Lambert-Eaton Myasthenic Syndrome, Botulism, and Immune Checkpoint Inhibitor–Related Myasthenia Gravis

By Amanda C. Guidon, MD

REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: **This article reviews the pathophysiology, epidemiology, clinical presentation, diagnosis, and treatment of Lambert-Eaton myasthenic syndrome (LEMS) and of botulism, and immune-related myasthenia gravis (MG) occurring in the context of immune checkpoint inhibitor therapy for cancer.**

RECENT FINDINGS: **The suspicion that LEMS is rare but also likely underdiagnosed is supported by recent epidemiologic data. A validated, LEMS-specific scale now exists to assess and monitor disease, and symptomatic and immunomodulatory treatments are available. As presynaptic disorders of neuromuscular transmission, LEMS and botulism share electrodiagnostic abnormalities but have important distinguishing features. Knowledge of the clinical features of botulism is needed, particularly with continued cases of infant botulism, the opioid epidemic increasing the incidence of wound botulism, and medical use of botulinum toxin, which may cause iatrogenic botulism. Foodborne botulism remains rare. Prompt recognition of botulism and administration of antitoxin can improve outcomes. MG may be exacerbated or may present de novo in the context of immune activation from immune checkpoint inhibitor therapies for cancer. Immune-related MG commonly overlaps with myositis and myocarditis. Corticosteroids typically result in improvement. However, immune-related MG can be more fulminant than its idiopathic counterpart and may cause permanent disability or death.**

SUMMARY: **The diagnosis of LEMS, botulism, or immune-related MG can generally be made from the patient's history, supplemented with directed questions, a physical examination designed to demonstrate abnormalities, and laboratory and electrodiagnostic testing. Early diagnosis and carefully selected treatment not only improve outcomes of the neuromuscular disease but can affect the prognosis of underlying malignancy, when present.**

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Address correspondence to Dr Amanda C. Guidon, Neuromuscular Diagnostic Center, 165 Cambridge St, Ste 820, Boston, MA 02114, *aguidon@partners.org*.

RELATIONSHIP DISCLOSURE:
Dr Guidon has served on the medical advisory board for Alexion Pharmaceuticals, Inc, and as a consultant for Momenta Pharmaceuticals, Inc. Dr Guidon has received clinical trial research/grant support from Momenta Pharmaceuticals, Inc; the Patient-Centered Outcomes Research Institute; and Ra Pharmaceuticals, Inc, and publishing royalties from Oakstone Publishing, LLC.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Guidon discusses the unlabeled/investigational use of immunosuppressant therapies for the treatment of myasthenia gravis and Lambert-Eaton myasthenic syndrome.

INTRODUCTION

Diseases that affect the neuromuscular junction cause fluctuating muscle weakness. Certain groups of muscles are characteristically involved in each disease. The most common disorder of neuromuscular transmission is myasthenia gravis (MG). Although they are distinct from and much less common than MG, it is important for neurologists to know how to recognize and treat Lambert-Eaton myasthenic syndrome (LEMS) and botulism. A variant of MG related to immune checkpoint inhibitor therapy for cancer has also recently been described. This article identifies the clinical features of these uncommon neuromuscular junction disorders and outlines their management.

LAMBERT-EATON MYASTHENIC SYNDROME

LEMS is the prototypical presynaptic disorder of neuromuscular transmission.

Pathophysiology

In the healthy neuromuscular junction, the P/Q-type voltage-gated calcium channel (VGCC) on the presynaptic nerve terminal provides the calcium influx that triggers acetylcholine (ACh) release. In LEMS, antibodies to the pore-forming α1 subunit of VGCCs result in reduced numbers of VGCCs, disorganized transmitter release sites, and upregulation of other calcium channels.[1,2] As a result, calcium influx into the nerve terminal is reduced, and depolarization results in fewer quanta of ACh released into the synaptic cleft. This may cause failure of neuromuscular transmission and muscle weakness. The same process at autonomic synapses produces autonomic dysfunction.[3–5] Patients with LEMS without measurable P/Q-type VGCC antibodies (who are "seronegative") likely have other autoantibodies to presynaptic proteins with the same physiologic outcome.[2,6]

