severe dysarthria, dysphagia, and difficulty using the arms and legs (generalized MG). In approximately 15% of patients, severe weakness of respiratory muscles causes restrictive respiratory failure (ie, myasthenic crisis), a true neurologic emergency that requires prompt treatment in an intensive care setting. MG is highly treatable with immunomodulation with corticosteroids, long-term immunosuppressive drugs such as azathioprine and mycophenolate mofetil, IV immunoglobulin (IVIg), and plasma exchange. Thymectomy has also been shown to improve clinical outcome. Pharmacologic remission is common, and the prognosis is currently good with a mortality of less than 5%. Treatment should be tailored to the individual patient, and special consideration should be given to women of childbearing age, pregnant women, children, and the elderly when choosing the most suitable immunosuppressant medication.

Congenital myasthenic syndromes are very rare genetic diseases affecting the neuromuscular junction and causing ocular, bulbar, and limb muscle weakness of varying severity and usually with an onset early in life. The diagnosis is based on clinical signs and symptoms, a lack of serum antibodies, an abnormal repetitive nerve stimulation test with compound muscle action potential (CMAP) decrement, and no response to immunosuppressive therapy. Multiple genes encoding proteins expressed at the neuromuscular junction are associated with different subtypes of congenital myasthenic syndromes.

EPIDEMIOLOGY

Although the prevalence of MG has been steadily increasing for the past 50 years because of better diagnosis, improved treatment modalities, and increased life expectancy, MG remains an uncommon disease with approximately 60,000 estimated cases in the United States.[1,2] Prevalence is reported at about 20 in 100,000 and varies in different countries.[3–5] In patients younger than 40, women are more commonly affected with a ratio of 7:3, whereas men are more

commonly affected among patients older than 50, with a ratio of 3:2. Cases are evenly distributed in patients in their forties. Pediatric MG is very rare.[6,7]

ETIOLOGY

MG is a well-understood autoimmune disease affecting epitopes in the postsynaptic membrane of the neuromuscular junction.[8] The antibody-mediated, T-cell–dependent immunologic attack on the postsynaptic membrane results in damage of the postsynaptic muscle membrane, simplification of the highly folded surface, and a reduced number and density of AChRs, resulting in abnormal neuromuscular transmission and clinical fatigable muscle weakness. Antibodies against the AChR that bind to the main immunogenic region of the α subunit of the AChR are the most common and cause destruction of the postsynaptic endplate region through complement activation. Autoantibody production in MG is a T-cell–dependent process, and the thymus is thought to play an important role in the dysregulation of self-tolerance.[9,10] Thymic pathology, including thymoma (about 15% of patients with MG) and thymic hyperplasia with lymphofollicular hyperplasia (about 65% of patients with MG), has been recognized for a long time, and the thymus is believed to play an important role in the pathogenesis of MG.

In some patients with MG, MuSK is the autoantigen and antibodies to MuSK are found in the serum of about one-third of patients with MG who are AChR seronegative. MuSK plays a role in the clustering of AChR at the endplate region and in endplate formation and maintenance, but the role of anti-MuSK antibodies in the pathogenesis of MG is not yet fully understood.[11,12]

CLINICAL SIGNS AND SYMPTOMS AND CLINICAL CLASSIFICATION

The core clinical feature of MG is fluctuating and fatigable weakness of muscle groups that worsens with exercise and improves with rest. Ptosis, frequently asymmetric, and binocular diplopia are the most common presenting symptoms and eventually appear in most cases early in the disease course. In some patients, bulbar weakness resulting in flaccid dysarthria, dysphagia, jaw closure weakness, and facial weakness (weak smile or a "myasthenic snarl") can be the initial presentation. Patients with weak bulbar and facial muscles report nasal speech after prolonged speaking; liquids escaping through the nose when drinking; an inability to drink through a straw or to whistle; food getting stuck in the throat when eating; an inability to smile, which is noticed by other people and sometimes wrongly interpreted as a flat mood or depression; and jaw fatigue when chewing harder foods.

Neck flexion is usually more affected than neck extension, but dropped head syndrome can occur. Weakness of limb muscles is usually proximal (more than distal) and symmetric, but fingers and wrist extension and foot dorsiflexion are also commonly affected. Limb weakness results in difficulty performing tasks that require the arms to be above the head, getting up from low seats or toilets, walking for prolonged distances, and climbing stairs. Selective or predominant weakness of triceps muscles has been described especially in African American patients.[13–15] Focal distal predominant weakness affecting finger flexors or extensors, sometimes asymmetric, and foot drop have also been described.

Patients with anti-MuSK antibody can have atypical clinical presentations, including one with predominantly neck extensor, shoulder, and respiratory

KEY POINTS

- Autoimmune myasthenia gravis can occur at any age.
- Thymoma is found in about 15% of patients with myasthenia gravis and should always be surgically removed. Thymoma is more frequently found in males and patients older than 40, and about 50% of patients with thymoma develop myasthenia gravis.

muscle weakness and one with severe oculobulbar weakness, fixed facial muscle weakness, and weakness of the tongue and pharyngeal muscles that respond poorly to treatment.

