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Relationship Disclosure: Dr Nicolle has given expert medical testimony in court cases for the Canadian Medical Protective Association.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Nicolle discusses the unlabeled/investigational use of azathioprine, mycophenolate, and rituximab for the treatment of myasthenia gravis and Lambert-Eaton myasthenic syndrome and the use of 3,4-diaminopyridine for the treatment of Lambert-Eaton myasthenic syndrome.

Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome

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ABSTRACT

Purpose of Review: This article discusses the pathogenesis, diagnosis, and management of autoimmune myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS).

Recent Findings: Recognition of new antigenic targets and improved diagnostic methods promise to improve the diagnosis of MG, although the clinical phenotypes associated with newer antibodies have not yet been defined. Future therapies might specifically target the aberrant immune response. The apparent increase in the prevalence of MG is not fully explained. Results of a long-awaited trial of thymectomy support the practice of performing a thymectomy under specific conditions.

Summary: The current treatment options are so effective in most patients with MG or LEMS that in patients with refractory disease the diagnosis should be reconsidered. The management of MG is individualized, and familiarity with mechanisms, adverse effects, and strategies to manage these commonly used treatments improves outcome. Patient education is important. LEMS, frequently associated with an underlying small cell lung cancer, is uncommon, and the mainstay of treatment is symptomatic in most patients.

Continuum (Minneap Minn) 2016;22(6):1978–2005.

INTRODUCTION

Immune myasthenia gravis (MG) is the best delineated of human autoimmune diseases. Fatigable weakness is the hallmark of both MG and Lambert-Eaton myasthenic syndrome (LEMS). The expanding repertoire of antibody assays has improved the diagnosis of MG and may allow treatments to be tailored to specific antibodies. Management options for MG include symptomatic as well as immunosuppressive and immunomodulatory treatments and, in select circumstances, thymectomy. LEMS is uncommon and often occurs as a paraneoplastic disorder with an underlying small cell lung cancer.

NEUROMUSCULAR JUNCTION AND NEUROMUSCULAR TRANSMISSION

Understanding normal neuromuscular transmission is important to appreciate the rationale for diagnostic tests and treatments in MG and LEMS.[1] The neuromuscular junction includes the presynaptic nerve terminal, basal lamina–containing synaptic cleft, and postsynaptic muscle fiber endplate.

Nerve depolarization allows calcium influx through nerve terminal voltage-gated calcium channels (VGCCs). This results in release of acetylcholine into the synaptic cleft. Acetylcholine binds to its receptor (acetylcholine receptor [AChR]), opening AChR channels and producing an influx of cations, mostly sodium, at the endplate. Depolarization of the muscle membrane produces an endplate potential, which, if of sufficient amplitude, results in an all or none muscle fiber action potential and eventually muscle movement. An excess of released acetylcholine and AChRs at the muscle endplate provides a safety factor of neuromuscular transmission.

Acetylcholine binds to its receptor transiently and either diffuses out of the neuromuscular junction or is hydrolyzed by acetylcholinesterase, anchored in the basal lamina. This terminates the effects of nerve depolarization.

AChR localization at the neuromuscular junction and its function are influenced by several other proteins at the muscle endplate. Agrin, secreted by the nerve terminal, interacts with muscle-specific tyrosine kinase (MuSK) via its coreceptor, low-density lipoprotein receptor-related protein 4 (LRP4). The resultant MuSK-LRP4 complex results in the activation and clustering of AChRs at the neuromuscular junction. MuSK also anchors acetylcholinesterase at the synaptic basal lamina. In MG, antibodies against the AChR or other neuromuscular junction targets reduce the number, function, or clustering of AChRs at the neuromuscular junction. In LEMS, antibodies against the VGCC inhibit calcium influx into the nerve terminal and reduce acetylcholine release into the synaptic cleft after nerve depolarization.

Three other phenomena during normal neuromuscular transmission are important to understand; these phenomena are seen electrophysiologically and clinically in MG and LEMS. First, during low-frequency (2 Hz to 5 Hz) stimulation, acetylcholine release gradually declines as presynaptic stores are depleted, with a nadir at the fourth or fifth stimulation in a train of stimuli. In healthy individuals, this never reaches significance because of the safety factor. However, when the amount of acetylcholine available for release is diminished (as in LEMS) or the number of available AChRs is reduced (as in MG), muscle fiber depolarization may fail. If this fails at a single fiber, this is detected on single fiber EMG as blocking or is detected as jitter if the endplate potential amplitude is sufficient to produce a delayed muscle fiber depolarization. When many fibers fail, this results in a decrement with low-frequency repetitive nerve stimulation studies and weakness clinically. Second, during high-frequency (20 Hz to 50 Hz) stimulation or after brief (10 seconds) maximal voluntary contraction, intracellular calcium is increased in the presynaptic nerve terminal, increasing acetylcholine release. Maximal voluntary contraction mimics high-frequency stimulation, as the nerve fires at approximately 20 Hz during a maximal contraction. The increased intracellular calcium may overcome defective neuromuscular transmission; in MG, this results in postexercise repair on repetitive nerve stimulation studies, and in LEMS, this results in facilitation or increment after high-frequency stimulation or maximal voluntary contraction. This also explains the return of a deep tendon reflex after maximal voluntary contraction in LEMS. Third, longer periods of exercise result in less well understood pre- and postsynaptic effects, which also worsen neuromuscular transmission and cause postexercise exhaustion as is seen in repetitive nerve stimulation studies or fatigable weakness, which is seen clinically.

KEY POINTS

- The function of acetylcholine at the neuromuscular junction is influenced by several other key proteins, which are now known to be targets of the autoimmune response in some patients with myasthenia gravis.
- Antibodies against the most common antigenic target in myasthenia gravis, the acetylcholine receptor, are found in 85% of patients with generalized myasthenia gravis and 50% of patients with ocular myasthenia gravis and disrupt neuromuscular transmission through several mechanisms.

MYASTHENIA GRAVIS

MG is a disorder where neuromuscular transmission is disrupted as a result of an autoimmune attack on postsynaptic antigenic targets, producing weakness of skeletal muscles. The clinical hallmark of the weakness is its variability and fatigability.

Pathophysiology

In MG, antibodies against proteins at the neuromuscular junction interfere with neuromuscular transmission. Antibodies against the most common antigenic target in MG, the AChR, are found in 85% of patients with generalized MG and 50% of patients with ocular MG and disrupt neuromuscular transmission through several mechanisms. They can reversibly block acetylcholine binding,

KEY POINTS

- In more than one-half of the remaining patients who have acetylcholine receptor–negative generalized myasthenia gravis, antibodies target other proteins at the neuromuscular junction. The first described and still most prevalent are antibodies against muscle-specific tyrosine kinase.
- The frequent pathologic involvement of the thymus, especially with thymic hyperplasia, in some forms of myasthenia gravis supports the rationale for its removal in select circumstances, as shown by a recent international clinical trial.
- The different ways of classifying myasthenia gravis are useful when considering the sensitivity of diagnostic tests as well as management options.
- Congenital myasthenic syndromes are genetic disorders with a mutation in a presynaptic, synaptic, or postsynaptic protein involved in neuromuscular transmission.

cross-link adjacent cell surface AChRs resulting in their internalization into the muscle cell, or, for some immunoglobulin subclasses, cause complement fixation and destruction of the neuromuscular junction.[2,3] A mixture of antibodies with each of these mechanisms occurs in an individual patient, although complement-fixing antibodies are likely the most common.

In more than one-half of the remaining patients who have AChR-negative generalized MG, antibodies target other proteins at the neuromuscular junction. The first described and still most prevalent are antibodies against MuSK. Anti-MuSK antibodies are mostly of the non–complement-fixing IgG4 subclass and disrupt neuromuscular transmission by interfering with LRP4/MuSK interaction, reducing AChR clustering at the muscle endplate.[4] More recently, antibodies against LRP4, agrin, and cortactin have been described.[5] The significance of these antibodies is less well delineated.

Pathologic thymic involvement, either thymic hyperplasia or a thymoma, is found in the majority of patients with AChR MG.[6] Thymic hyperplasia occurs in 50% to 80% of postpubertal juvenile cases and early-onset adult cases of AChR MG.[6] Thymic hyperplasia is uncommon in MuSK MG and less common in seronegative and late-onset MG, where the thymus is often normal, atrophic, or a thymoma is found.[6,7] The hyperplastic thymus is a significant source of anti-AChR antibodies.[6,8] A thymoma is found in 10% to 20% of patients with MG, and MG occurs in 30% to 50% of thymoma cases.

Although the etiology for MG remains unknown, some subsets of AChR MG are associated with specific human leukocyte antigen (HLA) determinants, and subsets of MuSK MG are associated with other HLA determinants. A recent genome-wide association survey in white patients with AChR MG showed association with specific loci that might influence the pathogenesis of MG.[9] Although not a hereditary disorder in the mendelian sense, about 3% to 5% of patients with MG will have a family member with immune MG, similar to the data from more than 800 patients in the author's MG clinic.[10] The prevalence of other autoimmune disorders, especially thyroid, is increased in patients with MG and their family members, occurring in 13% to 30% of patients with MG compared with 5% to 8% in the general population.[11,12] This suggests a genetic influence to autoimmune diseases, of which MG is one of the least frequent.

Epidemiology

Studies show significant heterogeneity in the incidence and prevalence of MG, in part because of geographic and ethnic variation. However, recent evidence suggests that MG is increasingly common, especially in the elderly.[13] The incidence of MG ranges between 9 to 30 out of 1 million, and the prevalence ranges from 100 to 140 out of 1 million. However, recent studies have shown a prevalence of more than 200 in 1 million.[7,14] Women are more likely to have MG than men in the first 5 decades of life whereas men are more likely to be diagnosed with MG after the age of 50.[9] Ocular MG is more common in patients with prepubertal juvenile MG, especially in people of Asian descent and in men with late-onset MG. MuSK MG is more frequent in younger women and possibly in the nonwhite population.