In paraneoplastic LEMS, the immune system develops antibodies against cancer proteins. Because tumor cells in small cell lung cancer have neuroendocrine origin, they express the same types of VGCCs as nerve terminals.[1,2] VGCCs are also expressed in the cerebellum. Patients with small cell lung cancer, with or without LEMS, may also have cerebellar dysfunction and VGCC antibodies.[7,8] Paraneoplastic LEMS also occurs in lymphoproliferative disorders in children and rarely in other adult cancers. The etiology of nonparaneoplastic LEMS is unknown. It often coexists with other autoimmune disorders and, rarely, with MG.[9,10]

Epidemiology and Natural History

A 2017 US Department of Veterans Affairs (VA) population study provided additional insight into the contemporary epidemiology and natural history of LEMS.[11] Confirmed cases were 2.6 per one million, which mirrors an earlier study from the Netherlands.[7,11,12] The VA prevalence rose to 3.3 per million when probable cases were included and 5.5 per million when possible cases were included.[11,13] Based on 2018 population estimates, about 1000 patients likely have LEMS in the United States, with an estimated 170 new cases annually.[14–16] To put this in perspective, in two large academic neuromuscular clinics, LEMS was typically diagnosed approximately one-tenth as frequently as MG.[17,18]

In addition to being a rare disease, LEMS is also likely underdiagnosed.[12,19] In patients with cancer, weakness may be attributed to malignancy and

associated treatments; some patients with LEMS likely never seek neurologic care. A prospective study illustrated that approximately 3% of patients with small cell lung cancer have LEMS. However, routine measurement of VGCC antibodies in patients with small cell lung cancer is not currently recommended in the absence of clinical symptoms.[20] In non-neoplastic LEMS, proximal weakness may be mistaken for a limb-girdle muscular dystrophy. Additionally, in LEMS, patient-reported symptoms typically outweigh abnormal findings on examination. This is different than what neurologists are accustomed to seeing in patients with MG, who often have objective weakness in excess of symptoms. All these factors contribute to the diagnostic challenge in LEMS. Several strategies may help clinicians suspect and diagnose LEMS:

- Ask about symptom fluctuation in patients with proximal lower extremity weakness and gait dysfunction
- Obtain electrodiagnostic studies in patients who describe symptoms of LEMS even if bedside examination is normal
- During nerve conduction study testing, check for postexercise facilitation and decrement on 3-Hz repetitive nerve stimulation in patients with low-amplitude compound muscle action potentials (CMAPs)

LEMS is infrequently reported in children[21] and typically affects patients in their fifties and sixties, with an overall male predominance of about 60%. Approximately 50% to 60% of patients have an underlying malignancy (cancer-associated LEMS). The duration from symptom onset to diagnosis averages 10 to 11 months overall, but the range is significant (mean of 4 months in cancer-associated LEMS to 16 months in non–cancer-associated LEMS).[11] Cancer-associated LEMS may have a more fulminant course, which is a possible explanation for earlier diagnosis.[12] In approximately 60% of the LEMS cases associated with small cell lung cancer in the VA study, the diagnoses of cancer and LEMS were made concurrently. It is important to remember, however, that cancer may precede LEMS or may only be found on follow-up surveillance.[11]

Neurologists are tasked with counseling patients about expectations for natural history. It may reassure patients to know that they typically reach their maximum disease severity upon or shortly after LEMS diagnosis. This is different from MG, in which early disease fluctuation is common for the first few years. In a retrospective analysis in a varied cohort with a mixture of treatments, approximately 70% of patients had some clinical improvement with treatment. Marked improvement was seen in some cases, but complete resolution of symptoms was rare.[11] No LEMS-specific quality-of-life scale exists at this time. Prognosis is determined by the patient's underlying malignancy, if present. The presence of LEMS appears to improve the cancer-related prognosis in small cell lung cancer.[22]

Clinical Features

The clinical presentation of LEMS is quite distinct and does not typically mirror the presentation of MG; therefore, neurologists often will suspect one disease or the other in any individual patient. LEMS most commonly presents with lower extremity weakness. A triad of gait dysfunction/lower extremity

KEY POINTS

- In Lambert-Eaton myasthenic syndrome (LEMS), pathogenic P/Q-type voltage-gated calcium channel antibodies cause fewer quanta of acetylcholine to be released from presynaptic nerve terminals.
- Failure of neuromuscular transmission in LEMS results in symptoms of skeletal muscle weakness and autonomic dysfunction.
- LEMS is a rare disease that affects mostly adults and is likely underdiagnosed.
- More than half of patients with LEMS have an underlying cancer, most commonly small cell lung cancer, diagnosed within 2 years of disease onset.
- LEMS is generally a treatable disorder that may even improve the prognosis related to small cell lung cancer, when present.

