Update in the Management of Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome

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KEYWORDS

- Lambert Eaton myasthenic syndrome • Myasthenia gravis • Weakness
- Complement inhibitor • Thymectomy

KEY POINTS

- History, acuity of presentation, family history, medication and physical exam are very important when evaluating a patient with muscle weakness.
- Disorders of the NMJ often have fatigable weakness. MG usually present with ocular and/ or bulbar symptoms, while LEMS have more arm and leg weakness.
- Choice of medication needs to be taken in contexts of severity of disease, co-morbid diagnosis, and antibody status.

MYASTHENIA GRAVIS
Clinical Features

Fatigable or variable weakness is a hallmark of myasthenia gravis (MG). Ocular symptoms such as diplopia and ptosis are seen in approximately 50% of patients at onset of illness. Within 1 month of onset of symptoms, 80% of patients will have some degree of ocular involvement. Presenting symptom of generalized weakness, leg weakness, or bulbar symptoms each account for about 10% of the patients. Patients lack sensory symptoms and prominent muscle pain. On examination patients may demonstrate variable extraocular movement with normal pupillary reflexes, ptosis, nasal speech, flaccid dysarthria, and/or variable weakness with manual muscle strength testing. However, at times the patient's examination maybe completely normal at the time of their clinic visit.

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Diagnosis

Acetylcholine receptor

MG is an autoimmune disorder caused by the production of antibodies directed against the nicotinic acetylcholine receptor (AChR). Roughly 80% to 90% of patients with MG will have measurable antibodies to the AChR in their serum. Overall antibody testing for AChR is fairly specific, with false-positive antibodies being extremely rare from a reliable laboratory. Thymoma is present in about 10% of patients with AChR-positive MG (and most of them have thymic hyperplasia). Therefore, patients positive for AChR antibodies must be screened with a computed tomography (CT) or MRI of the chest for thymoma.

In patients without AChR antibodies, muscle-specific receptor tyrosine kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4) antibodies maybe found.

Muscle-specific receptor tyrosine kinase

The second most common antibody found is MuSK antibody. Series vary in the percentage found to be positive for MuSK but in general about one-fourth of all patients negative for AChR will be found positive for MuSK (roughly 25% of all patients negative for the AChR Ab or 5% of all patients with autoimmune MG). MuSK patients often have distinctive clinical characteristics. Such patients tend to be younger women (younger than 40 years) with disproportionate bulbar, neck extensor, shoulder, and respiratory symptoms with increased likelihood of "fixed weakness" and have a lower likelihood of abnormal repetitive stimulation and edrophonium test results. MuSK patients have no associated thymus abnormalities (and are not candidates for thymectomy) and are more likely to be refractory to a variety of therapies (such as cholinesterase inhibitors and many immune therapies). Conversely the MuSK patients tend to respond very favorably to rituximab and plasmapheresis.

Low-density lipoprotein receptor-related protein 4

A less common MG antibody seen in patients without AChR and MuSK (often referred to as the "double-negative" patients) is the LRP4. The LRP4 antibody is found in about 1% to 2% of all patients with autoimmune MG. The LRP4-positive patients do not have association with thymic pathology, and thymectomy is not indicated in their management. Patients with LRP4 MG were noted to have a younger age of onset and was more common in women compared with other "double-negative" patients who do not have LRP4. LRP4 patients tend to have relatively mild severity and often have pure ocular manifestations, and LRP4 patients are observed to generally respond favorable to pyridostigmine or prednisone.[1] Studies looking at patterns of clinical characteristics and distinctive responses to the various MG treatment options are ongoing. Regarding specificity, LRP4 antibodies have also been found in occasional patients with amyotrophic lateral sclerosis and thus positive results should be interpreted in the proper clinical context.[2]

Anti-agrin

Occasional patients without AChR, MuSK, and LRP4 ("triple-negative" patients) are found to have anti-agrin antibodies.[3] However, most cases of anti-agrin antibodies are also found along with MuSK, LRP4, or AChR antibodies.[4] Agrin is a protein of the basal lamina with 2 isoforms. Neural agrin seems to bind to LRP4, which activates MuSK, leading to clustering of AChR.