Classification

MG can be classified in several ways, each of which is useful when considering diagnostic tests, therapeutic options, and prognosis.[15,16]

Age at onset. Congenital myasthenic syndromes are genetic disorders with a mutation in a presynaptic, synaptic, or postsynaptic protein involved in neuromuscular transmission. Congenital myasthenic

syndromes are not discussed in detail in this article but are considered in the differential diagnosis of immune MG.

Neonatal MG occurs after the transplacental transmission of AChR or MuSK antibodies and had been said to occur in about 10% to 15% of babies of mothers with MG. However, it may be less frequent now, and in more than 50 mothers that the author has managed through pregnancy, not a single case of neonatal MG has occurred. The antibody-producing cells are not transmitted, so neonatal MG is a self-limited disorder.

Juvenile myasthenia makes up 10% to 15% of most series of patients with MG and is arbitrarily defined as an age of onset of less than 18, excluding congenital myasthenic syndromes and neonatal MG. Cases of prepubertal onset are more likely to be seronegative, have a benign clinical course, a higher prevalence of ocular and mild generalized disease, and are more common in Asians. Postpubertal juvenile MG has similar rates of seropositivity and thymic hyperplasia compared to early-onset adult MG.

Early-onset MG is variably defined as age at onset after 18 years but before 40 to 60 years of age, with 50 being the most common age cutoff. A cutoff age of 45 years was suggested by a cluster analysis of patients with MG that considered age at onset and thymic hyperplasia.[15] Women outnumber men in early-onset MG. This is an important classification as the likelihood of thymic hyperplasia and of response to thymectomy in nonthymomatous MG is greater in early-onset MG. Patients with MuSK MG are also more likely to have an early onset.

Late-onset myasthenia gravis. Late-onset MG includes patients with onset after 50 years of age who are more often men and have ocular MG. In late-onset MG, a thymoma is more common than thymic hyperplasia. Evidence exists for an increasing prevalence of MG in the elderly, especially those older than age 65, although it is often not recognized and is most commonly misdiagnosed as a stroke.[13,14,16]

Thymic pathology. The likelihood and type of thymic pathology is associated with age at onset, clinical manifestations, and serologic status. Thymic hyperplasia is present in 50% to 80% of patients with AChR-positive early-onset MG, is less common in late-onset MG, and is rare in MuSK MG.[6–8] The benefits of thymectomy in MG are presumed to relate to the removal of a hyperplastic thymus. A thymoma, found in 10% to 20% of all cases of MG, is more common with onset after 40 years of age, where it occurs in 25% to 35% of cases.[17] Thymomatous MG is usually more severe and less likely to be ocular.[18] A thymoma is usually discovered at the time of MG diagnosis although can present later. The vast majority of thymomatous MG cases have positive AChR antibodies, so AChR negativity essentially rules out a thymoma.[19,20] A report of a possible mediastinal abnormality on a CT chest in a patient negative for AChR will almost always turn out to be something other than a thymoma. Patients with AChR-positive thymoma without clinical manifestations of MG have been described. However, a careful history and examination will almost always reveal features suggesting MG, or the patient will eventually develop MG.[20] A thymoma is almost never found in MuSK MG.

Serologic status. Serologic status is arguably the most important classification. Given their high specificity, if either AChR or MUSK antibodies are positive, a diagnosis of MG is certain. The specificity of antibodies against agrin, LRP4, or cortactin is less well defined. As described previously, when AChR antibodies are negative, an underlying thymoma is very rare, and thymic hyperplasia is less frequent. In MuSK MG the thymus is usually normal, the disease may be more severe, and patients are less responsive to pyridostigmine

KEY POINTS

- Neonatal myasthenia gravis is a self-limited disorder that occurs after the transplacental transmission of acetylcholine receptor or muscle-specific tyrosine kinase antibodies.
- Juvenile myasthenia makes up 10% to 15% of most series of patients with myasthenia gravis and is arbitrarily defined as an age of onset of less than 18, excluding congenital myasthenic syndromes and neonatal myasthenia gravis.
- Thymic hyperplasia is present in 50% to 80% of patients with acetylcholine receptor–positive early-onset myasthenia gravis, is less common in late-onset myasthenia gravis, and is rare in muscle-specific tyrosine kinase myasthenia gravis.
- A thymoma, found in 10% to 20% of all cases of myasthenia gravis, is more common with onset after 40 years of age, where it occurs in 25% to 35% of cases.
- Given their high specificity, if either acetylcholine receptor or muscle-specific tyrosine kinase antibodies are positive, a diagnosis of myasthenia gravis is certain.

KEY POINTS

- When antibodies are negative in myasthenia gravis, especially when patients do not respond to treatment as expected, the diagnosis should be reconsidered.
- The way in which a history of fatigue is elicited is important; direct questioning about worsening weakness at the end of the day may falsely suggest a diagnosis of myasthenia gravis.
- Most patients (50% to 85%) with myasthenia gravis present with ocular symptoms with or without generalized weakness. About 50% to 60% of patients with myasthenia gravis present with isolated ocular involvement, although many of these (50% to 60%) develop generalized weakness often within the first 3 years after onset.

or IV immunoglobulin (IVIg).[21] In the 5% to 10% of patients with immune MG who are negative for all known antibodies, the diagnosis of MG must always be questioned, especially when patients do not respond to treatment.

Clinical manifestations and severity. About 50% to 60% of patients present initially with isolated ocular involvement, most of whom will generalize. Fifteen percent to 25% of patients have only ocular involvement throughout their course (ocular MG).[22,23] Ocular MG is more likely seronegative for AChR antibodies and rarely positive for MuSK. The role for thymectomy in ocular MG is less certain, and sensitivities of most diagnostic tests are lower than in generalized MG. Generalized MG includes patients with weakness outside of the ocular muscles, many of whom will also have ocular manifestations. The Myasthenia Gravis Foundation of America, Inc classification is used mostly for research studies but is useful when considering the management options for MG.[3]

Taking the history. When taking the history, it is useful to have the patient describe what they mean by weakness. A history more suggestive of pain, lack of energy, exhaustion, diffuse nonspecific fatigue, or somnolence may not be consistent with MG. The prevalence of obstructive sleep apnea is higher in patients with MG; therefore, somnolence secondary to a sleep disorder may coexist with MG.[24]

The distinguishing clinical feature in MG is fatigable weakness. Fluctuation in symptoms is characteristic, although not universal, and can occur over short or longer periods of time. Worsening at the end of the day is common, although some patients experience worse symptoms first thing in the morning. The patient who has no ptosis first thing in the morning and whose eyes are completely closed at night almost certainly has MG. Fluctuation over longer periods is sometimes spontaneously described. However, patients commonly may not remember previous symptoms unless asked specifically. They may have been told that previous symptoms were because of a transient ischemic attack or Bell's palsy, so a careful history of both current and previous symptoms is important. The patient with unilateral ptosis who had a previous episode of self-limited ptosis on the opposite side almost certainly has MG.

Although characteristic for MG, fatigability should be distinguished from fatigue. The way that a history of fatigue is elicited is important. An unprompted history of significant fluctuation given by the patient is the most specific. Less directed questions (eg, ''Are there times when your weakness is better or worse?'') are more useful than asking directly whether the weakness is worse at the end of the day. No matter what the cause for weakness, direct questions will often elicit a history suggesting fatigable weakness and will result in MG being inappropriately considered in the differential.

Ocular symptoms. Most patients (50% to 85%) with MG present with ocular symptoms with or without generalized weakness. About 50% to 60% of patients with MG present with isolated ocular involvement, although many of these (50% to 60%) develop generalized weakness often within the first 3 years after onset. Ocular involvement includes ptosis, diplopia, or a combination of these.

Ptosis can be unilateral and, if bilateral, is usually asymmetric. Persistently symmetric ptosis is more suggestive of a myopathic etiology, especially chronic progressive external ophthalmoplegia. MG is one of few disorders that can cause complete unilateral (or rarely bilateral) ptosis or a history of ptosis alternating sides over time.

Many patients describe diplopia. Milder involvement may produce blurred vision

or a halo around objects instead. Resolution of these symptoms when one eye is covered suggests subtle diplopia, although many patients have not attempted this. Persistent diplopia with one eye covered suggests an ophthalmic or functional cause. Monocular vision is not affected in MG, and abnormalities in monocular vision require an ophthalmologic assessment. Photophobia, with worsening of either ptosis or diplopia in bright lights, is not uncommon although the reasons for this are unclear. Some patients are so troubled by this that they wear dark sunglasses. Patients with LEMS rarely, if ever, present with ocular symptoms.[25]

Generalized weakness. The weakness experienced by patients with MG can involve any striated muscle but characteristically affects some muscles more than others. The reasons for this are not clear given that antibodies can access any neuromuscular junction. Bulbar weakness can affect almost any of the craniobulbar striated muscles. Facial weakness is often not recognized subjectively. Some patients describe difficulties keeping water out of their eyes in the shower or while swimming. Dysphagia when consuming solids or liquids is common and can occur because of facial (labial), tongue, masseter, or pharyngeal weakness. The temperature dependency of neuromuscular transmission means that, rarely, patients will describe more difficulty swallowing hot liquids than cold. Having patients point to where food gets stuck is useful. Localization below the sternal notch implies esophageal involvement and is not typical for MG. Nasal regurgitation when swallowing is sometimes described in MG. Clearing the throat or coughing after eating, even in the absence of subjective dysphagia, suggests possible aspiration, which is often silent. Fatigable weakness of chewing is also suggestive of MG, with jaw closure much more affected than jaw opening. When severe, patients may manually move their jaws to chew. Fatigable dysarthria is also common. Complete aphonia is extremely rare in MG. Laryngeal involvement with stridor is rare but can be life-threatening. Neck weakness can affect flexors, extensors, or both. Although flexor weakness is more common, MG should be considered in the differential of patients presenting with a head drop. MG is painless, although sometimes patients can develop secondary myofascial pain including neck and shoulder pain with a head drop without recognizing that weakness is the cause for this pain.