weakness, areflexia/hyporeflexia, and autonomic dysfunction may be observed, but not all three symptoms are present in every patient. Weakness in LEMS is rarely life-threatening, and respiratory dysfunction is rare. In contrast to MG, ocular, bulbar, and axial muscle weakness is often mild and may be absent altogether.[23]

Patients rarely present with reports of autonomic symptoms in LEMS. Neurologists must ask about autonomic symptoms directly and observe for signs of autonomic dysfunction on examination. Autonomic dysfunction can present as dry mouth, with some patients describing a characteristic metallic taste. A clue to this symptom can be the patient carrying a water bottle or sucking on a hard candy. Dry eyes, orthostatic hypotension, constipation, and, in men, erectile dysfunction may also be present. Autonomic dysfunction is typically accompanied by skeletal muscle weakness and rarely exists in isolation.[23]

Patients with LEMS frequently report subjective symptoms that exceed abnormal findings on examination. This mismatch may contribute to underdiagnosis. On motor examination, patients have proximal lower extremity weakness, which may improve after brief exercise. A waddling gait is sometimes observed. This may be appreciated by having patients walk down a hallway for a distance and observing for fatigability or facilitation. Deep tendon reflexes are attenuated or absent, particularly in the lower extremities. It is helpful to test reflexes before manual muscle testing to avoid inadvertent facilitation and then observe for any reflex augmentation after 10 seconds of exercise of the corresponding muscle or repeated tapping of the tendon. If gait ataxia is pronounced, concurrent cerebellar dysfunction must be considered and tested for on examination. Autonomic dysfunction manifests on examination as orthostatic hypotension with an invariant heart rate, dry mouth, or poorly reactive pupils.[23]

Diagnosis

LEMS diagnosis is made by a combination of the clinical history, serologic testing for pathogenic autoantibodies, and electrodiagnostic studies.

ANTIBODY TESTING. Positive serologic testing for P/Q-type VGCC antibodies or characteristic abnormalities on electrodiagnostic studies, or both, confirms diagnosis. Approximately 85% of patients overall and nearly 100% of patients with paraneoplastic LEMS have P/Q-type VGCC antibodies, which are pathogenic. PQ-type VGCC antibodies may be tested as part of a paraneoplastic panel. N-type VGCC antibodies may also be positive in the same patient but are nonspecific in isolation.[24] It is important to remember that P/Q-type VGCC antibodies may be present in patients without manifestations of LEMS. In one study, 1.7% of healthy controls and 4% of neurologically asymptomatic lung cancer controls had VGCC antibodies (including N-type and P/Q-type).[24] To the author's knowledge, the exact specificity of P/Q-type VGCC antibodies for LEMS has not been rigorously evaluated. However, given these data and personal experience, the author performs focused electrodiagnostic studies to confirm a presynaptic disorder of neuromuscular transmission even in patients with antibodies.[25] If patients have persistently abnormal P/Q-type VGCC antibodies on repeat testing in the absence of LEMS, the author recommends an initial malignancy screen.

ELECTRODIAGNOSTIC STUDIES. It is not uncommon for a diagnosis of LEMS to be first suspected by an astute electromyographer during electrodiagnostic testing, when a patient referred for another indication has diffusely low-amplitude CMAPs and further study is performed. Tailored electrodiagnostic studies for LEMS include routine nerve conduction studies with assessment for postexercise facilitation, concentric needle EMG, and slow (3-Hz) repetitive nerve stimulation, if needed.[26] Routine electrodiagnostic studies also help exclude other causes of proximal weakness (eg, myopathy or polyradiculopathy). In LEMS, CMAPs have low baseline amplitudes that facilitate after 10 seconds of maximal voluntary contraction. The amount of postexercise facilitation is often 100% to 400% (ie, resulting in double to quadruple the baseline amplitude). Muscles must be warmed to 34°C (93.2°F) and tested after 5 minutes of rest to maximize the sensitivity for diagnosis. High-frequency (20-Hz to 50-Hz) repetitive nerve stimulation can demonstrate facilitation if patients cannot exercise voluntarily. This high-frequency testing is uncomfortable, prone to artifact, and typically unnecessary. While low baseline CMAP amplitudes are the hallmark of LEMS, an amplitude decrement of greater than 10% on 3-Hz repetitive nerve stimulation of distal muscles is more sensitive for diagnosis, particularly in patients with mild weakness (CASE 13-1). Importantly, facilitation or decrement may not be present in every muscle.[27] The author tests two to three distal nerve-muscle combinations in the hand and foot (eg, median abductor pollicis brevis, ulnar abductor digiti minimi, and fibular [peroneal] nerve and extensor digitorum brevis) to maximize diagnostic sensitivity.[26]

Single-fiber EMGs are almost always abnormal but usually unnecessary for diagnosis given the high sensitivity of routine electrodiagnostic studies. Abnormal jitter directly correlates with disease and electrodiagnostic severity and may be dependent on firing rate.[28] The author uses single-fiber EMG for diagnosis only in patients who have signs/symptoms of LEMS but no evidence of a disorder of neuromuscular transmission on routine studies.