Electrophysiological testing

When antibody testing is negative (10%–15% of patients with MG), Electromyography (EMG) can aid in the diagnosis. An EMG can confirm a disorder of the NMJ as well as evaluate for other possible causes of weakness including myopathy or motor neuron disease. Repetitive stimulation of a motor nerve at a slow frequency (2–3 Hz) can demonstrate decrement greater than 10% in patients with dysfunction of the NMJ. Decrement is more prominent in patients with postsynaptic disorders than presynaptic. Overall sensitivity is about 50% but higher in clinically weak muscles and lower with ocular MG. Single-fiber EMG is more sensitive (about 90%) than repetitive stimulation.

Treatment

First part of management is patient education. The Muscular Dystrophy Association and Myasthenia Gravis Foundation are the 2 organizations that offer educational material and pamphlets for patients. Another crucial part of management is recognizing when to hospitalize a patient with MG. Patients with rapidly worsening symptoms, moderate-to-severe dysphagia, or dyspnea should be evaluated and admitted urgently. Signs of respiratory failure should be monitored closely. Evaluation of MG crisis triggers, such as surgery, medication, infection, hyper- or hypothyroidism, or medication change, should be performed and addressed promptly.

Cholinesterase inhibitors

Pharmacologic treatment should be individualized and based on patient's symptoms and comorbid diagnosis. First-line treatment in MG is reversible cholinesterase inhibitors (CEI) such as pyridostigmine or neostigmine. CEI are generally safe without significant long-term complications. However, too much of CEI can lead to skeletal muscle weakness (cholinergic weakness), uncommon in patients on oral CEI.

Immunotherapy

Corticosteroids

Corticosteroids are commonly used for moderate to severe MG, although prospective controlled trials documenting benefits are lacking. Expert opinion and patient compliance despite complications support its use in patients with moderate to severe symptoms. There is no consensus on dosing of corticosteroids but typically aim for a higher dose (60–80 mg/d of prednisone) initially. Most of the patients (approximately 80%) will show marked improvement or remission, and only 5% have no response. A lack of response should raise the question of the diagnosis. Typical improvement begins around the 1 to 2 weeks and gradually continues over the next 3 to 9 months. Approximately half of the patients will experience temporary worsening of weakness starting 1 to 2 days after initiating steroids and lasting 3 to 4 days. The weakness can be severe enough in 10% of patients to require ventilation or a feeding tube. Therefore, many patients with moderate to severe disease should be hospitalized for initiation of steroids. An alternating dose (AD) schedule is often used to avoid early exacerbations (prednisone, 25 mg, AD with increasing 12.5 mg every third dose to a maximum dose of 100 mg AD or until optimal improvement occurs). Improvement typically takes longer, with improvement starting around 1 month. Low-AD prednisone with gradual titration was beneficial in ocular MG compared with placebo, although recruitment was much lower than planned.[5] To avoid myasthenia crisis or flare-up of disease, steroids should be slowly tapered at about 10 mg every 1 to 2 months when greater than 20 mg/d and slower taper less than 20 mg/d. If symptoms recur while tapering steroids, a steroid-

sparing medication is initiated to aid in the steroid taper and minimize long-term complications with prednisone.

Alternative Immunosuppressive Drug Therapy

Steroid-sparing immunosuppressive medication is often needed in patients who suffer relapse in symptoms with tapering of steroids, whose steroids are contraindicated, and are intolerant or continue to have symptoms. Azathioprine, mycophenolate mofetil, and cyclosporine have historically been used as steroid-sparing agents. Double-blind controlled studies with cyclosporine demonstrated improvement in strength and symptoms.[6] Mycophenolate mofetil failed to show improvement in 3 months in a controlled double-blind trial.[7] In a second trial mycophenolate was no more effective than placebo in reducing prednisone dose over 9 months in patients who were steroid dependent. However, retrospective studies of mycophenolate mofetil suggest that time to improvement takes longer than 6 to 12 months, and therefore 3 months in the controlled trial may have been too short in duration to demonstrate a statistical improvement.[8] Tacrolimus is used in some centers for refractory MG although studies have failed to demonstrate a major benefit.[9,10] Methotrexate is also used although a recent prospective study failed to demonstrate steroid-sparing benefit in 12 months.[11]