Clinical exacerbations can be induced by some medications, surgery, and infections (TABLE 12-1)

Myasthenic crisis occurs in about 15% of patients and is caused by severe weakness of the diaphragm and accessory breathing muscles, causing respiratory failure. It is a true neurologic emergency that needs to be recognized promptly and managed in an intensive care setting with ventilatory support and treatment with corticosteroids along with IVIg or plasma exchange. Patients should be offered elective ventilation on clinical diagnosis without waiting for blood gas changes to show hypoxemia.

TABLE 12-1 **Factors That Can Trigger or Worsen Myasthenia Gravis**

Surgery

Pregnancy and Postpartum Period

Heat

Stress

Viral Infections

Bone Marrow Transplantation

Medications

- **Antibiotics**
  - Aminoglycosides
  - Fluoroquinolones
  - Tetracyclines
  - Sulfonamides
  - Penicillins
  - Nitrofurantoin
  - Telithromycin
- **Magnesium and magnesium-containing medications (eg, laxatives, antacids)**
- **Botulinum toxin**
- **Interferon alfa**
- **D-Penicillamine**
- **Cardiovascular medications**
  - Quinidine, quinine
  - Beta-blockers
  - Calcium channel blockers
- **Anesthetics (eg, methoxyflurane)**
- **Neuromuscular blockers (eg, succinylcholine)**
- **Checkpoint inhibitors (eg, pembrolizumab)**

Refractory MG is clinically defined by unchanged or worsened symptoms after corticosteroid treatment and at least two other immunosuppressants used at adequate doses for an adequate duration or until intolerable side effects occurred.

A clinical classification has been developed and published by the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America to achieve a more uniform description of the different subgroups of patients affected by MG and their disease severity (TABLE 12-2).[16] This classification has been accepted by the community of MG experts, not only for clinical research purposes but also for use in clinical practice, and has replaced the many preexisting classifications, including the Osserman classification.

Myasthenia Gravis Foundation of America Clinical Classification[a] TABLE 12-2

Class	Description
I	Any ocular muscle weakness May have weakness of eye closure All other muscle strength is normal
II	Mild weakness affecting other than ocular muscles May also have ocular muscle weakness of any variety
IIa	Predominantly affecting limb or axial muscles or both May also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal or respiratory muscles or both May also have lesser or equal involvement of limb or axial muscles or both
III	Moderate weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb or axial muscles or both May also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal or respiratory muscles or both May also have lesser or equal involvement of limb or axial muscles or both
IV	Severe weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IVa	Predominantly affecting limb or axial muscles or both May also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal or respiratory muscles or both May also have lesser or equal involvement of limb or axial muscles or both
V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management; the use of a feeding tube without intubation places the patient in class IVb

[a] Reprinted with permission from Jaretzki A, et al, Neurology.[16] © 2000 American Academy of Neurology.

DIAGNOSTIC TESTS

Serologic testing is the first diagnostic step when MG is suspected. Positive AChR-binding antibodies are very specific for autoimmune MG and are found in 80% of patients with generalized MG, 50% of patients with ocular MG, and in about 50% of children with autoimmune MG.[10] False-positive results are extremely rare and have been found in some patients with other autoimmune disorders such as Guillain-Barré syndrome and in patients with thymoma without signs of MG. AChR antibodies have also been rarely reported in patients with amyotrophic lateral sclerosis (ALS). Some patients may be seronegative at the time of initial testing and seroconvert after a period of time, usually 6 months. AChR-blocking and AChR-modulating antibodies are tested when AChR-binding antibodies are negative, but they only increase the diagnostic sensitivity by less than 5%. Antistriational antibodies are found in about 30% of patients with adult-onset MG and in 80% of patients with thymoma without MG. Antistriational antibodies are more commonly found in older patients; in younger patients with MG, they are found in the presence of thymoma or thymoma recurrence.

CASE 12-1

A 37-year-old woman presented for a second opinion after she received a diagnosis of bulbar amyotrophic lateral sclerosis due to a 6-month history of dysphagia, dysarthria, shortness of breath, the observation of an atrophic tongue, and negative acetylcholine receptor antibody.

On examination, she had profound weakness of eye closure and facial muscles with a flat smile; nasal dysarthria; limited eye movements without subjective diplopia; neck flexion, shoulder abduction, and hip flexion weakness; mild atrophy of the tongue with severe limitation of tongue movement; and absent jaw jerk. Her limb reflexes were normal, and her toes were downgoing.

Her anti–muscle specific tyrosine kinase antibody level was found to be 15.3 nmol/L (range: 0.00 nmol/L to 0.02 nmol/L). Treatment with pyridostigmine 60 mg 3 times a day caused severe facial muscle twitching and increased lacrimation and salivation and had to be discontinued. Her symptoms did not improve with 2 g/kg IVIg total dose divided over 5 days but did dramatically and persistently improve with plasma exchange.

She was managed with mycophenolate mofetil monotherapy for 3 years with only residual eye closure and facial weakness, and then she presented with intermittent severe vocal cord stridor, shortness of breath, and dysphagia that did not respond to plasma exchange or prednisone. She received two cycles of rituximab 6 months apart, and she has subsequently been in pharmacologic remission on mycophenolate mofetil monotherapy for the past 2 years.