Respiratory involvement in MG usually occurs associated with significant bulbar weakness. Exertional dyspnea is nonspecific and can occur in elderly patients with comorbidities or in any patient after deconditioning or weight gain. More useful for diagnosis is orthopnea, which suggests diaphragm weakness, although this too is not specific for MG. Some patients describe almost instantaneous dyspnea on bending over, presumably secondary to the abdominal contents pushing against a failing diaphragm.

Extremity weakness in MG almost always occurs along with ocular and bulbar manifestations, although isolated limb-girdle weakness occurs in about 5% of patients with MG. Extremity weakness affects proximal arms more than legs and is usually symmetric. Patients may describe increasing difficulties with the prolonged use of their arms over their heads. However, fatigable weakness of the arms, of which the patient may be unaware, may be found on examination. Less common manifestations include distal or asymmetric weakness, which happens in about 5% of patients with MG. This almost always occurs later in the course of the disease in patients with more characteristic ocular, bulbar, and proximal extremity weakness. Distal weakness can produce a finger drop, which can sometimes be surprisingly

KEY POINT

- Distal weakness, which is sometimes surprisingly asymmetric, occurs in about 5% of patients with myasthenia gravis.

KEY POINTS

- The diagnosis of myasthenia gravis is made based on clinical suspicion, the history and neurologic examination, and is then supported by electrophysiologic and serologic studies.
- Myasthenia gravis can produce any pattern of pupil-sparing extraocular muscle involvement, including sixth or third cranial nerve palsy or internuclear ophthalmoplegia mimics.

asymmetric and even focal within a hand and, very rarely, a footdrop.[26]

Muscle-specific tyrosine kinase. When considered as a group, clinical differences exist between patients with AChR and MuSK MG. However, significant overlap occurs with the clinical manifestations of AChR MG so that predicting MuSK antibody positivity in an individual patient is difficult. Patients with MuSK antibodies are more likely to be female, have early-onset MG, and have more severe disease, especially affecting bulbar and respiratory muscles. Rarely is MuSK MG purely ocular. Patients with MuSK MG may be more likely to be oligosymptomatic or monosymptomatic. Isolated dysphagia, a head drop, or dyspnea without other bulbar weakness is uncommon in AChR MG but occasionally occurs in MuSK MG (**Case 11-1**).

Diagnosis

The diagnosis of MG is made based on clinical suspicion, the history and neurologic examination, and is then supported by electrophysiologic and serologic studies. Few diagnostic tests are infallible and some, such as single fiber EMG, are not specific for MG. Undue reliance on diagnostic tests when the clinical picture does not fit may lead to a false diagnosis of MG.[27] Although diagnostic tests in patients with mild, especially ocular, MG may be normal, if no objective support exists for the diagnosis on at least one test in a patient with significant weakness, other diagnoses should be considered.

Clinical. The biggest delay in diagnosis often results from failure to consider MG in the differential. MG is uncommon, and most non-neurologists are not familiar with its clinical features. Patients who report significant weakness the previous day but have no objective weakness the next morning are often labeled as functional. Most elderly patients with MG are first diagnosed as having a stroke or transient ischemic attack. Once MG is suspected, the examiner should look for the characteristic and fatigable weakness.

To examine a patient for suspected fatigable ptosis, the examiner should hold the test object up for at least 60 seconds and watch for obvious worsening. Repeated blinking, which mimics a brief maximal voluntary contraction, may transiently improve neuromuscular transmission and mask fatigable ptosis. As the differential for unilateral ptosis is different than for bilateral, looking for enhanced ptosis in the patient with what appears to be unilateral ptosis can be useful. Manual elevation of the obviously ptotic eyelid may bring on fatigable ptosis on the opposite side as the patient is less reliant on the compensatory use of the frontalis muscle, which may have obscured ptosis on the less affected side. The specificity and sensitivity of the Cogan eyelid twitch sign (twitching of the upper eyelid seen when the eyes are moved from downgaze back to the primary position) is widely variable; the author does not find this sign useful in diagnosing MG.

The first step when assessing diplopia is to establish that it is binocular. If monocular (two objects persist when one eye is covered), an ophthalmic or functional origin is likely. MG can produce any pattern of pupil-sparing extraocular muscle involvement, including sixth or third cranial nerve palsy or internuclear ophthalmoplegia mimics. Downgaze is less affected in MG. Although objective limitations in extraocular muscle movement may be present, usually the weakness is subtle and not appreciated by the examiner. It is important for the examiner to ask the patient to report double vision when assessing the extraocular muscles. Complete symmetric ophthalmoplegia, especially if early in the course, is very uncommon in MG and more suggestive of chronic progressive external ophthalmoplegia. Although ptosis can take 60 seconds to fatigue,

Case 11-1

A 47-year-old woman presented for evaluation of a possible myopathy. While fishing 3 years earlier, she had developed a painless head drop after leaning over a railing for several hours. This symptom had improved but several days later, after a sudden forced flexion of her neck, her head drop returned and persisted. Initially she was thought to be functional and was referred to a chiropractor, which did not help her condition. Shortly after, she developed severe orthopnea and had to sleep in a chair, and she also developed acute dyspnea on bending over. She required bilevel positive airway pressure (BiPAP) for her dyspnea and developed severe pulmonary hypertension. Her symptoms became worse at the end of the day. On questioning she reported dysphagia.

Studies done prior to her visit included concentric needle EMG that showed increases in spontaneous activity with 1+ positive sharp waves in paraspinal and trapezius muscles. Repetitive nerve stimulation of ulnar, axillary, and facial nerves was reported as normal. Single fiber EMG in extensor digitorum communis was also reported as normal.

On examination at age 47, she had no diplopia or ptosis. She had mild facial and severe neck flexor and extensor weakness and moderate fatigable deltoid and triceps weakness with equivocal hip flexor weakness. Repeat nerve conduction studies and EMG showed 1+ fibrillation potentials and numerous ''myopathic'' motor unit potentials in the cervical paraspinals, trapezius, and deltoid muscles. Repetitive nerve stimulation of the median nerve was normal, but a 40% decrement was seen in spinal accessory studies. Single fiber EMG in orbicularis oculi showed abnormal jitter in 14 of 21 fiber pairs with blocking in four of the 14. Acetylcholine receptor antibodies were negative, and the CT chest showed no thymic abnormalities.

She was treated with pyridostigmine, prednisone, and azathioprine but worsened and required IV immunoglobulin (IVIg). She improved, although she required several more treatments over the next 2 years, improving after each treatment. When testing for muscle-specific tyrosine kinase (MuSK) antibodies became available 2 years after presentation, the patient was found to be positive. She slowly improved, and at follow-up 5 years later, she was off pyridostigmine and prednisone and remained on azathioprine alone. Her dyspnea improved, and she was able to sleep supine, although she remained on BiPAP for severe obstructive sleep apnea.

Comment. This case demonstrates the characteristic features of MuSK myasthenia gravis with female predominance, prominent bulbar and respiratory weakness, and atypical findings on electrophysiologic studies with abnormalities much more frequent in bulbar and proximal muscles. Frequently, patients with MuSK myasthenia gravis either do not respond or may even worsen after treatment with pyridostigmine.

KEY POINTS

- Although ptosis can take 60 seconds to fatigue, diplopia usually appears within 15 to 30 seconds of sustained gaze.
- A single breath count, in which the patient counts out loud at approximately 2 Hz from full inspiration until he or she needs to take a breath, correlates roughly with the forced vital capacity in pulmonary function studies.

diplopia usually appears within 15 to 30 seconds of sustained gaze.

In any patient who reports dysphagia or other significant bulbar weakness, bedside testing of swallowing is best left to a speech and language pathologist with experience in assessing patients with MG.

A simple bedside assessment of respiratory function involves observing whether the patient can speak in full sentences. A single breath count, in which the patient counts out loud at approximately 2 Hz from full inspiration until he or she needs to take a breath, correlates roughly with the forced vital capacity in pulmonary function studies. Counting to 20 or more suggests that significant respiratory involvement is unlikely. During

KEY POINTS

- The tests used to diagnose myasthenia gravis include repetitive nerve stimulation and single fiber EMG.
- Routine nerve conduction studies and needle EMG are usually normal in patients with myasthenia gravis but should almost always be done first as myopathic or neurogenic conditions may confuse the interpretation of repetitive nerve stimulation and single fiber EMG.
- Reduced motor amplitudes on motor nerve conduction study is suggestive of Lambert-Eaton myasthenic syndrome.
- Abnormalities on needle EMG, including fibrillation potentials, positive sharp waves, and ''myopathic'' motor unit potentials, can be seen in some patients with myasthenia gravis, especially in patients with muscle-specific tyrosine kinase myasthenia gravis.

the single breath count the examiner should listen for fatigable dysarthria. The dysarthria in MG is bulbar and can usually be readily distinguished from dysarthria in other disorders that might be mistaken for MG.

When assessing fatigable limb weakness in patients with possible MG, the author prefers the hands-on method, in which the patient contracts repeatedly for at least five contractions against resistance. The examiner then looks for gradual worsening in power with the last few contractions. With profound weakness at baseline, demonstrating additional fatigue is difficult. Others prefer to assess power of a single contraction followed by the patient exercising (eg, clapping hands over the head 20 times) and then reassessing power. The hands-on technique allows a better assessment of the pattern of fatigue to differentiate from nonorganic fatigue, which is often sudden with tremulous recruitment. Muscles easily assessed for fatigue include deltoids, triceps, and hip flexors. It is more difficult to convincingly demonstrate fatigue in distal muscles, which are easily overcome in normal individuals. Limb weakness in MG is almost always proximal and symmetric and affects arms more than legs. In the arms, involvement of deltoids and triceps is typical for MG, whereas myopathies more commonly cause weakness of deltoids and biceps.

The quantitative myasthenia gravis test and similar scales incorporate measures of ocular, bulbar, respiratory, and extremity strength and fatigue.[28] Although used mostly for research trials, the quantitative myasthenia gravis test score can be used in clinical practice to follow patients during treatment.