Complement inhibitors

Given that the pathogenesis of MG involves AChR-binding antibodies at the postsynaptic membrane attracting complement and leading to complement-mediated lysis, there is a logical interest in using a monoclonal antibody to block C5 complement and ostensibly reduce complement-mediated lysis and reduce malfunction at the neuromuscular junction. Eculizumab blocks C5 complement and was originally Food and Drug Administration (FDA)-approved for treatment of paroxysmal nocturnal hemoglobinuria. This drug binds to human terminal complement protein C5 and inhibits enzymatic cleavage of C5 to C5a and C5b, thus preventing C5a-induced attraction of proinflammatory cells and related lysis of the postsynaptic membrane. Recent studies (REGAIN) have demonstrated clinical benefit in the treatment of MG.[12] In a 6-month randomized, double-blind, placebo-controlled REGAIN study of eculizumab in 125 patients with refractory generalized, AChR + MG, the primary analysis showed no significant difference between eculizumab and placebo. However, MG exacerbations were seen in 6 (10%) of the patients in the eculizumab group compared with 15 (24%) in the placebo group. A requirement for rescue therapy was seen in only 6 (10%) of the patients in the eculizumab group compared with 12 (19%) in the placebo group. Eculizumab was well tolerated and associated with improvement in activities of daily living, muscle power, functional, and quality of life. Given the mechanism of action of eculizumab, patients are recommended to receive meningococcal vaccination before the first infusion to limit the risk of meningococcal meningitis. Complement is not thought to play a major role in MuSK MG pathophysiology, and therefore complement inhibitors would not be indicated in MuSK + patients.

A subsequent analysis of an open-label extension reported on eculizumab's long-term safety and efficacy (1200 mg every 2 weeks for a median duration of 22.7 month in 117 patients), indicating a favorable safety profile including no cases of meningococcal meningitis. The MG exacerbation rate was 75% less than what patient experienced in the year before beginning eculizumab, and statistically significant improvement in activities of daily living, muscle power, functional, and quality of life were maintained. During this time 56% of patients improved to a clinical state of minimal manifestations or pharmacologic remission. And those patients initially on

placebo in the initial study demonstrated rapid and sustained improvement on open-label eculizumab.[13]

Rituximab

Rituximab is a monoclonal antibody directed against the CD20 antigen on B cells, which has over the last decade become widely used in the treatment of patients with AChR-positive MG and MuSK MG. Major benefit is well established for most of the MuSK-positive patients. Hehir and colleagues[14] reported results of a prospective controlled double-blind trial in MuSK-positive patients with MG. The primary clinical endpoint was the "Myasthenia Gravis Status and Treatment Intensity" (MGSTI), a measure reflecting Myasthenia Gravis Foundation of America (MGFA) postintervention status as well as requirements for additional immunotherapy. With median follow-up of 3.5 years 58% (14/24) of the rituximab-treated patients achieved the primary outcome target compared with 16% (5/31) of controls. In addition, at the time of last visit, 29% of rituximab-treated patients were taking prednisone (mean dose 4.5 mg/d) compared with 74% of controls (mean dose 13 mg/d). This study provides class IV evidence for benefit of rituximab in MuSK patients with MG.

For patients with AChR-positive myasthenia there is abundant anecdotal and retrospective evidence for benefit but overall a more limited success rate in such patients compared with MuSK-positive patients with MG.[15–17] A large retrospective national study in patients with MG from Austria included 56 patients, 70% of which were AChR positive and 25% with MuSK-positive MG (5% seronegative). Three months after rituximab, 14 of 53 (26.4%) patients were in remission. At last follow-up after a median of 20 (10; 53) months, remission was present in 42.9% of patients and another 25% had minimal manifestations. Remission was observed in 71% of the MuSK patients with MG compared with 36% of those with AChR MG. Rituximab usage was without major side effects in this retrospective study.[16]

Plasmapheresis

Plasma exchange (plasmapheresis or PLEX) removes antibodies (including AChR antibodies) from the plasma. Improvement is typically seen within 1 to 2 weeks but only lasting 1 to 2 months. Because of the rapid improvement with PLEX, it is commonly used in MG crises. A typical exchange removes 5 L of plasma every other day for about 5 exchanges. Complications included bradycardia, hypotension, electrolyte imbalance, hemolysis, infection, and access problems. Maintenance PLEX (one exchange every 1–8 weeks) has been used in patients with refractory myasthenia, especially MuSK patients.[18,19]