COMMENT

This case exemplifies the importance of considering anti-muscle specific tyrosine kinase myasthenia gravis in the differential diagnosis of bulbar weakness, especially when ocular signs are present.

MuSK antibodies are tested if AChR antibodies are negative; MuSK antibodies are found in about one-third of seronegative patients with generalized MG, usually female patients (85%) (**CASE 12-1**).[17]

In about 20% of patients who are double-seronegative (ie, negative for both AChR and MuSK antibodies), autoantibodies against the low-density lipoprotein receptor–related protein 4 (LRP4) have been identified. Antibody testing should be used for diagnostic purpose only and not to follow clinical response to treatment or disease severity over time.

Electrodiagnostic testing is very helpful in seronegative patients. Two-hertz to 5-Hz repetitive nerve stimulation studies are more sensitive in generalized than ocular MG. A CMAP decrement greater than 10% is indicative of a neuromuscular transmission defect. It is important to be aware that technical factors such as movement artifact, submaximal stimulation, and limb temperature less than 35°C (95°F) during repetitive nerve stimulation testing can affect the validity of the results.[18–20]

Single-fiber EMG, when performed in a weak muscle, is the most sensitive diagnostic test to confirm a neuromuscular transmission disorder (positive in 97% of affected patients). Usually, the extensor digitorum communis muscle is studied first, and if it is normal, a facial muscle (frontalis or orbicularis oculi) should be tested next. If single-fiber EMG is normal in clinically affected muscles, the diagnosis of MG is excluded.[21,22]

Several diagnostic tests, such as the edrophonium test and ice pack test, are less frequently performed to confirm the diagnosis of MG. The edrophonium test uses IV edrophonium chloride, a fast-acting acetylcholinesterase inhibitor with a 30-second onset and about 5-minute duration. Incremental doses starting at 2 mg and up to a total 10 mg are administered with intervals of 1 to 2 minutes to observe for improvement, at which time the test is stopped. Muscarinic side effects include increased sweating, lacrimation and salivation, nausea, vomiting, diarrhea, and possible severe bradycardia and bronchospasm; therefore, atropine should be available at the bedside. It is very important to select a clear parameter that can be objectively graded, such as ptosis, or limited ocular movements.

The ice pack test is a simple bedside test with high diagnostic specificity and sensitivity for distinguishing myasthenic ptosis from other causes of ptosis. An ice pack is applied to the weak eyelid for 5 minutes, ensuring that the ice is covered to prevent ice burns, and an improvement of palpebral fissure of at least 2 mm is considered a positive test. This test is a good alternative to the edrophonium test, especially for patients for whom acetylcholinesterases are contraindicated because of cardiac or respiratory comorbidities.[23–25]

Chest CT should be performed in patients with MG to rule out thymoma or thymoma recurrence.

Since other autoimmune disorders, especially autoimmune thyroid disease, are commonly associated with MG, thyroid function testing should be performed at the time of diagnosis.

DIFFERENTIAL DIAGNOSIS

MG needs to be differentiated from other neuromuscular junction disorders, such as Lambert-Eaton myasthenic syndrome, congenital myasthenic syndromes, and botulism; Lyme disease, which causes multiple cranial neuropathies; bulbar ALS; brainstem ischemia; and acute inflammatory demyelinating polyradiculoneuropathy (AIDP), such as Miller Fisher syndrome and pharyngeal-cervical-brachial variants.

KEY POINTS

- **Antibody testing should be used for diagnostic purpose only and not as a repeat test to assess response to therapy. False-positive results are extremely rare.**
- **Patients with anti–muscle specific tyrosine kinase–positive myasthenia gravis are more often women and may present with predominant facial, pharyngeal, tongue, and respiratory weakness with or without ocular weakness. Patients respond more frequently to plasma exchange than IV immunoglobulin and may have less improvement and more side effects (prominent fasciculations) from cholinesterase inhibitors.**

Purely ocular MG needs to be differentiated from mitochondrial disorders, such as chronic progressive external ophthalmoplegia, and from oculopharyngeal muscular dystrophy. The ptosis in these disorders is usually symmetric, chronically progressive, and non-fatigable or fluctuating, unlike in MG. Ophthalmoplegia in chronic progressive external ophthalmoplegia and oculopharyngeal muscular dystrophy, unlike in MG, rarely causes significant diplopia because of the slow progression and uniform involvement of all intrinsic ocular muscles. Muscle biopsy and DNA testing can help confirm the diagnosis of chronic progressive external ophthalmoplegia or oculopharyngeal muscular dystrophy.

In patients with predominantly bulbar weakness and minimal or no ocular symptoms, bulbar ALS is the main alternative diagnosis: upper motor neuron signs and atrophy and fasciculations in the tongue and other weak muscles help distinguish ALS from MG. The dysarthria in MG is typically flaccid and nasal, while in bulbar ALS there is frequently a spastic quality due to upper motor neuron pathology. One confusing feature is the recognized presence of fasciculations and atrophy of the tongue reported in some MuSK-positive MG patients (CASE 12-1).