The ice pack and edrophonium tests have similar sensitivities and specificities.[29] Increasing difficulties in obtaining edrophonium means that this test is rarely done. If performed, there must be a clear end point (usually ptosis) that can be objectively assessed. Ideally, the edrophonium test should be done double blinded, with syringes of saline or edrophonium drawn up by a third person, and the response to each assessed by both patient and examiner blinded to what is being administered. As there is often a subjective element to the interpretation of this test, by blinding the edrophonium test, the risk of examiner and patient bias is reduced. In the ice pack test, crushed ice in a plastic bag is applied over a ptotic eyelid for 2 to 5 minutes and then removed.[30] Pre– and post–ice pack test eyelid positions are then compared, ideally by a blinded examiner looking at photographs.

Electrophysiologic studies. The tests used to diagnose MG include repetitive nerve stimulation and single fiber EMG.[1] Routine nerve conduction studies and needle EMG are usually normal in patients with MG but should almost always be done first as myopathic or neurogenic conditions may confuse the interpretation of repetitive nerve stimulation and single fiber EMG. Reduced motor amplitudes on motor nerve conduction study is suggestive of LEMS. Both LEMS and amyotrophic lateral sclerosis may also produce a decrement on repetitive nerve stimulation and an abnormal single fiber EMG. Denervation on needle EMG suggests motor neuron disease. However, abnormalities on needle EMG, including fibrillation potentials, positive sharp waves, and ''myopathic'' motor unit potentials, can be seen in some patients with MG, especially in patients with MuSK MG.[31]

When a diagnosis of MG is serologically proven, electrophysiologic testing may not be necessary. However, repetitive nerve stimulation is a useful extension of the clinical examination when determining whether the patient's symptoms are secondary to MG. However, many muscles, including extraocular and most bulbar and leg muscles, are not accessible for repetitive nerve stimulation

studies. Normal repetitive nerve stimulation results in a weak muscle suggests that the weakness is not related to MG. Patients with MG who have what appears to be severe weakness should have at least one objective abnormality on diagnostic testing, particularly electrophysiologic testing.

Repetitive nerve stimulation can be performed in several different nerve-muscle pairs. Sensitivities are higher in proximal muscles. If accessible, the weakest muscles should be studied. With oculobulbar and mild proximal arm weakness, normal studies in a distal hand muscle do not exclude MG. Useful proximal nerve-muscle pairs are facial to nasalis or orbicularis oculi, spinal accessory to trapezius, axillary to deltoid, and sometimes radial to extensor forearm muscles. In the leg, studies of the fibular (peroneal) nerve to tibialis anterior are possible, but for technical reasons it is not possible to study proximal leg muscles. In ocular MG, the sensitivity of repetitive nerve stimulation is low (approximately 20%) but in generalized MG, the sensitivity is higher (approximately 80%), providing that studies of symptomatic or proximal muscles are done. In MuSK MG the yield of both repetitive nerve stimulation and single fiber EMG is higher in proximal or bulbar muscles.

Single fiber EMG provides no additional diagnostic information when the diagnosis has been established serologically or if a significant decrement is seen on repetitive nerve stimulation, both of which have a higher specificity for MG. As single fiber EMG is most useful when all other tests are negative, it is used mostly to diagnose ocular MG. Studies of orbicularis oculi or frontalis are more sensitive than distal muscles. Although highly sensitive, an abnormal single fiber EMG is not specific for MG, and results need to be correlated with the clinical features (**Figure 11-1**). The performance and interpretation of single fiber EMG requires an experienced electromyographer. One of the reasons for a false diagnosis of MG is undue reliance on abnormal single fiber EMG studies without considering specificity. Single fiber EMG can be abnormal in a wide range of neurogenic and myopathic conditions including congenital myasthenic syndromes, LEMS, progressive external ophthalmoplegia, and amyotrophic lateral sclerosis.[32–34] Abnormalities on single fiber EMG can persist for at least a year after botulinum toxin injection, especially with repeated injections, and can be found in

KEY POINT

■ Although highly sensitive, and sometimes the only positive diagnostic test in ocular myasthenia gravis, abnormalities on single fiber EMG are nonspecific and can be seen in many other myopathic or neurogenic conditions. Single fiber EMG results should always be correlated with the clinical presentation.

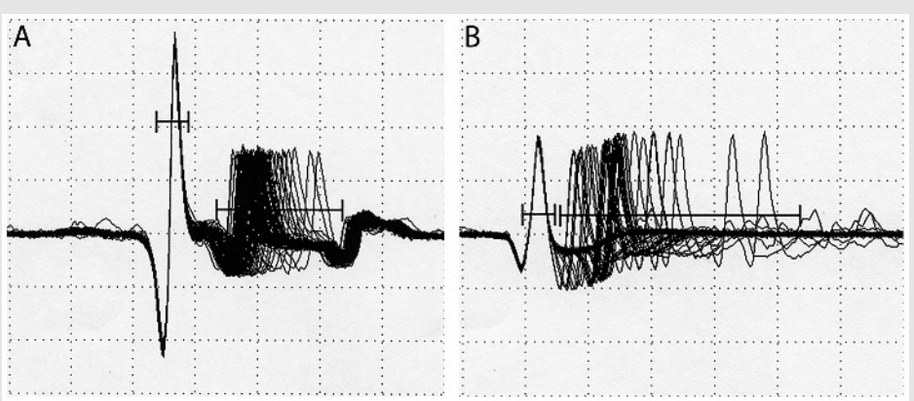

FIGURE 11-1 Single fiber EMG showing *A,* jitter at more than 200 μsec; *B,* jitter at more than 700 μsec and blocking in more than 60% of muscle fiber action potentials.

KEY POINTS

- The acetylcholine receptor antibody titer does not correlate well with clinical severity in an individual patient, and it is not useful to follow antibody levels serially.
- Novel antigenic targets have been recently discovered in patients with myasthenia gravis.
- Positive serologic tests in myasthenia gravis both confirm the diagnosis as well as help guide management options.
- Response to treatment, especially to pyridostigmine and IV immunoglobulin, may be useful as a diagnostic test but only when supported by clinical features and, preferably, other objective diagnostic tests.

muscles remote from the injection site so that an abnormal single fiber EMG must always be considered with caution after botulinum toxin.[35]

Serologic studies. Although the sensitivity of antibody testing is low in some situations (eg, ocular MG), the specificity for the diagnosis of MG is very high (more than 99% for AChR antibodies).[29,36] In the right clinical context, positive antibodies confirm a diagnosis of MG. Positive AChR antibodies also correlate with thymic pathology (either thymic hyperplasia or a thymoma), whereas MuSK antibodies, for the most part, do not.[15] Thus, knowledge of the serostatus guides investigations and treatment options.

AChR antibodies are present in approximately 50% of patients with ocular MG and 85% of patients with generalized MG.[29] A small percentage of initially AChR-negative patients may become seropositive, usually in the first year.[37] More recent improvements in the assay using clustered AChRs in cell-based assays reveal positive AChR antibodies in 50% of previously seronegative patients. This assay is more demanding technically and is not yet widely available.[7,38] The AChR antibody titer does not correlate well with clinical severity in an individual patient, and it is not useful to follow antibody levels serially.[39] Negative AChR antibodies make a thymoma extremely unlikely.[15,40]

MuSK antibodies are found in approximately 40% (range of 0% to 70%) of the 15% AChR-negative generalized MG group but are rarely positive in patients with ocular MG.[21,37,41] The range of MuSK sensitivities may reflect geographic and ethnic variation as MuSK is more common in the nonwhite population.[14,21,42,43]

More recently, LRP4 antibodies have been found in a small number (approximately 18%) of patients who are negative for AChR and MuSK,[42] although other studies suggest a lower frequency.[44] Their role in MG is less certain as they may occur in patients who are positive for AChR or MuSK as well as in other disorders, including amyotrophic lateral sclerosis.[42] It is uncertain whether a specific clinical phenotype is associated, although early evidence suggests that LRP4 is found in ocular as well as in mild to moderate generalized MG.[42]

Even more recently, antibodies against agrin or cortactin have been reported in MG. Their pathogenic relevance and associated clinical phenotype are uncertain[21,45,46]

Although often used as a diagnostic criterion in published studies of MG, especially ocular MG, a frequent diagnostic pitfall is overreliance on "response" to treatment. This false-positive response is especially common with pyridostigmine and IVIg (**Case 11-2**) for several reasons, including a placebo effect, especially in patients with "pseudo-MG." Many patients with nonspecific fatigue pursue an Internet diagnosis leading to a self-diagnosis of MG. Improvement with treatment is taken to confirm the diagnosis of MG, even when all other diagnostic tests are negative. Some patients come to the neurologist well versed in the symptoms of MG, and asking about specific details of each symptom is essential to help patients differentiate what is occurring from what they have read about. Subjective response to treatment should only be used to diagnose MG if it is unequivocally and objectively verified. IVIg may produce a nonspecific sense of well-being, independent of its specific benefits in MG. Finally, some disorders in the differential for immune MG may also respond to symptomatic treatments including congenital myasthenic syndromes, mitochondrial myopathies, and LEMS. If in doubt, with the patient's consent, a blinded trial of active therapy versus placebo can sometimes establish whether the benefit is biological (**Case 11-2**).

Ancillary investigations. A CT chest is indicated in patients with AChR MG, although many neurologists will arrange one in all MG patients. Its main indication

Case 11-2

A 45-year-old woman was referred for a neurologic consultation after receiving a diagnosis of myasthenia gravis (MG) made by her internist 1 year earlier and because of ongoing symptoms despite treatment. Her symptoms included a hoarse voice with aphonia after prolonged talking, dysphagia for solids and liquids with choking, weakness of jaw muscles when chewing, facial weakness, exertional dyspnea without orthopnea, and a head drop. No diplopia or ptosis had occurred. In addition, the patient had described generalized exhaustion, fatigue, and daytime somnolence. Because of her extremity weakness, she would often fall to the ground and could not work. She had read extensively about MG. She had thought that pyridostigmine had made a ''huge difference'' in her symptoms. Despite continued use of pyridostigmine, she had worsened and had become unable to walk. Prednisone and azathioprine had been started by her previous physician, and she was also being treated with IV immunoglobulin (IVIg), which she had continued on a monthly basis thereafter. Both the patient and her previous physician had perceived significant benefit after IVIg, although it had caused headaches requiring narcotics. Because of worsening weakness, her frequency of IVIg treatments had been increased to every 2 weeks prior to referral for the second opinion.