Intravenous immunoglobulin

High-dose intravenous immunoglobulin (IVIg) and subcutaneous Ig have been associated with clinical improvement in MG symptoms similar to the time-frame of PLEX.[20,21] Improvement can be seen within the first week and last 4 to 8 weeks. The usual dose for IVIg is 2 g/kg spread out over 5 days. Common practice in the management of patients with moderate to severe MG, especially those refractory or intolerant of multiple immune therapies, is to use IVIg not only for acute crisis and exacerbations (for which there are prospective controlled double-blind trial data to support such use) but also for maintenance therapy.[22] Many experienced neuromuscular clinicians use maintenance IVIg in selected cases and provide anecdotal attestation as to its effectiveness in a significant proportion of patients. The lack of published prospective controlled double-blind evidence for IVIg benefit as a maintenance therapy is an understandable barrier to access for IVIg in many patients, particularly given the substantial cost of the drug. Although prospective double-blind trials are in progress, there is substantial

published anecdotal and retrospective literature providing support for this form of maintenance therapy.

A report of 52 patients with MG from one center who had not responded to pyridostigmine, prednisone, azathioprine, or combination were given IVIg as maintenance treatment. Sustained improvement was seen in 37 of these patients, and treatment was continued for an average of 6 years. The improvement was generally mild to moderate in degree without full remission. Favorable response was associated with AChR seropositivity including higher titers, older age-group, and those with bulbar onset. Use of maintenance IVIg was associated with reduced needs for other treatments including CEI, prednisone, and azathioprine.[23]

Complications with IVIg include flulike symptoms, fever, chills, and headache. Decreasing the rate of the infusion and pretreatment with diphenhydramine may improve the side effects. Rare cases of stroke, nephritic syndrome, and renal failure have been reported. Screening for selective IgA deficiency is recommended to avoid anaphylaxis reaction. Compared with PLEX, IVIg is considerate and equally efficacious for severe generalized MG.[22] However, IVIg seems to be superior for pretreatment before thymectomy.[24]

Exercise

Historically patients with MG have often been advised to be cautious about prolonged physical exertion. To learn if progressive resistance training or aerobic training are possible and effective in patients with MG 15 patients with generalized MG were randomly assigned to 20 sessions over an 8-week period. Overall only 1 patient dropped out of the training session, and adverse events were seen in both groups, including 2 with increased bulbar symptoms and 3 with increased fatigue. The progressive resistance-training group showed increases in maximal strength and functional capacity. This study would suggest that most of the patients with MG can tolerate exercise therapy and some demonstrate improved strength and function.[25]

Thymectomy

Association of the thymus gland with MG was first noted around the 1900s, and thymectomy for treatment of myasthenia was initially reported in the 1930s. Around the 1940s this procedure had been considered a standard of care, especially for younger patients and those with moderate to severe disease. Debate over the effectiveness of thymectomy persisted for decades[26] until recently when results of a large randomized international multicenter controlled trial indicated clear benefit in patients having AChR-positive generalized nonthymoma MG.[27]

The MGTX randomized 126 patients to thymectomy plus prednisone or prednisone alone. Patients in this study had been symptomatic for less than 5 years, were seropositive for AChR antibodies, and had MGFA class II to IV clinical involvement. Follow-up was 3 years. Patients in both groups received oral prednisone titrated up to 100 mg alternate day until acquiring a clinical status of minimal manifestations. Extended transsternal thymectomy was performed. Primary outcome measures included clinical status and total prednisone requirement. Secondary outcome measures included serious adverse events, total hospitalization over the 3 years, and surveys for quality of life. Patients randomized to thymectomy had significant improvement in MG symptoms, including an average Quantitative Myasthenia Gravis (QMG) scale (6.15 vs 8.99). Lower dose of prednisone was needed to maintain optimal clinical status (44 mg vs 60 mg alternate day). Complications were similar in both groups. Additional favorable measures the time-weighted average score on the Myasthenia Gravis Activities of Daily Living scale (2.24 vs 3.41), requirement for azathioprine

use (17% vs 48%), and the percent of patients with minimal-manifestation status at month 36 (67% vs 47%). Hospitalizations were lower in the thymectomy group (9% vs 37%).[27]