Patients with a primary symptom of generalized fatigue without weakness in specific muscle groups, especially if pain is also present, are usually not affected by MG.

Electrodiagnostic evaluation that includes EMG, repetitive nerve stimulation, and single-fiber EMG of affected muscles is very helpful in differentiating the above disorders.

TREATMENT

An international consensus for management of MG published by experts in MG guides clinicians caring for patients with MG.[26] The goal in the management of MG is to achieve remission (no signs or symptoms of myasthenic weakness) or minimal manifestations (no subjective symptoms and only mild weakness found on objective neurologic examination that does not interfere with normal function). This goal should be achieved with the minimal possible side effects from medications.

Plasma exchange and IVIg are used in generalized MG as rapid-onset short-term immunotherapy, for severe acute exacerbations, and preoperatively to optimize the patient's strength prior to surgery. In refractory patients and in patients who do not respond to or cannot tolerate oral immunosuppressants, IVIg and plasma exchange are used more chronically. Plasma exchange, usually 5 to 6 exchanges of 2 to 3 liters on alternating days, is effective in improving strength in the vast majority of patients with MG and is the treatment of choice in true myasthenic crisis because of its fast onset (usually after the second or third exchange). Plasma exchange is contraindicated in sepsis and hypotension. Complications are mostly related to the use of central venous catheters and to fluid shift or overload.

IVIg at a total dose of 1 g/kg to 2 g/kg divided over 2 to 5 days is effective in improving strength in patients with MG and is used to treat moderate to severe exacerbations and for patients who do not respond to or cannot tolerate any oral immunosuppressant.[27] Improvement occurs between a few days and up to 2 weeks and usually lasts weeks to months. Side effects include idiosyncratic reactions with chills, fever, headaches, and aseptic meningitis. Premedication

with acetaminophen, ibuprofen, diphenhydramine, and hydrocortisone or methylprednisolone is usually helpful in preventing or mitigating the side effects. Caution should be used when using IVIg in patients with cardiomyopathy or valve disease and in patients with renal insufficiency due to the risk of volume overload.

Pyridostigmine is the most commonly used acetylcholinesterase inhibitor for the symptomatic treatment of MG symptoms. It is used for symptom management alone in purely ocular and mild generalized cases or in combination with immunosuppressants in more severe cases. The symptomatic effect starts in 30 to 60 minutes and lasts for 3 to 4 hours. The dose should be administered 30 minutes before meals if dysphagia is the targeted main symptom (this schedule should be clarified in the inpatient setting so as not to prescribe 3 times a day instead when writing orders) or every 4 hours while the patient is awake if diplopia is the main symptom (rather than 4 times a day so as not to waste an unnecessary evening dose). Common side effects include abdominal cramps, diarrhea, and excessive lacrimation.

Because of their almost universal and rapid onset effect (2 to 3 weeks), corticosteroids are usually the first choice for patients with ocular and generalized MG who require more than pyridostigmine alone. The dose is usually 60 mg/d to 80 mg/d until improvement is obtained. Prednisone can be started at the goal dose of 50 mg/d to 80 mg/d, but because of the possible risk of short-term exacerbation especially in bulbar weakness, this option is usually reserved for the inpatient setting whereas in the outpatient setting a slower taper up to the goal dose is usually preferred. More commonly and in in the outpatient setting, prednisone is started at 10 mg/d to 20 mg/d and increased by 5 mg/d every week until the target dose is achieved. Once significant improvement is reached, a slow taper should be started on an alternating-day schedule to minimize adrenal suppression and a long-term steroid-sparing immunosuppressant added if symptoms recur at a dose considered too high for long-term treatment.

Mycophenolate mofetil and azathioprine are the most commonly used long-term oral immunosuppressants and steroid-sparing agents used in the management of MG. They are also first choice in patients for whom corticosteroids are contraindicated. Mycophenolate mofetil is an inhibitor of monophosphate dehydrogenase that suppresses cell-mediated immune response and antibody formation. Therapeutic doses in adults are 2 g/d to 3 g/d divided in 2 doses given 12 hours apart. Side effects are usually mild and include abdominal pain, diarrhea, and nausea. Because of potential leukopenia and anemia, periodic monitoring of complete blood cell counts needs to be performed. Azathioprine is a 6-mercaptopurine that blocks nucleotide synthesis and T-lymphocyte proliferation. The target therapeutic dose is 2 mg/kg/d to 3 mg/kg/d , and side effects include myelosuppression, toxic hepatitis, idiosyncratic allergic flu-like reaction, and pancreatitis. Monitoring of complete blood cell count and liver enzymes is required. The therapeutic effect takes 4 to 8 months with azathioprine and few weeks to 2 months with mycophenolate mofetil.