On examination, she had blepharospasm but no objective weakness. All investigations were normal including repetitive nerve stimulation (several times), single fiber EMG, CT chest, acetylcholine receptor (AChR) (several times) antibodies, and muscle-specific tyrosine kinase (MuSK) antibodies. A speech and language pathology consultation did not show any objective evidence of dysarthria or dysphagia consistent with MG.

When suggested by the neurologist, she agreed to an n-of-1 (ie, double blinded trial of treatment in a single patient) placebo versus IVIg trial in which she would receive IVIg or placebo every 3 weeks for a total of three treatments of each, with each treatment received in randomized order and with a standardized objective clinical and electrophysiologic assessment at each visit. Both she and the neurologist were blinded to the treatment received. After the fourth scheduled treatment, she asked for the trial to be stopped as she was convinced that IVIg produced significant improvement (as well as a headache requiring narcotics) on each of the three occasions that she felt she had received it. No significant changes in the clinical examination were noted by the neurologist, and no changes in the quantitative MG scoring or any abnormalities on repetitive nerve stimulation were noted with any of the four treatments. When the neurologist was unblinded to her treatment, she had received placebo each of the three times she felt that she had improved and had received IVIg on the occasion she perceived no benefit. She chose not to continue follow-up with the neurologist as she disagreed with his opinion that she did not have MG. She sought a second opinion with another neurologist. Despite being told again by that neurologist that her condition was not MG, 3 years later she continued to be treated with pyridostigmine, prednisone, azathioprine, and IVIg every 2 to 4 weeks, prescribed by her first physician for a ''myasthenialike syndrome.''

Comment. This case demonstrates the perils of accepting a patient's response to treatment as definitive evidence that the diagnosis is MG. Ultimately, response is often subjective and, if it is the only diagnostic clue, may lead to a false-positive diagnosis of MG.

is to look for a thymoma, although it can be difficult to distinguish focal hyperplasia from a small thymoma.[47] Thymic hyperplasia is a pathologic diagnosis made at the time of thymectomy. A normal thymus in a young, healthy control can look

KEY POINT

- Vitamin B_{12} deficiency or thyroid disease may produce nonspecific symptoms that can complicate the management of myasthenia gravis if not recognized.

enlarged, and a normal or small thymus on CT may still be hyperplastic.[47] Thymic hyperplasia can occur in other autoimmune conditions including systemic lupus erythematosus and autoimmune thyroid disease. If considering thyroid eye disease, looking for enlarged extraocular muscles on a CT or MRI of the orbits is useful.

The prevalence of other autoimmune diseases is increased in MG. Without suggestive clinical features, the yield of screening for most autoimmune diseases is low. However, the routine determination of vitamin B_{12} and thyroid levels is useful as vitamin B_{12} deficiency or thyroid disease may produce nonspecific symptoms that can complicate the management of MG if not recognized.

Differential Diagnosis

With a characteristic history of fluctuating weakness and an appropriate pattern of weakness, a clinical diagnosis of MG often seems secure. However, many patients report worsening of their weakness at the end of the day even when the ultimate diagnosis is not MG, and some conditions can mimic the symptoms and signs of MG.

Ocular. Ocular MG is often more difficult to diagnose than generalized MG, and the sensitivity of diagnostic tests is lower. Many conditions can mimic ocular MG (**Table 11-1**).[27] Ophthalmologic conditions, including levator dehiscence or a decompensated phoria, are common eventual diagnoses when ocular MG is

TABLE 11-1 Differential for Myasthenia Gravis

Anatomic	Ocular Myasthenia Gravis	Generalized Myasthenia Gravis
Ophthalmic	Thyroid eye disease, levator dehiscence, phoria, tropia	Not applicable
Central nervous system	Blepharospasm, brainstem lesion (eg, multiple sclerosis, ischemia, mass lesion, Wernicke encephalopathy)	Amyotrophic lateral sclerosis, Parkinson disease/parkinsonism
Peripheral nervous system		
Nerve	Microvascular/diabetic cranial neuropathies, Horner syndrome, Miller Fisher syndrome, isolated/combined III, IV, and VI cranial neuropathies	Amyotrophic lateral sclerosis, Guillain-Barré syndrome, focal neuropathies affecting craniobulbar function
Neuromuscular junction	Lambert-Eaton myasthenic syndrome,[a] botulism, congenital myasthenic syndrome	Lambert-Eaton myasthenic syndrome, botulism, congenital myasthenic syndrome, organophosphate toxicity
Muscle	Chronic progressive external ophthalmoplegia, oculopharyngeal muscular dystrophy, myotonic dystrophy	Chronic progressive external ophthalmoplegia, other mitochondrial myopathies, oculopharyngeal muscular dystrophy, myotonic dystrophy
Other	Idiopathic, convergence spasm	Systemic disease, thyroid disease, idiopathic, chronic fatigue, functional/conversion disorder

[a] Ocular manifestations are rare at onset of Lambert-Eaton myasthenic syndrome.

being considered. Microvascular neuropathies, including diabetic or hypertensive microvascular cranial neuropathies, affecting the III, IV, or VI cranial nerves should be considered, especially with periorbital pain or headache at the onset of diplopia. Symmetric restriction in extraocular muscles and progressive symmetric ptosis, even with a history of minor fluctuations, suggests chronic progressive external ophthalmoplegia. Thyroid eye disease may mimic or coexist with ocular MG. In about 25% of patients who have a combination of ptosis and diplopia, no diagnosis is determined.[48]

Generalized. In a typical case of generalized MG, the differential is limited (**Table 11-1**), and the sensitivity of diagnostic tests is higher.[27] A congenital myasthenic syndrome should be considered in patients who are seronegative and who have onset at birth, early in life, and even in adulthood. Some congenital myasthenic syndromes can present in adolescence or even adulthood caused by mutations in the genes *RAPSN*, *DOK7*, or *COLQ*. When ocular symptoms are absent and hyporeflexia or areflexia and autonomic dysfunction occur, consider LEMS. Other conditions to be considered when the deep tendon reflexes are reduced include Guillain-Barré syndrome and its Miller Fisher variant and rare cases of multifocal neuropathy with conduction block with cranial nerve muscle involvement. In oculopharyngeal muscular dystrophy, ptosis and generalized weakness can occur, but extraocular muscle involvement is usually absent. Mitochondrial myopathies can be difficult to distinguish clinically from MG, and single fiber EMG can be abnormal in many myopathic disorders including oculopharyngeal muscular dystrophy and mitochondrial myopathies.[34] Central nervous system disorders such as Parkinson disease, progressive supranuclear palsy, or brainstem lesions are usually not difficult to distinguish from MG after a careful history and examination. Functional weakness is also commonly in the differential.

Management

The crucial first steps in managing MG are to ensure that the diagnosis is correct and that the symptoms being treated are those of MG. Causes of refractory MG include an incorrect diagnosis or symptoms that are not due to MG. When patients do not improve as expected, it is useful to reconsider the diagnosis, especially if the patient is seronegative. If a patient is seropositive, it is important to establish that the symptoms are consistent with MG. A patient with MG who improves with treatment but then reports increasing weakness may be describing fatigue, exhaustion, or daytime somnolence, which may be symptoms of obstructive sleep apnea.[24] In addition to a clinical assessment, repeat electrophysiologic studies (ie, repetitive nerve stimulation) may help determine whether the weakness is secondary to MG. Other reasons for worsening symptoms include adverse effects from medications (prednisone in particular), mood disorders, and social circumstances.

Education of patients and primary care physicians is crucial. Expectations of the treating physician or patient about when treatments should start being effective are sometimes unreasonable.[49] Underdosing (or occasionally overdosing) or abandoning a treatment too early can both result in treatment ''failure.'' A discussion about each medication, possible adverse effects and strategies to manage them, expected time course of benefits (hours to days for pyridostigmine, weeks to many months for prednisone, and many months to a year or more for azathioprine) is crucial. For some medications, monitoring for adverse effects is essential, and a discussion of the importance of this increases compliance. For physicians managing many patients with MG, having this educational information

KEY POINTS

- A congenital myasthenic syndrome should be considered in patients who are seronegative and who have onset at birth, early in life, and even in adulthood.
- Causes of refractory myasthenia gravis include an incorrect diagnosis or symptoms that are not due to myasthenia gravis. When patients do not improve as expected, it is useful to reconsider the diagnosis, especially if the patient is seronegative.

KEY POINTS

- A complete lack of response to treatment is unusual in patients with myasthenia gravis and should prompt physicians to reconsider the diagnosis of myasthenia gravis in patients who are seronegative or reconsider whether myasthenia gravis is the cause of the symptoms in patients who are seropositive.
- Many treatments of myasthenia gravis take time to reach maximal efficacy, and another cause for nonresponse to treatment is unreasonable expectations about how long it should take before improvement begins.

in print form in addition to a verbal discussion saves time and reinforces the message. Sending a list of the medications that should be avoided in patients with MG to the primary care physician is useful, although this is not infrequently ignored. Finally, a discussion of which symptoms might be secondary to MG (weakness) and which almost never occur (eg, pain, memory loss, sensory symptoms, systemic disorders) maximizes efficiency of the neurologist's time.

Management of ocular myasthenia gravis. Although not life-threatening, ocular MG can be disabling. The first decision is whether symptoms require treatment. When symptoms are mild and infrequent, it may be best to defer treatment until they become troublesome. A trial of pyridostigmine may be warranted, but the medication is often ineffective or minimally effective, especially for diplopia. The risk to benefit ratio of prednisone may not be worth accepting. Retrospective evidence suggests that prednisone may reduce the risk of generalization.[50] However, it may be better to avoid prednisone when not required, knowing that it is just as likely to be effective if and when MG becomes generalized.