A subsequent rater-blinded 2-year extension study for patients who completed the initial 3-year MGTX further supported the benefit of thymectomy. Endpoints in the extension study included time-weighted means of the QMG score and the alternate-day prednisone dose from month 0 to month 60. Sixty-eight (61%) of the 111 patients who completed the initial 3-year MGTX entered the extension study and 50 patients completed the 60-month study. At 5 years, patients in the thymectomy plus prednisone group had significantly lower QMG scores and mean alternate-day prednisone doses (24 mg vs 48 mg) than did those in the prednisone group. There is now clear evidence supporting the benefit of thymectomy in the treatment of MG.[28]

In a recent American Academy of Neurology Practice Advisory: Thymectomy for Myasthenia Gravis (Practice Parameter Update) the guidelines listed 2 level B recommendations:

1. "Clinicians should discuss thymectomy with patients who have AChR antibody + generalized MG and are 18 to 65 years of age. The discussion should clearly indicate the anticipated benefits and risks of the procedures and uncertainties surrounding the magnitude of these benefits and risks."
2. Clinicians should counsel patients with AChR antibody + generalized MG considering minimally invasive thymectomy techniques that it is uncertain whether the benefit attained by extended transsternal thymectomy will also be attained by minimally invasive approaches.

Because extended transsternal thymectomy is a big procedure with multiple days of hospitalization, there is an increasing practice to consider the less invasive approach to thymectomy.[29] The International consensus guidance for management of myasthenia gravis states, *"Endoscopic and robotic approaches to thymectomy are increasingly performed and have a good track record for safety in experienced centers. Data from randomized, controlled comparison studies are not available. Based on comparisons across studies, less invasive thymectomy approaches appear to yield similar results to more aggressive approaches."*[22]

Regarding presurgical treatment with IVIg or plasma exchange a randomized clinical trial of 24 patients with MG (IVIg group) received IVIg 1 g/kg/d for 2 consecutive days was compared with plasma exchange 5 L every other day, 10 to 30 days before thymectomy. Intubation period and duration of surgery differed between the plasma exchange and IVIg groups, suggesting that IVIG may be a more effective preoperative option.[24]

Historically there has been limited acceptance of thymectomy for treatment of ocular MG. A recent meta-analysis of studies assessing the outcome of thymectomy in patients with nonthymomatous ocular MG was favorable.[30]

The International consensus guidance for management of MG also provides consensus opinion regarding other clinically relevant question with respect to thymectomy.

"Thymectomy may be considered in patients with generalized MG without detectable AChR antibodies if they fail to respond adequately to IS therapy, or to avoid/minimize intolerable adverse effects from IS therapy." And, *"Current evidence does not support an indication for thymectomy in patients with MuSK, LRP4, or agrin antibodies."*[22]

Neonatal Fc receptor–targeted therapy for myasthenia gravis
Of the many new strategies being considered as novel treatment of MG, there is particular interest in the role of the neonatal Fc receptor. The neonatal Fc receptor

(FcRn) plays an important role in the regulation of IgG levels. The FcRn "saves" IgG from degradation by rescuing and recycling, leading to a longer half-life and greater blood levels than other immunoglobulins. FcRn is present in myeloid cells and in endothelial cells throughout the lifespan. With monoclonal antibody inhibition of FcRn there is an overall reduction in the levels of pathogenic IgG and in preliminary studies in MG biomarker and clinical evidence to suggest a meaningful therapeutic role for treatment of patients with MG. Current ongoing clinical trial results should be anticipated to clarify the role of such strategy in patient management.[31,32]

Medications to avoid

There is an extensive list of medications that have been observed to interfere with neuromuscular transmission and aggravate symptoms in patients with MG. Those drugs most commonly observed to increase symptoms and thus wise to avoid if possible in patients with known MG include chloroquine, quinine, quinidine, procainamide, and botulinum toxin. Aminoglycoside antibiotics should be avoided unless needed for a life-threatening infection. Fluoroquinolones (ciprofloxacin) and erythromycin have significant neuromuscular blocking effects, and some patients will experience worsening of their symptoms on exposure. Telithromycin has been reported to cause life-threatening weakness in patients with MG and should not be used. Neuromuscular blocking drugs such as pancuronium and D-tubocurarine can produce marked and prolonged paralysis in patients with MG. Depolarizing drugs such as succinylcholine can also have a prolonged effect and should be used by a skilled anesthesiologist who is well aware of the patient's MG. Debate continues over the likelihood of current-day iodinated contrast agents to aggravate MG, but the overall risk seems to be low.[33]