Rituximab is a synthetic CD20 antibody given intravenously and has been reported to induce significant improvement and even remission in some patients with severe and refractory generalized MG, especially in MuSK-positive patients.[28–30] The results of a randomized, multicenter trial in AChR antibody–positive MG are pending. Side effects include hepatitis B virus

KEY POINTS

- **In predominantly bulbar myasthenia gravis with minimal or no ocular weakness, the differential diagnosis with bulbar amyotrophic lateral sclerosis can be challenging: the absence of tongue atrophy and fasciculations, jaw jerk, and spastic speech is helpful for diagnosis. Electrodiagnostic tests, including EMG and single-fiber EMG of weak muscles, are most helpful in confirming the correct diagnosis.**

- **The most limiting side effect of pyridostigmine is abdominal cramping and diarrhea because of its muscarinic effect. One of the advantages of using pyridostigmine is its lack of long-term side effects.**

- **A common mistake in practice, especially in the inpatient setting, is prescribing pyridostigmine 3 or 4 times a day rather than as needed 30 minutes prior to meals when dysphagia is the targeted symptom.**

reactivation, infusion reactions, skin and mouth ulcers, and progressive multifocal leukoencephalopathy.

Eculizumab is a complement inhibitor recently approved by the FDA for the treatment of adult patients with AChR-antibody positive generalized MG.[31] Its use is indicated for patients with severe or refractory disease who either have not responded to or are unable to tolerate other immunosuppressants. Because of the risk of meningococcal and other serious bacterial infections, vaccination recommendations should be followed prior to use.

An international, multicenter, randomized, double-blind trial comparing thymectomy plus prednisone with prednisone alone in patients 18 to 65 years old with generalized MG with positive AChR antibodies has recently demonstrated that thymectomy improves clinical outcome.[32] Thymectomy is generally not indicated in patients older than 65 years. When thymectomy is indicated, it should be planned as soon as the patient has been treated and symptoms have improved sufficiently to undergo surgery safely.

TABLE 12-3 **Treatment Modalities in Pregnancy and Lactation**

Treatment	Pregnancy	US Food and Drug Administration Category	Lactation
Pyridostigmine	Safe at a total daily dose of <600 mg/d; treatment of choice in mild cases	B/C	Larger doses can cause gastrointestinal symptoms in the fetus
Corticosteroids	Safe; treatment of choice if immunosuppressive therapy is required	C	No limitations
IV immunoglobulin	Safe; treatment of choice for exacerbation or myasthenic crisis	C	No limitations
Plasma exchange	Safe; treatment of choice for exacerbation or myasthenic crisis	C	No limitations
Azathioprine	Continuation of therapy can be considered	D	Considered acceptable by most experts
Cyclosporine	Continuation of therapy can be considered	C	Can be considered
Mycophenolate mofetil	Contraindicated; discontinuation recommended prior to conception and during pregnancy	D	Not recommended because of lack of information
Methotrexate	Contraindicated	X	Contraindicated
Rituximab	Not recommended because of lack of information	C	Not recommended because of lack of information
Eculizumab	Not recommended because of lack of information	C	Limited published data do not report detectable levels of eculizumab in human milk; not recommended because of lack of information on milk production and on the breast-fed infant

PROGNOSIS

With the current availability of mechanical ventilation and intensive supportive care for myasthenic crisis and the increased options available for immunomodulation therapy, the mortality due to MG is less than 5%. Patients with thymoma and patients with a more refractory type of generalized MG, as well as older patients with complex comorbidities, have higher morbidity and mortality.

Approximately 15% of MG patients do not respond to treatment, and factors associated with refractory disease include thymoma, anti-MuSK antibody, younger age at onset, and female sex.

Some patients with MG develop fixed weakness that no longer responds to immunomodulation ("burned-out weakness"). Severe isolated fixed weakness of triceps muscles has been reported especially in African American patients and needs to be recognized to avoid unnecessary tests and surgical intervention (eg, cervical root decompression).[13,14] When fixed ophthalmoplegia and ptosis no longer respond to immunomodulation, surgical intervention should be considered. The maximal severity of symptoms and signs is typically reached in the first years from symptom onset in the majority of patients, and generalization in purely ocular cases usually occurs in the first 2 years from onset.

MG exacerbations are more common in the early stages of disease and before treatment has been fully implemented. Exacerbations can be triggered by viral infections, intercurrent illnesses, pregnancy, surgery, stress, and use of certain medications (TABLE 12-1).

MYASTHENIA IN PREGNANCY

Special considerations apply to the care of women of childbearing age and during pregnancy (TABLE 12-3).[33] While the pregnancy outcome for mothers with MG is generally very good, 20% to 30% of women can experience an exacerbation, most commonly in the first trimester or in the postpartum period. Improvement can occur in the second and third trimesters. Ideally, women who are planning a pregnancy should discuss a plan of care and review their risk with their neurologist before becoming pregnant and allow time to adjust medications if needed. The goals should be to minimize the mother's MG symptoms and risk of exacerbation and to avoid the potentially harmful exposure of the fetus to the immunosuppressants. Pyridostigmine, IVIg, plasma exchange, and prednisone are generally safe during pregnancy, while mycophenolate mofetil has a definite risk for fetal malformations and should be avoided during pregnancy (TABLE 12-3).