DIFFERENTIAL DIAGNOSIS AND WORKUP. The differential diagnosis of LEMS includes other causes of proximal weakness or autonomic dysfunction. The leading mimics are myopathy, lumbosacral radiculopathy, and general cachexia or failure to thrive from cancer or cancer therapy. Other causes of autonomic dysfunction and MG can also be considered. The author recommends the following investigations:

- For the initial workup, check VGCC antibodies with a paraneoplastic panel, which should also include ACh receptor antibodies
- Test creatine kinase and proceed with routine electrodiagnostic testing
- Once the diagnosis is made, perform age- and sex-appropriate malignancy screening and a CT of the chest, abdomen, and pelvis
- If the initial CT is negative, perform a positron emission tomography (PET) CT
- If the initial malignancy workup is negative, repeat screening at 3- to 6-month intervals during the first year
- Continue periodic screening until 2 years after LEMS diagnosis[29]

Measuring Disease Severity

Recent clinical trials in LEMS used different outcome measures to monitor disease and demonstrate drug efficacy.[16,30] The Triple Timed Up and Go test (3TUG) is a

KEY POINTS

- Symptoms of LEMS include a triad of gait dysfunction/lower extremity weakness, areflexia or hyporeflexia, and autonomic dysfunction.
- Patients should be specifically asked about autonomic symptoms of LEMS, including constipation, dry mouth, and orthostasis.
- Symptoms of LEMS typically exceed abnormal findings on examination; therefore, a high clinical suspicion is needed for diagnosis.
- Most patients with LEMS have diagnostic P/Q-type voltage-gated calcium channel antibodies.
- Electrodiagnostic studies are warranted in patients with LEMS, even in patients with positive antibody testing, to confirm a presynaptic disorder of neuromuscular transmission.
- In LEMS, low-amplitude compound muscle action potentials that facilitate after 10 seconds of exercise and show a decrement in distal nerve-muscle combinations with 3-Hz repetitive nerve stimulation are seen.
- Once the diagnosis of LEMS is suspected, patients should be screened for malignancy. If initial testing is negative, screening continues for up to 2 years.

simple, noninvasive assessment that measures weakness in thigh and hip girdle muscles. To perform the 3TUG, the patient stands up from being seated on a standard armless hard chair and walks 3 meters (approximately 10 feet), then returns and sits back down, touching his/her back to the back of the chair. This is repeated for two more laps, and then the times for the three laps are averaged.[31] The 3TUG has been shown to be reliable and valid in LEMS.[31,32] Repeated laps measure fatigability or improvement of neuromuscular weakness. MG-specific

CASE 13-1

A 50-year-old man presented with a several-month history of trouble climbing stairs. He was taking statins for hyperlipidemia and had a 30 pack-year history of tobacco abuse. He denied sensory symptoms but reported chronic low back pain.

Examination revealed mild bilateral proximal upper and lower extremity weakness. Sensation was normal, and deep tendon reflexes were attenuated but present throughout. Creatine kinase level was normal. Electrodiagnostic evaluation was performed for possible myopathy or lumbosacral radiculopathy.

Nerve conduction studies showed that upper and lower extremity sensory nerve action potentials (SNAPs) were normal. Compound muscle action potentials (CMAPs) were reduced in amplitude with facilitation of 100% to 300% after 10 seconds of exercise (FIGURE 13-1). Repetitive nerve stimulation of the ulnar abductor digiti minimi and fibular (peroneal) extensor digitorum brevis nerve-muscle combinations at 3 Hz showed postexercise facilitation followed by postactivation exhaustion. An amplitude decrement of more than 10% was seen (FIGURE 13-2). Needle EMG was normal in upper and lower extremities and thoracic paraspinal muscles, except for motor unit potential instability. Laboratory testing showed the presence of P/Q-type voltage-gated calcium channel antibodies.