A distinctive drug concern is that several therapeutic agents have been found to "induce" autoimmune MG (cause the disease as opposed to aggravating preexisting MG). The most widely studied and reported historically is D-penicillamine, in which about 5% of patients seem to develop MG symptoms and the presence of AChR antibodies. When penicillamine is stopped most patients clinically improve and serology reverts to normal. More recently α-interferon has been observed to induce autoimmune MG. Patients having received a bone marrow transplant may develop MG as part of a chronic graft versus host syndrome.

Of greater recent concern is the observation for immune checkpoint inhibitors (ICI) to induce or aggravate MG and be associated with a relatively severe and at times refractory clinical presentation. The ICI are increasingly and widely used as standard care in the treatment of a variety of malignancies. They include ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab. Checkpoint inhibitor complications include the induction of a variety of immune-mediated conditions that can in some cases be severe and require discontinuation of the ICI and the addition of aggressive immune therapy. Checkpoint inhibitor use in patients with known preexisting autoimmune disease seems to be associated with exacerbation of the preexisting autoimmune disorder in half of such patients and the induction of new autoimmune disease in 30%.[34] Although most patients improved, 17% required a permanent discontinuation of checkpoint inhibitor treatment.[34]

Specific neurologic complications from checkpoint inhibitors are less common, but the risk of MG is of sufficient frequency and severity to warrant attention from the practicing neurologist. Patients can have new onset MG induced by checkpoint inhibitors or a flare-up of preexisting MG. A retrospective review of a large cohort of 65 patients with MG with checkpoint inhibitor exposure emphasized the severity and the rapidly progressive course of MG in such patients and indicated potential benefit with early use of plasma exchange and IVIg.[35]

Congenital myasthenia encompasses a group of rare hereditary disorders of the neuromuscular junction. The patients tend to have life-long relatively stable symptoms of generalized fatigable weakness. These disorders are not immune-mediated and do not respond to immune therapy (steroids, thymectomy, and plasma exchange). Most patients improve on CEI. Although there are many established subtypes of congenital myasthenia, several are noteworthy for their therapeutic options. The *fast-channel congenital myasthenic syndrome* tends to be static or slowly progressive but usually very responsive to combination therapy with amifampridine and pyridostigmine. In *congenital slow-channel myasthenic syndrome* the disease typically worsens over years as the endplate myopathy progresses. Cholinesterase inhibitors typically worsen symptoms, but quinidine and fluoxetine, which reduce the duration of AChR channel openings, are both effective treatments for *slow-channel syndrome*. The *congenital myasthenic syndrome associated with AChR deficiency* tends to be nonprogressive and may even improve slightly as the patient ages. Treatment includes pyridostigmine and/or amifampridine, and ephedrine produces benefit in some. Patients with *endplate acetylcholinesterase deficiency* usually present in infancy or early childhood with generalized weakness, muscle underdevelopment, slow pupillary responses to light, and either no response or worsening with CEI therapy. Albuterol is reported effective in treating patients with *endplate acetylcholinesterase deficiency*. A homozygous mutation of *Dok-7* is responsible for a form of congenital myasthenia characterized by weakness in limbs and trunk but largely sparing the face, eyes, and oropharyngeal muscles. The formation of neuromuscular synapses requires the MuSK. Dok-7 is necessary for the activation of MuSK. Albuterol is reported effective in treating patients with *Dok-7* congenital myasthenia.[36]