Fatigue during the second stage of delivery is possible, and protracted labor and fetal distress can occur. The obstetrician should be prepared to assist with forceps or vacuum extraction in this stage if needed. Neostigmine 1.5 mg IM or 0.5 mg IV is equivalent to 60 mg of oral pyridostigmine and can be used if needed during delivery. MG is not, per se, an indication for Cesarean delivery, which, like any other operations, can exacerbate MG and should be reserved for obstetric indications.

Patients with MG are more sensitive to anesthetic agents, and nondepolarizing muscle relaxants should especially be avoided as they can trigger prolonged and severe muscle weakness. For women with MG, epidural analgesia is the anesthetic intervention of choice for delivery.

KEY POINTS

- Thymectomy improves clinical outcome in patients with nonthymomatous myasthenia gravis who are between 18 and 65 years old. Thymectomy is generally not indicated in patients older than 65. The timing and role of thymectomy in children are not yet standardized.
- Pregnancy outcome in women with myasthenia gravis is generally good. Exacerbation of myasthenia gravis occurs in 20% to 30% of women during pregnancy and more commonly in the first trimester or postpartum period. Myasthenia gravis, per se, is not an indication for Cesarean delivery.
- IV immunoglobulin, plasma exchange, prednisone, and pyridostigmine are generally safe in pregnancy and lactation. Mycophenolate mofetil should be avoided during conception and pregnancy.

Magnesium for the management of eclampsia should be used with caution and with supervision in myasthenic women because of its negative effect on neuromuscular transmission and potential for precipitating muscle weakness. Maternal deaths have been reported from magnesium use in pregnant women with MG.

PEDIATRIC MYASTHENIA

MG in children is very rare, and the diagnosis is more difficult, in part, because of the higher percentage of seronegative cases and the possible differential diagnosis of genetic myasthenic syndromes. Juvenile, or childhood, myasthenia is an acquired autoimmune postsynaptic disorder of neuromuscular transmission that occurs in prepubertal patients and shares most of the same clinical features and response to treatment of adult, acquired MG. It needs to be distinguished from genetic forms of neuromuscular transmission defect (congenital myasthenic syndromes). Treatment modalities are similar to those used in adults and are usually very effective with a high rate of remission. Evidence-based guidelines are lacking for this group because therapeutic trials in the field of MG have been excluding patients younger than 18 years and because of the rarity of the disease in this age group.[34] The role and timing of thymectomy, while well-established in adult patients with MG, is still not well established or standardized in children. Thymectomy is usually considered as a therapeutic option in seropositive generalized childhood myasthenia when the response to pyridostigmine and immunosuppressants is incomplete or to avoid the long-term side effects of immunosuppressants, especially prednisone in very young patients.[26] In children with seronegative generalized MG, the role of thymectomy is even more unclear, and ruling out a congenital myasthenic syndrome is imperative. While children with purely ocular acquired MG have a high rate of spontaneous remission, ocular MG can be refractory to treatment in Asian and African American children and frequently results in fixed ocular muscle weakness amenable to surgical correction. Purely ocular MG in children should be initially treated with pyridostigmine; immunosuppressants should be considered in refractory cases, and prednisone should be used at the lowest possible dose because of growth retardation, decreased bone mineralization, and interference with the vaccination schedule in young children. IVIg is generally the preferred therapeutic choice in this age group.[35]

Transient neonatal MG is a transient form of autoimmune myasthenia that affects newborns of mothers with autoimmune myasthenia, and it is caused by placental transfer of maternal AChR antibodies.[36] It is self-limited and resolves after the maternal antibody clears, usually within 1 month, and care is supportive. It is very rare, occurring in 10% to 15% of infants born from myasthenic mothers. Although very rare, it should be considered in the differential diagnosis of floppy infant syndrome, and all babies of myasthenic mothers should be monitored for signs of muscle weakness and especially for bulbar and respiratory function impairment (feeble cry, poor sucking). The onset of symptoms is usually between 12 and 48 hours after delivery, with the delay due to transfer of α-fetoprotein, with its immunosuppressant effect, or anticholinesterase medications from the mother to the newborn.

The effect of maternal antibodies on the fetus can also rarely cause arthrogryposis multiplex congenita, which can lead to intrauterine fetal death or neonatal death and can occur even in fetuses of asymptomatic mothers. Arthrogryposis multiplex congenita in myasthenia has a high recurrence risk

and should be discussed during prepregnancy counseling. Maternal MG should be always considered in the differential diagnosis of arthrogryposis multiplex congenita.

CONGENITAL MYASTHENIC SYNDROMES

Congenital myasthenic syndromes are very rare inherited neuromuscular junction diseases caused by pathogenic variants in genes encoding for different proteins expressed at the neuromuscular junction (TABLE 12-4).[37,38] The most commonly associated genes are the those coding for the AChR subunits (*CHRNE*, *CHRNA1*, *CHRNB1*, *CHRND*) and causing AChR deficiency or AChR abnormal kinetic function with loss or gain of function. Other commonly associated genes include some encoding for proteins essential for endplate development and function (*DOK7*, *RAPSN*, *AGRN*, *LRP4*, *MUSK*). *COLQ* mutations cause endplate acetylcholinesterase deficiency; *CHAT* mutations cause a presynaptic congenital myasthenic syndrome due to acetyltransferase deficiency (TABLE 12-4).