MG is treated symptomatically with pyridostigmine, which inhibits acetylcholinesterase at the neuromuscular junction and increases available acetylcholine but does not treat the underlying immunopathogenesis. Pyridostigmine is the usual first step in treating ocular MG. It has few serious side effects and, if effective, works quickly. Starting at 30 mg every 4 hours during the waking day, with the first tablet taken within an hour of arising, is a reasonable strategy. Unless nocturnal symptoms occur, a bedtime tablet is wasted. If required, the dose can be increased to 60 mg every 4 hours in 3 to 7 days. The regular 60 mg pyridostigmine pills have a more consistent bioavailability, and the author rarely uses the sustained-release formulation. Rarely, patients need lower initial doses or a slower rate of escalation. Having already discussed the next options with the patient at the time of medication initiation, the author has the patient call to provide an update on his or her response 2 weeks after starting the medication. Even when a complete response occurs, occasionally symptoms will break through over the next several months. If a partial response occurs, further increases of 30 mg to 60 mg at each dose can be made at intervals of 1 to 2 weeks up to a maximum of 480 mg/d, depending on tolerance. Higher doses are unlikely to produce additional benefit. Diarrhea, one of the more common side effects, is often self-limited, but loperamide helps in most cases. If no response occurs, the author moves on to immunosuppression, usually adding to pyridostigmine, although if it is clear that no response has occurred, the medication could be stopped.

Prednisone is very useful in patients with ocular MG, although patience is required. The evidence in adults that prednisone given on alternate days is less likely to cause adverse effects is practically nonexistent, but starting low doses (eg, 25 mg every other day) of prednisone will help most patients in about 3 to 4 months.[51] Occasionally, patients fluctuate and are worse on the off day, and glycemic control using the alternate-day approach is difficult in diabetics, so sometimes starting or reverting to an equivalent daily dose is required. If at 3 to 4 months the symptoms are not improving (they may not be completely gone), doubling the dose to either 25 mg/d or 50 mg on alternate days helps most of the remaining patients. Physicians should be familiar with common side effects of prednisone and discuss these with the patient.[3] Anticipating worsening in hypertension and glycemic control and enlisting the help of the primary care physician in managing these is helpful. Individuals older than age 50 taking more

than 7.5 mg/d for more than 3 months should be on osteoporosis prophylaxis at the outset.[52]

With patience, prednisone doses higher than 25 mg/d to 30 mg/d are rarely required in patients with ocular MG. About 2 to 3 months after the symptoms have resolved, it may be appropriate to start tapering the dose. With doses of more than 20 mg/d, taper by 10 mg a month, and with doses of less than 20 mg/d, taper by 5 mg a month (10 mg on the alternate day). It is often useful to taper by 2.5 mg or even 1 mg reductions every 1 to 2 months with doses of less than 5 mg/d to 10 mg/d. Symptoms often recur at doses of less than 5 mg/d to 10 mg/d, and many patients require long-term low-dose prednisone. Tapering too quickly or while the patient is still symptomatic will almost always result in a relapse, often several months after a reduction.

The databases used by most pharmacies in North America sometimes flag the combination of prednisone and pyridostigmine as a potentially harmful interaction. The vast majority of patients with MG will be on this combination at some point. The literature supporting this warning is decades old and likely relates to the early worsening that can be seen with the use of high-dose prednisone and not to an interaction between the two. To avoid future telephone calls and confusion on the part of the patient, the author often sends a form letter with the prescription politely suggesting that the pharmacist ignore this warning.

Azathioprine can be used in ocular MG, either alone (if the patient is willing to wait) or along with prednisone in patients where long-term/high-dose prednisone is best avoided. Azathioprine can also be added later if no response to prednisone occurs by 6 to 9 months or if the patient worsens when tapering. Other immunosuppressants can also be used in patients with ocular MG. The author avoids combining more than two (prednisone and one other) immunosuppressants because of the increased risk of infections.

Management of generalized myasthenia gravis. The treatment of MG is highly individualized, and only general guidelines are discussed. The options chosen depend on serostatus (AChR versus other), age, comorbidities, and disease severity. For most choices, no trial evidence exists to establish effectiveness.[53] However, the collective experience supports the most commonly used medications and treatments. The choice often comes down to physician experience and familiarity as well as patient tolerance. For all treatment options, a discussion of expected benefits, including the time frame that is involved, as well as common adverse effects and monitoring required, is useful.

Symptomatic. As is the case for ocular MG, in mild to moderate generalized MG, pyridostigmine may be the only treatment at first. The same strategy and advice about pyridostigmine previously discussed for ocular MG also applies to the treatment of generalized MG. A cholinergic crisis, in which weakness is worsened by increased doses of pyridostigmine, rarely occurs. Almost always, a careful history will reveal worsening in MG symptoms prior to increases in the dose of pyridostigmine. In mild to moderate generalized MG, the concomitant use of prednisone and sometimes another immunosuppressant is often required. In more severe MG, immunosuppression and sometimes immunomodulation should be started at the same time as pyridostigmine.

Immunosuppression. For mild generalized MG, when pyridostigmine alone is not helpful, low-dose alternate-day prednisone is useful. For moderate generalized MG, higher doses may be required. For severe MG, especially if bulbar or respiratory weakness occurs, higher

KEY POINT

- With patience, most patients with myasthenia gravis will respond to lower doses of prednisone, although this may take several months.

KEY POINT

■ Caution is advised when starting patients with myasthenia gravis who have any bulbar or respiratory weakness on high doses of prednisone as patients may worsen initially.

doses are effective more rapidly. However, if high doses (the author considers doses higher than 30 mg/d as the cutoff for concerns about this phenomenon) are used initially, about 40% of patients with MG may worsen initially before they start to improve, and 10% overall worsen significantly.[54] This usually starts 4 to 5 days after beginning prednisone and lasts about 4 to 7 days before improvement then occurs. Strategies to avoid this initial worsening of symptoms include starting at low doses (eg, 10 mg/d) with increases every 3 to 5 days in 10 mg steps until the desired dose is reached.[55] The use of IVIg or plasma exchange when prednisone is started may also prevent initial worsening. Prednisone doses of more than 1 mg/kg/d are rarely required, and the author usually uses a maximum dose of 0.5 mg/kg/d to 0.75 mg/kg/d. Recent trial evidence suggests that, with patience, most patients respond to relatively low doses of prednisone.[56] Prednisone takes months (usually 3 to 6 months and sometimes longer) before maximum benefit occurs. Higher doses might accelerate this slightly but definitely increase the risk of adverse effects. With bulbar or respiratory weakness, when a more rapid response is required, immunomodulatory treatments should be used (see the following section on immunomodulation).

In mild generalized MG, if prednisone is best avoided, azathioprine can be used alone provided the patient can wait the 12 to 18 months (or more) that it may take before optimal benefit is seen.[57] Starting prednisone and azathioprine at the same time takes advantage of the earlier benefits from prednisone as well as the eventual steroid-sparing effects of azathioprine. Tapering regimens are similar to ocular MG (larger reductions at doses of more than 30 mg/d and smaller below this). Starting azathioprine at 25 mg/d with increases every 2 weeks to 50 mg/d, 100 mg/d, and 150 mg/d lessens some adverse effects. In the author's experience, about 1% to 2% of patients, higher in others' experience, will experience a flulike reaction within the first 2 weeks that almost always requires discontinuation. Monitor hepatic transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and most importantly γ-glutamyltransferase [GGT]) and a complete blood count and differential weekly for the first 8 weeks and monthly thereafter. Hepatotoxicity, usually mild and reversible, occurs in 15% and myelosuppression in 10% at a median of about 6 weeks after starting.[58] Both will resolve after a dose reduction, although if these adverse effects are rapid or significant, discontinuation may be required. Neutropenia is the main concern, whereas lymphopenia and macrocytosis are common and benign findings that are seen when monitoring blood work with long-term azathioprine use. After 6 to 12 months on azathioprine, if no improvement occurs at 150 mg/d, in most patients not at maximal doses based on weight (ie, the patient weighs more than 50 kg [110 lb]), the dose can be increased in 50 mg to 100 mg steps every 3 to 6 months to a maximum of 2.5 mg/kg/d to 3.0 mg/kg/d based on actual body weight. Long-term azathioprine use may increase the risk of malignancies, particularly dermatologic, although the absolute risk of this is low.[59] Strategies to reduce this are prudent.[60] If a risk of or previous history of skin cancers already exists, using mycophenolate might pose a lower risk.[61]

In patients who do not respond to or tolerate azathioprine, other immunosuppressants can be used. Mycophenolate (either mofetil or sodium) is a common next step. Although two trials failed to show an additional benefit compared to prednisone alone over 36 weeks, this may reflect the efficacy of prednisone in relatively mild MG within the first 9 months rather than a failure of

mycophenolate.[56] Mycophenolate is widely used in MG and likely takes at least 6 months and perhaps longer to produce significant benefit. Mycophenolate is generally well tolerated and may be more suitable in patients with skin cancer. Other immunosuppressants used frequently in MG include cyclosporine, tacrolimus, methotrexate, and cyclophosphamide. Some retrospective and limited trial evidence supports the efficacy of each of these. Most of these agents have greater toxicity than azathioprine and mycophenolate and require more intense monitoring.

Patients with MuSK antibodies may be less likely to respond to (and may even worsen) and have more adverse effects from pyridostigmine.[42,62] MuSK MG may also be less likely to respond to IVIg and perhaps immunosuppressants in general, but azathioprine in particular.[42,63]

Immunomodulation. In a myasthenic crisis, respiratory weakness requires intubation. Historically, a myasthenic crisis occurred in 15% to 30% of patients with MG but is less common now with effective management options. A myasthenic crisis usually occurs within the first few years after disease onset and is sometimes the presenting incident. Along with severe bulbar weakness producing aspiration, a myasthenic crisis was the cause of mortality rates of 50% or more prior to effective treatment. With the current options and improved intensive care, mortality from a myasthenic crisis is less than 5%. Severe MG with dyspnea managed with noninvasive ventilation or severe dysphagia should be managed similarly to a crisis. Common precipitants for a myasthenic crisis include underlying infection (often pneumonia), aspiration, surgery including thymectomy, hormonal changes during or after pregnancy, tapering or discontinuation of MG medications, and high doses of prednisone or other medications, which can interfere with neuromuscular transmission.[64] In almost one-third of cases, a cause is not identified.