LAMBERT-EATON MYASTHENIC SYNDROME
Clinical Features

Lambert-Eaton myasthenic syndrome (LEMS) (also commonly referred to as Lambert-Eaton syndrome and Lambert-Eaton myasthenia) is a presynaptic disease characterized by chronic fluctuating weakness of proximal limb muscles. Symptoms (**Table 1**) include difficulty walking, climbing stairs, or rising from a chair. In LEMS there may be some improvement in power with sustained or repeated exercise. Although the predominant symptoms are those of symmetric proximal weakness particularly involving the lower extremities, up to half of patients have some degree of bulbar involvement[37] and half may complain of ptosis or diplopia,[38] although ocular and bulbar symptoms are typically less pronounced than in patients with MG. In contrast with the MG severe respiratory failure is less common. In addition, patients with LEMS often complain of myalgia, muscle stiffness of the legs and back, limb paresthesia, metallic taste, severe

Table 1	
Symptoms and signs of Lambert-Eaton myasthenic syndrome	
Symptoms	**Signs on Examination**
Proximal limb weakness (legs > arms)	Proximal weakness
Cranial weakness (20%)	Mild cranial weakness
Fluctuating symptoms	Objective weakness is less than predicted based on symptoms
Dry mouth	
Other anticholinergic autonomic symptoms	Absent/reduced muscle stretch reflexes
Metallic taste	Lambert sign (2–3 s of maximal grip produces increase strength)

dry mouth, impotence, and other autonomic symptoms from muscarinic cholinergic insufficiency. The examination typically shows proximal lower extremity weakness, although the objective bedside assessment may suggest relatively mild weakness relative to the patient's history. The muscle stretch reflexes are absent. On testing sustained maximal grip there is a gradual increase in power over the initial 2 to 3 seconds (Lambert sign).

Overall LEMS is rare compared with MG, which is about 100 times more common. About half of patients with LME have an underlying malignancy that is usually small cell carcinoma of the lung. Occasional patients will have a small cell carcinoma originating elsewhere in the body.[39] Patients with LEMS should be evaluated with CT scan and fluorodeoxyglucose PET to evaluate for underlying tumor. If no tumor is found, evaluation and screen should be repeated at regular intervals (ie, every 6 months for about 2–4 years). In patients without malignancy, LEMS is an autoimmune disease and is often associated with other autoimmune diseases. In general, patients older than 40 years are more likely to be men and have an associated malignancy, whereas younger patients are more likely to be women and have no neoplasm. LEMS symptoms can precede detection of the malignancy by 1 to 2 years. Another serologic indicator of associated small cell lung cancer is the SOX1 antibody, an immunogenic tumor antigen in SCLC. SOX1 antibodies were detected in 64% of patients with LEMS with SCLC but in none of 50 patients with nonparaneoplastic LEMS.[40]

Diagnosis

The pathogenesis involves autoantibodies directed against presynaptic P/Q-type voltage-gated calcium channels at cholinergic nerve terminals, resulting in reduced presynaptic calcium concentration and reduced quanta release of acetylcholine These IgG antibodies also inhibit cholinergic synapses of the autonomic nervous system. More than 90% of patients with LEMS are seropositive, and thus serologic testing is essential in screening and confirming the diagnosis. The diagnosis is confirmed with EMG studies, which typically show low amplitude of the compound muscle action potentials and a decrement to slow rates or repetitive stimulation in more than 95% of patients. Following brief exercise, there is marked facilitation of the CMAP amplitude (greater than 100% increase) in 90% of patients. At high rates of repetitive stimulation, there may be an incremental response. Single-fiber EMG is markedly abnormal in virtually all patients with LEMS.

Treatment of Lambert-Eaton Myasthenic syndrome

Treatment options include treating of the underlying small cell lung cancer when present, use of cholinesterase inhibitors such as pyridostigmine, use of voltage-gated potassium channel blocker 3,4-diaminopyridine/amifampridine, and for severe and refractory patients, treatment with immunotherapy.[41]

Cancer treatment: successful treatment of small cell lung cancer can in some patients be "curative" for LEMS. Evaluation of the impact of concurrent LEMS on the survival of patient with small cell lung cancer suggests that the presence of LEMS with small cell lung cancer conferred a significant survival advantage independently of the other prognostic variables.[42]