Congenital myasthenic syndromes are inherited in a recessive or dominant manner, and onset of symptoms is usually at birth or early childhood, rarely later in childhood or early adulthood. The main clinical features include skeletal muscle fatigable weakness affecting ocular, bulbar, limb, and respiratory muscles in different patterns and degrees of severity. In infants, symptoms include a weak cry and suck, respiratory insufficiency, apnea, cyanosis, feeding difficulty, stridor, ptosis, facial weakness, and sudden infant death. Later in childhood, motor milestones can be delayed, and fatigable muscle weakness causes fluctuating ptosis and difficulty running, climbing stairs, and jumping. Cardiac and smooth muscles are not involved, and cognitive function is normal in the majority of patients.

The main differential diagnosis includes seronegative MG, congenital myopathies, and other causes of floppy infant syndrome.

Some clinical features are most typical of certain types of congenital myasthenic syndromes and provide important clues to guide the diagnosis. For example, acute exacerbations and apneic episodes triggered by fever or excitement, family history of sudden infant death, and improvement over time are typical of congenital myasthenic syndrome with episodic apneas (previously named *familial infantile myasthenia*) caused by *CHAT* mutations.[39–41] Arthrogryposis multiplex congenita, contractures, floppy infant syndrome, early respiratory failure, and episodic apneas occur in infants with congenital myasthenic syndrome caused by *RAPSN* defects. Stridor in infancy, tongue wasting, ptosis with sparing of eye movements, myopathic facial features and worsening with acetylcholinesterase inhibitors and dramatic improvement with ephedrine or albuterol are typical features of *DOK7* defects (CASE 12-2).[42]

Diagnosis is based on typical clinical features. These include the absence of serum AChR or MuSK antibodies; the absence of typical stigmata of congenital myopathies on muscle biopsy; a CMAP decrement on low-rate repetitive nerve stimulation; repetitive CMAP after single stimulation ("double response to single nerve stimulation," which is typical of slow-channel congenital myasthenic syndrome and endplate acetylcholinesterase deficiency/*COLQ* congenital myasthenic syndrome); abnormal jitter on single-fiber EMG; no clinical response to plasma exchange or other immunosuppressants; a positive response to acetylcholinesterase in most cases but not all; and genetic confirmation of a defect in one of the genes known to cause a congenital myasthenic syndrome. Genetic tests can start with single gene testing in cases with typical features of

KEY POINTS

- Seronegative autoimmune myasthenia gravis in children can be difficult to differentiate from congenital myasthenic syndrome, and DNA testing, repetitive nerve stimulation, and the response to a trial of IV immunoglobulin or plasma exchange can help establish a definite diagnosis of seronegative autoimmune myasthenia gravis.
- Of newborns of mothers with myasthenia gravis, 10% to 15% develop transient neonatal myasthenia gravis, and it can resolve spontaneously after the maternal antibodies transmitted through the placenta are cleared. Arthrogryposis multiform congenita can occur, although rarely, in newborns of mothers affected by myasthenia gravis, even of mothers who are asymptomatic.

TABLE 12-4 **Most Common Congenital Myasthenic Syndromes and Their Features**

Gene Affected	Percentage of Congenital Myasthenic Syndrome	Congenital Myasthenic Syndrome Type	Clinical Features	Response to Therapy
CHRNE*, *CHRNB1*, *CHRND*, *CHENA1*, *CHRNG	50%	Slow-channel congenital myasthenic syndrome	Onset usually in the first decade, neonatal onset possible Wrist and finger extensor weakness, sparing of ocular muscles, mild asymmetric ptosis in some patients; neck weakness; progressive respiratory failure possible	Improvement with fluoxetine, quinine, quinidine Worsening with pyridostigmine and 3,4-diaminopyridine (3,4-DAP)
		Fast-channel congenital myasthenic syndrome	Mild to severe phenotype	Improvement with pyridostigmine and 3,4-DAP
		Acetylcholine receptor deficiency	Ptosis and eye movement weakness almost always present; fixed ophthalmoplegia possible; mild to severe bulbar and limb weakness	Improvement with pyridostigmine and 3,4-DAP Albuterol if no response to above
RAPSN	15–20%	Endplate rapsyn deficiency	Arthrogryposis, contractures, respiratory failure, episodic apneas; later onset with limb weakness resembling seronegative myasthenia gravis, no ocular signs	Improvement with pyridostigmine, 3,4-DAP, and albuterol
COLQ	10–15%	Endplate acetylcholinesterase deficiency	Diffuse muscle weakness with severe axial muscle involvement; slow pupillary light response	No improvement or worsening with pyridostigmine and 3,4-DAP
DOK7	10-15%	*DOK7*-associated limb-girdle myasthenia	Limb girdle proximal symmetric weakness, waddling gait, ptosis, stridor, vocal cord paralysis; no eye movement deficit	Improvement with ephedrine and albuterol; no improvement or worsening with pyridostigmine
CHAT	5%	Congenital myasthenic syndrome with episodic apnea	Episodic apnea triggered by crying, excitement, fever, and infections; sudden infant death; hypotonia; ptosis	Improvement with pyridostigmine; IM neostigmine should be made available for use in case of sudden apneas