For patients who have an acute exacerbation of MG, pyridostigmine is often insufficient, and its adverse effects of increased oral and tracheobronchial secretions may worsen the situation. Immunosuppressants may take months; therefore, in addition to treating the underlying precipitant, immunomodulatory treatments are useful for a crisis or severe exacerbation and include IVIg and plasma exchange.[65,66] Both treatments are similarly effective, although plasma exchange may be slightly faster and more effective in a myasthenic crisis and more useful in patients with MuSK MG.[42,67] Either IVIg or plasma exchange is also used preoperatively, before thymectomy or other urgent surgery, in a patient with MG who is significantly symptomatic. Neither is required routinely, and their use should be restricted to those patients with significant preoperative respiratory or bulbar weakness. IVIg or plasma exchange have no effect on the long-term course of MG and, with few exceptions, are not indicated for the chronic management of MG.[68] Rarely, a patient will require ongoing treatment with IVIg or plasma exchange for refractory MG.

Immunomodulatory treatments targeting B lymphocytes have shown significant promise in patients with MuSK or AChR MG. Rituximab, which targets CD20 on the B lymphocyte cell surface, works in many patients with MG with severe disease and who are refractory to the usual treatments. It has been suggested that MuSK MG is more likely to respond to rituximab.[21,42] However, a meta-analysis showed efficacy of rituximab in more than 80% of patients with MG regardless of which antibody was positive.[69] The onset of action is probably slower than IVIg or plasma exchange but the duration of improvement is often 6 to 12 months or

KEY POINT

- In a myasthenic crisis, pyridostigmine is often not sufficient, and immunosuppressive options, although effective, can take months to produce benefit. Immunomodulation, with either IV immunoglobulin or plasma exchange, produces earlier improvement in most patients and bridges the gap while waiting for immunosuppression to work.

KEY POINTS

- Although the specifics of each indication are still somewhat controversial, the most accepted indications for a trans-sternal thymectomy include patients with generalized early-onset myasthenia gravis who are acetylcholine receptor antibody positive and within 5 years of disease onset.
- Many commonly used medications to treat myasthenia gravis, including pyridostigmine, prednisone, and azathioprine, are safe for use during pregnancy.

more.[70] Rituximab may offer significant benefits in severe or refractory MG, especially in those being treated with long-term IVIg or plasma exchange.

IgG3 and, to a lesser extent, IgG1 and IgG2 AChR antibodies, which fix complement, can destroy the muscle endplate. Therapies targeting complement including eculizumab have been assessed in MG and its experimental model and appear promising.[70]

Thymectomy. Indications for a thymectomy in patients with MG include removal of a thymoma and to increase the chance of a sustained drug-free remission, but these two indications are not synonymous. Removing a thymoma probably does not improve the course of MG but is almost always indicated to reduce the chance of local growth, invasion, and metastases.[71] If removed at an early stage, the long-term survival is good. Once local invasion or metastases occur, adjuvant therapy with radiation or chemotherapy is usually indicated.

Given its role in the production of AChR antibodies, removal of a hyperplastic thymus has long been considered a management option for generalized MG. The evidence supporting this is mostly retrospective, and evidence-based reviews concluded that thymectomy may be a management option in some patients with MG.[72,73] A recently concluded randomized trial supports the role for thymectomy under specific conditions in MG.[74] Although the specifics of each indication are still somewhat controversial, the most accepted indications for a trans-sternal thymectomy include patients with generalized early-onset MG who are AChR antibody positive and within 5 years of disease onset. The role for thymectomy outside these indications is less certain. Improvement may take 1 to 2 years after thymectomy. Patients with MG should be medically well controlled and ideally on lower doses of prednisone prior to thymectomy.

Other surgical approaches are used in some centers. Most consider a cervical thymectomy suboptimal because of the risk that thymic tissue will be left behind. The role for minimally invasive approaches (robotic or video-assisted thoracoscopy) remains to be proven, although these approaches are increasingly used in many centers. Despite occasional reports of efficacy of thymectomy in MuSK MG, given the lack of thymic pathology in MuSK MG this remains a controversial indication.[21] Thymectomy in seronegative MG, where thymic hyperplasia is less prominent, is also less proven and a chance always exists that a patient who is seronegative does not have MG.

Pregnancy. For the most part MG is managed during pregnancy as usual. Planning any changes in management in advance, including before conception when possible, is important. When MG is well controlled, the risks to mother and child are minimal. Vaginal deliveries are encouraged, and indications for a cesarean delivery are no different than in a mother without MG.[75] Although neonatal MG is rare in the author's experience, mothers with MG should be managed as a high-risk pregnancy in a center capable of caring for both neonate and mother. Most medications used in MG, including pyridostigmine, prednisone, and azathioprine, appear to be safe in pregnancy.[21,76,77] Methotrexate and mycophenolate must be avoided as they are teratogenic. IVIg and plasma exchange are also relatively safe in pregnancy. The severity of the weakness in MG may improve or worsen, the latter especially in the puerperium, during pregnancy.

Other medications and myasthenia gravis. There are many lists of drugs to avoid in MG as they might worsen the weakness in a patient with MG. The evidence supporting inclusion of some of these is often weak. Many patients with MG, especially the elderly, will be on one or more of these (beta-blockers

and calcium channel blockers in particular) with no worsening in their MG.[78] Some antibiotics (aminoglycosides, macrolides, and fluoroquinolones, for instance) are probably best avoided if possible but even then, many patients with MG have been on one or more of these without ill effect. Most should be considered a relative contraindication, and patients and physicians should weigh the benefits of that specific medication versus the risk that the MG may be worsened while on the medication. If worsening does occur, it is sometimes difficult to exclude worsening because of an underlying infection, which is a common reason for exacerbation in MG. Patients with MG undergoing a general anesthetic may be more sensitive to nondepolarizing neuromuscular blocking agents and less sensitive to depolarizing neuromuscular blocking agents. Spinal or local anesthetics are generally safer options. Any patient with MG who has significant weakness, especially if bulbar or respiratory, and who is started on one of the potentially offending medications should be monitored carefully.

Trends

Recent advances in identifying new antigenic targets and improved assays for existing antibodies promise to further reduce the cases of generalized MG that are difficult to diagnose. Therapies that are directed to specific components of the aberrant immune response, including complement and CTLA4, may prove interesting. Trials that demonstrate efficacy of current off-label options will expand the list of available treatments for many patients with MG.

LAMBERT-EATON MYASTHENIC SYNDROME

Although much less common than MG, it is important for neurologists to recognize the clinical features of LEMS and be familiar with its management.

Pathophysiology

The antigenic target in LEMS is the P/Q type voltage-gated calcium channel (VGCC) on the presynaptic nerve terminal.[79] VGCC antibodies reduce calcium influx into the nerve terminal and, therefore, reduce the amount of acetylcholine released into the synaptic cleft. At the neuromuscular junction of skeletal muscle, this can result in neuromuscular transmission failure. Involvement of the same VGCC at autonomic synapses produces autonomic dysfunction. VGCC antibodies can be found in other paraneoplastic disorders including subacute cerebellar degeneration.

LEMS is divided into paraneoplastic and primary autoimmune groups. In paraneoplastic LEMS, an underlying small cell lung cancer is almost always present. In children with LEMS, lymphoproliferative disorders may be associated instead.

Epidemiology

LEMS is rare, with an estimated incidence of 0.5 out of 1 million and a prevalence of 2.3 out of 1 million. Relative to MG, the prevalence of LEMS is reduced compared to its incidence.[80] This reflects the poor survival in paraneoplastic LEMS. Approximately 40% to 50% of patients with LEMS have a primary autoimmune disorder, and in 50% to 60%, LEMS occurs as a paraneoplastic disorder, almost always with an underlying small cell lung cancer.[81] Studies suggest that LEMS occurs in 2% to 3% of small cell lung cancer cases and is likely underrecognized.[81,82]

Clinical Features

The clinical triad characteristic for LEMS is best remembered by the three *A*'s: apraxia, areflexia, and autonomic involvement.[83,84] Although not true apraxia, this is a useful way of remembering that leg weakness producing difficulties with gait is the most prominent clinical

KEY POINT

- Although some medications might produce worsening in patients with myasthenia gravis, few medications are absolutely contraindicated, and the potential benefits of a medication should be weighed against the evidence that it might produce worsening weakness.

KEY POINT

- Patients with Lambert-Eaton myasthenic syndrome often present with difficulty walking and with leg weakness, with areflexia and autonomic involvement comprising the other two key features.

feature and that, frequently, patients with LEMS have more functional difficulties than predicted by the strength of individual muscles.

The clinical features of LEMS usually precede the diagnosis of underlying small cell lung cancer, which is more often at a limited stage or occult when compared to small cell lung cancer without LEMS. Weakness almost always begins in the proximal legs and causes difficulties walking.[83,85] Arm weakness is also common. The onset is often subacute, and fluctuation is less prominent than in MG. However, ocular and bulbar weakness may be absent or, if present, occur as a late manifestation. The presence of ocular and perhaps bulbar involvement at onset is strongly against a diagnosis of LEMS and suggests MG.[25] Thus, LEMS starts in the legs and ascends while MG often starts with craniobulbar involvement and descends. Respiratory involvement is uncommon.

Deep tendon reflexes are almost always reduced or absent, especially in the legs. Involvement of sympathetic and perhaps more frequently parasympathetic systems occurs eventually in 80% to 90% of patients with LEMS and can produce almost any autonomic manifestation. A dry mouth, constipation, and erectile dysfunction in men are particularly common but loss of sweating, orthostatic hypotension, and pupillary abnormalities are also seen.[84]

Sensory loss or cerebellar features are not features of LEMS but might suggest an overlapping paraneoplastic disorder associated with an underlying small cell lung cancer.