3,4-diaminopyridine/amifampridine

First-line medical therapy involves the use of 3,4-diaminopyridine/amifampridine. Both names refer to the same drug. There are currently 2 slightly different preparations of this drug made by different manufacturers, both of which have received FDA approval for the treatment of LEMS. Amifampridine/3,4-diaminopyridine is a quaternary

ammonium drug that exerts its effect by blocking the presynaptic voltage-gated potassium channels and in doing so keeps the motor nerve terminal depolarized longer, thus allowing more time for calcium channels to remain open, leading to increased calcium concentration at the motor nerve terminal, thus enhancing the presynaptic release of ACh. Ever since the initial prospective double-blind placebo-controlled studies showing benefit of 3,4-diaminopyridine in the 1989,[43] patients have been required to receive such medication through approved research centers until the recent FDA approval of 2 forms of amifampridine resulting in the drug being commercially available. Amifampridine phosphate is the active ingredient of FDA-approved form named *Firdapse*.[44] In 2018 the FDA approved *Firdapse* amifampridine for treatment of adults aged 17 years and older with LEMS. The second form of amifampridine, historically referred to as 3,4 diaminopyridine, has also demonstrated clear benefit in patients with LEMS,[45] and in 2019 this base form of amifampridine called *Ruzurgi* became FDA approved for treatment of juvenile LEMS (age 6 years to <17 years). Accordingly, the potential access to these drugs with FDA approval has markedly improved. Both agents have proved efficacy. Although there are now 2 FDA-approved drugs for treatment of LEMS, a new challenge involves cost of the drug and insurance coverage. Before FDA approval patient would acquire the drug through neuromuscular centers having an investigation new drug program to allow access at no or minimal financial cost. As of 2020 the established charge for *Ruzurgi*-Jacobus is $80/10 mg pill. *Firdapse*-Catalyst established charge in 2020 is $180/10 mg pill. Programs exist although both manufacturers provide cost assistance for patients with limited resources. One difference in the 2 products is that *Ruzurgi* requires refrigeration and *Firdapse*, being more stable, does not. Concerns over the processes and policies of the FDA in approval for 2 competing manufacturers of similar drugs and potential negative consequences have been expressed by the neuromuscular physician community.[46] Side effects include transient paresthesia (10%) and rarely seizures, especially in high doses. A comparison of dosing recommendations for these agents is found in **Table 2**.

Table 2 Amifampridine[47,48]	Firdapse®	Ruzurgi®
FDA approval	>17 y/o with LES	617 y/o with LES
Starting Dose	15mg-30 mg PO divided 3–4 times a day[a]	Wt. ≥45 kg start 15–30 mg (wt. <45 kg start 7.5–15 mg) daily PO divided 2–3 times a day
Dose titration	5 mg daily every 3–4 d	Wt. ≥45 kg increase 5–10 mg divided (wt. <45 kg increase 2.5 mg to 5 mg) in up to 5 doses daily
Maximum dose	20 mg single dose and 80 mg daily	Wt. ≥45 kg 30 mg single dose and 100 mg daily Wt. <45 kg 15 mg single dose and 50 mg daily dose
Refrigeration	Not needed	Needed
Contraindications	Seizures	Seizures

[a] Starting dosage is 15 mg daily for patients with renal impairment, hepatic impairment and in known N-acetyltransferase 2 (NAT2) poor metabolizers.

Data from Jacobus Ruzergi prescribing information. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209321s000lbl.pdf); and Catalyst Firdapse prescribing information. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208078s000lbl.pdf).

Although pyridostigmine offer limited benefit in patients with LEMS, it is safe and in many patients significantly effective. This drug is also widely available and relatively inexpensive.

Lambert-Eaton myasthenic syndrome
Immune therapy Prednisone, azathioprine, rituximab, IVIg, and plasma exchange are all used in patients having limited benefit from amifampridine.[41]

CLINICS CARE POINTS

- Patients with a disorder of the NMJ and rapid deterioration or moderate to severe dysphagia or dyspnea should be hospitalized.
- Patients with MG may temporarily deteriorate after starting steroids before they improve, therefore patients should be monitored closely and may need to be hospitalized when initiating steroids.
- Tapering immunotherapy very slowly in patients with MG to prevent MG crisis.
- Patient's should receive meningococcal vaccination at least 2 weeks prior to starting a complement inhibitor.
- Providers should discuss thymectomy with patients who have AChR antibody with generalized MG and are 18 to 65 years of age.

DISCLOSURE

The authors have nothing to disclose.

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