CASE 12-2

A 9-year-old right-handed girl was referred to the neuromuscular clinic by orthopedics for evaluation of an undefined neuromuscular disorder causing muscle weakness and knee contractures. She was born at term via vaginal birth after an uncomplicated pregnancy. Her mother first noted that the child was different from her older sister when the girl showed low tone as an infant and delay with all motor milestones: she never crawled or walked until she was 18 months. She was weak in her neck, shoulder, and hip muscles, although she had no difficulty with fine motor skills. When she started to walk, she would take a few steps and then fall. She made some progress in her motor milestones up until age 6 when she learned to ride a bicycle, but since that time, she showed a slow and gradual decline and began to spend most of her time in a wheelchair, used a walker only for very short distances, and was unable to run, jump, or climb stairs. Over the past 2 years, she developed knee contractures. She denied any difficulty with swallowing or breathing and had no double vision, problems with hearing, numbness or tingling, or bowel or bladder dysfunction. She was recently diagnosed with scoliosis and was in the process of obtaining a brace. Her cognitive development was normal, and she did well in school. The following test results were obtained prior to her presentation to the neuromuscular clinic: normal creatine kinase level; negative DNA testing for spinal muscular atrophy, Pompe disease, lysosomal storage disorders, and limb-girdle muscular dystrophies; normal nerve conduction studies; and EMG consistent with a proximal myopathy without muscle fiber irritability. A muscle biopsy showed type 2 fiber atrophy.

On examination, she had fatigable proximal symmetric weakness greater in hip flexion and abduction than in shoulder abduction, normal distal strength, and absent reflexes. She had asymmetric ptosis, but no eye movement restriction, and a myopathic face with a high arched palate and a flat smile.

Three-Hertz repetitive nerve stimulation showed a 34% compound muscle action potential decrement, and gene testing for *DOK7* was positive for two compound heterozygous pathogenic mutations in exon 7, 1124_1127dupGCCT and 773G>A. She was started on albuterol 2 mg 2 times a day as this drug has been reported effective in this particular congenital myasthenic syndrome, and she experienced significant improvement in motor function. She is now able to walk without a walker, run, jump, and climb stairs while holding on to the railing.

COMMENT

This case highlights the importance of considering a congenital myasthenic syndrome in the differential diagnosis of patients with weakness mimicking a myopathy but with muscle biopsy and EMG without significant abnormalities, because weakness in patients with a congenital myasthenic syndrome is frequently reversible with treatment.

KEY POINT

● The diagnosis of congenital myasthenic syndrome should be considered in children with proximal muscle weakness and facial features consistent with a myopathy but in whom the creatine kinase level and muscle biopsy are normal.

a specific congenital myasthenic syndrome or a multigene panel or genomic testing in cases with less typical clinical clues. Panels of the most common genes affected in congenital myasthenic syndromes are commercially available.

Treatment with acetylcholinesterase inhibitors (pyridostigmine and 3,4-diaminopyridine) is effective in most cases of congenital myasthenic syndrome with the exception of fast-channel and *DOK7* congenital myasthenic syndrome. Albuterol and ephedrine are very effective in congenital myasthenic syndrome with *DOK7* and *COLQ* defects. Fluoxetine is beneficial in some patients with slow-channel congenital myasthenic syndrome.[43,44]

CONCLUSION

MG is a highly treatable neuromuscular autoimmune disease that needs to be promptly diagnosed and managed by neurologists. Myasthenic crisis is a neurologic emergency with good prognosis and low mortality when promptly diagnosed and treated with plasma exchange and intensive supportive care. Many immunomodulatory drugs are currently in preclinical and clinical trial development, and the treatment options available for patients with MG continue to improve.

Some unresolved issues remain, including when and how to discontinue immunosuppressant therapy for patients who have achieved remission and which patients are at a higher risk of relapsing; the role of early prednisone use in purely ocular MG in preventing generalization; and the role of thymectomy in anti-MuSK, seronegative, and childhood MG.

Acute generalized MG and myasthenic crisis have recently been recognized as emergent side effects triggered by the use of checkpoint inhibitors in patients with refractory cancer and with outcomes ranging from spontaneous remission to death. For more information on side effects of immune checkpoint inhibitors, refer to the article, "Lambert-Eaton Myasthenic Syndrome, Botulism, and Immune Checkpoint Inhibitor–Related Myasthenia Gravis," by Amanda C. Guidon, MD,[45] in this issue of *Continuum*.

Congenital myasthenic syndromes are very rare diseases that need to be differentiated from autoimmune forms of neuromuscular junction disorders because treatment can be very effective.

USEFUL WEBSITE

MYASTHENIA GRAVIS FOUNDATION OF AMERICA
This patient organization provides educational material and support group meetings for patients affected by myasthenia gravis.
myasthenia.org

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