Diagnosis

Once suspected, the diagnosis of LEMS can often be made based on characteristic electrophysiologic abnormalities, which distinguish it from MG. Serologic confirmation of the diagnosis is important.

Clinical. The biggest delay to a diagnosis of LEMS is not suspecting the condition. Abnormalities on the neurologic examination will usually be most prominent in the extremities, especially the legs. Reduced deep tendon reflexes in a patient where MG is being considered suggests LEMS instead. Prominent ocular findings at onset is against a diagnosis of LEMS.[25] Characteristic in LEMS is the paradox between significant functional impairment with walking but only mild weakness on examination.

The author has not found clinical facilitation in strength, in which the second contraction of a muscle group has increased power relative to the first, to be a reliable sign when elicited by an unbiased examiner. However, in up to 40% of patients with LEMS, a previously absent or significantly reduced deep tendon reflex will return to normal after 10 seconds of maximal voluntary contraction.[84] Autonomic involvement is best established by a careful history. Many patients will not volunteer symptoms suggesting autonomic involvement unless asked.

Weakness in a patient with small cell lung cancer is often blamed on cachexia, malnutrition, or chemotherapy, and paraneoplastic LEMS is often not suspected. LEMS should be considered when a patient with an underlying small cell lung cancer develops prominent leg weakness and the deep tendon reflexes are reduced or autonomic involvement occurs.

The prediction of an underlying small cell lung cancer in patients with LEMS may be increased when the patient has a higher Dutch-English LEMS Tumor Association Prediction (DELTA-P) score. This uses clinical features such as bulbar weakness (dysarthria, dysphagia, chewing weakness, and neck weakness), autonomic involvement (erectile dysfunction), weight loss, tobacco use, age of older than 50 years, and a Karnofsky Performance Status Scale score of less

than 70, with 1 point allocated for each. A total score of 3 or more predicted a greater than 90% chance of an underlying small cell lung cancer.[86]

Electrophysiologic studies. As for MG, routine nerve conduction studies and needle EMG should be done first. The triad of electrophysiologic abnormalities in LEMS consists of the following:

- Diffusely reduced motor amplitudes on motor nerve conduction studies, often less than 50% of the laboratory's lower limits of normal.
- Decrement with low-frequency stimulation; as opposed to MG, where the decrement is usually maximal at the fourth or fifth stimulation in the train, in LEMS the maximal decrement may occur later in the train.[87]
- Increment with high-frequency stimulation or facilitation after 10 seconds of maximal voluntary contraction (**Figure 11-2**);

KEY POINT

■ Although a decrement on repetitive nerve stimulation can be seen in either myasthenia gravis or Lambert-Eaton myasthenic syndrome, a reduction in baseline motor amplitudes and increment after either maximal voluntary contraction or high-frequency stimulation are characteristic of Lambert-Eaton myasthenic syndrome.

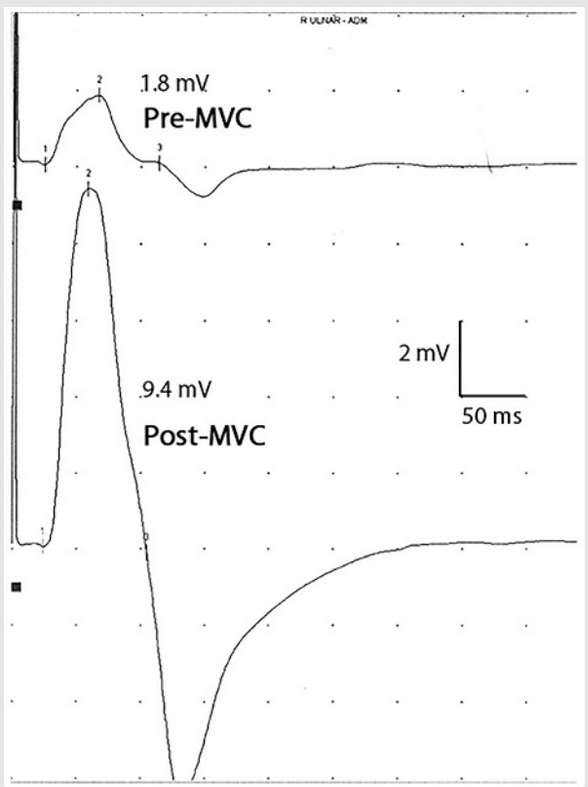

FIGURE 11-2 Pre– and post–maximal voluntary contraction ulnar motor nerve conduction study in a patient with Lambert-Eaton myasthenic syndrome. A 32-year-old woman presented with a 1-year history of fatigable weakness of her legs. She also described a dry mouth. She was a lifetime nonsmoker. On examination, in addition to mild weakness of hip flexors, she was areflexic. Pre– and post–maximal voluntary contraction motor nerve conduction studies of the ulnar nerve with stimulation at the wrist and recording over abductor digiti minimi are shown, demonstrating an over 500% increment in motor amplitude after maximal voluntary contraction.

MVC = maximal voluntary contraction.

KEY POINT

■ Whereas pyridostigmine may not produce significant benefit, 3,4-diaminopyridine is a very effective symptomatic treatment of Lambert-Eaton myasthenic syndrome.

post–maximal voluntary contraction studies are as sensitive and better tolerated than high-frequency stimulation.[88] Increments of more than 100% are very suggestive for LEMS but not specific for LEMS and occur in some cases of botulism and MG.

The abnormalities may be subtle early in the disease course. Although leg weakness is most predominant in LEMS, electrodiagnostic studies of the ulnar or median nerves have the highest sensitivities.[89] Single fiber EMG abnormalities usually do not distinguish LEMS from MG.

Serologic studies. VGCC antibodies are more than 90% sensitive in primary autoimmune LEMS and approach 100% in paraneoplastic LEMS.[84] VGCC antibodies are not specific and are found in small cell lung cancer without LEMS as well as other paraneoplastic disorders.[83,90]

Ancillary investigations. Given its association with LEMS, patients should be investigated for an underlying small cell lung cancer, especially in elderly smokers with weight loss. If an initial CT chest is negative, a bronchoscopy or positron emission tomography (PET) scan may be indicated in high-risk patients. When initial investigations are negative in a high-risk patient, repeating the CT chest every 3 to 6 months for at least the first 2 years is suggested, after which the chance of a small cell lung cancer being found is less.[91]

Differential Diagnosis

MG is the disorder most commonly in the differential for LEMS. A myopathy, especially dermatomyositis, might present like LEMS in the setting of an underlying small cell lung cancer. Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and other motor predominant subacute neuropathies occasionally mimic LEMS. In the context of small cell lung cancer, the clinical features of LEMS are often attributed to the effects of cachexia and malnutrition. Electrolyte and metabolic abnormalities affecting calcium or magnesium, as well as hypothyroidism are also in the differential.

Management

The most effective symptomatic treatment in LEMS is 3,4-diaminopyridine (3,4-DAP).[92] Through blocking voltage-gated potassium channels, 3,4-DAP prolongs nerve terminal depolarization and increases acetylcholine release.[79,92,93] In small trials, 3,4-DAP has been shown to produce clinical and electrophysiologic benefit in patients with LEMS.[92,94] Improvement after each dose is usually seen within 30 minutes and is maximal at 90 minutes.[92] Starting doses are usually 5 mg to 10 mg three to four times a day, with gradual increases up to 80 mg/d, divided into four to six doses. Many patients respond to 40 mg/d to 60 mg/d. Common adverse effects include perioral and acral paresthesia, maximal about an hour after each dose, nausea, abdominal pain, tachycardia, and palpitations.[92,95] Insomnia is minimized by avoiding the last dose at bedtime. Doses of more than 100 mg/d may increase the risk of seizures, although this is likely a rare adverse effect.[92,95] Seizures are more likely with other predispositions, so caution is advised with brain metastases or the use of other medications that might lower the threshold for seizures.

In theory, pyridostigmine should be synergistic with 3,4-DAP but many patients with LEMS have no benefit from pyridostigmine either on its own or in combination with 3,4-DAP.[96,97]

Given its immunopathogenesis, immunosuppression may also be useful to treat LEMS.[97] The choice of immunosuppressant drugs in LEMS is similar to MG. However, avoiding immunosuppression in paraneoplastic LEMS may

be advisable because of concerns about reduced immunosurveillance and tumor progression. Immunosuppressants can be useful in primary autoimmune LEMS if 3,4-DAP alone is insufficient. IVIg, plasma exchange, and rituximab might also be useful, although the evidence for their efficacy in treating LEMS is weaker.[94,97] Treatment of the underlying small cell lung cancer may improve paraneoplastic LEMS, although it is difficult to distinguish an effect of this from immunosuppression.[97,98]

Prognosis

Primary autoimmune LEMS has an excellent prognosis, and most patients respond well to treatment, although lifelong treatment is often required. The prognosis in paraneoplastic LEMS is poor and is determined by the underlying small cell lung cancer.[97] The presence of LEMS may improve the prognosis compared with small cell lung cancer without LEMS.[97,99,100]

Trends

3,4-DAP is likely to remain the mainstay of symptomatic treatment in patients with LEMS. Current trials hope to obtain regulatory approval, making it easier to obtain, although concerns exist about whether the cost of approved products will be out of reach of many patients. Experimental approaches to pharmacologic improvement of calcium influx and presynaptic acetylcholine release are also being investigated.[79]

CONCLUSION

The diagnosis and, to a certain extent, specifics of management of MG are aided significantly by results of serologic assays. Most patients with MG respond to treatment, and a lack of response may mean that the diagnosis is incorrect or that the target symptoms are not directly related to the disease. Symptomatic treatment with pyridostigmine helps many patients with MG, although it is less effective for patients with ocular MG. Many options exist for immunosuppression, the choice of which often depends on practitioner familiarity. The goal should be to balance benefits with potential adverse effects; with patience, most patients will respond to lower doses than are commonly used. An underlying small cell lung cancer will be found in more than one-half of patients with LEMS. 3,4-DAP is the most effective symptomatic treatment in LEMS, and immunosuppression is best reserved for nonparaneoplastic LEMS that does not respond to 3,4-DAP.

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