Upon further examination, the patient was noted to have dry mouth, orthostatic hypotension with an invariant heat rate, and facilitation of reflexes after brief exercise.

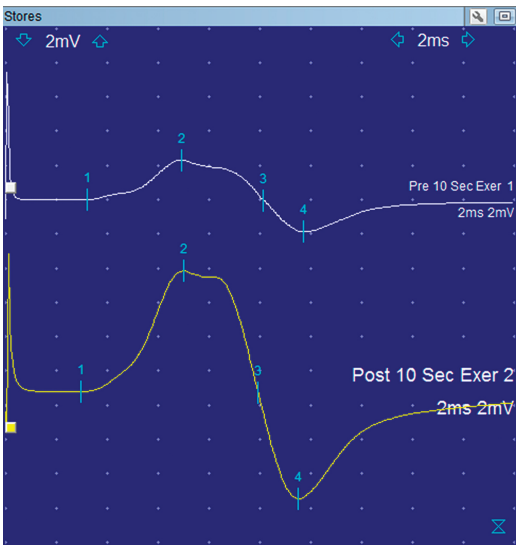

FIGURE 13-1
Electrodiagnostic study of the patient in CASE 13-1. Ulnar abductor digiti minimi response with stimulation at the wrist after 5 minutes of rest was 2.3 mV in amplitude. Amplitude facilitated to 7.1 mV after 10 seconds of exercise.

scales can also be used but often do not fully reflect disease severity; they focus on ocular and bulbar weakness, which is notably absent or minimal in LEMS.

Treatment

Treatment of LEMS first includes symptomatic therapy with either the free base 3,4-diaminopyridine (3,4-DAP) or amifampridine phosphate. By blocking presynaptic potassium channels, both drugs prolong depolarization, VGCCs

Chest CT revealed a pulmonary nodule, which was biopsied and found to be small cell lung cancer.

Treatment began with 3,4-diaminopyridine (3,4-DAP) and pyridostigmine before his cancer surgery, and he underwent subsequent chemotherapy. Medications that could worsen neuromuscular transmission were avoided. Symptoms improved markedly on 3,4-DAP and pyridostigmine, and he did not require immunosuppressive therapy.

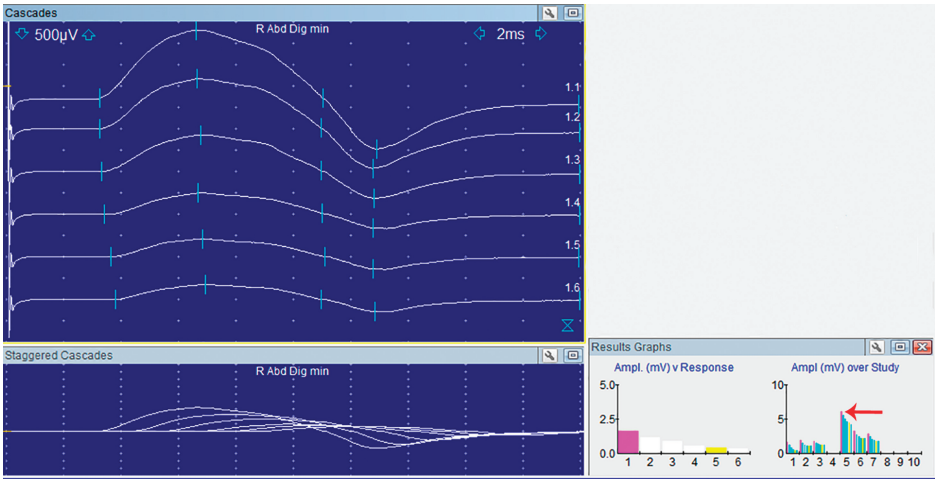

FIGURE 13-2

Electrodiagnostic study of the patient in CASE 13-1. 3-Hz repetitive nerve stimulation of the ulnar nerve recording from the abductor digiti minimi. Notice the baseline low amplitude (1.6 mV) with abnormal decrement without a saddle shape in the baseline trains. After 10 seconds of exercise, the amplitude of stimulus 1 facilitates to 6 mV (normal) briefly for one train (*red arrow*) and then decreases again. A significant decrement is also seen between stimuli 1 and 5 in subsequent trains.

COMMENT

This case represents an approach to the early diagnosis and treatment of cancer-associated Lambert-Eaton myasthenic syndrome. The prognosis was based on the patient's malignancy.

remain open longer, and presynaptic entry of calcium is increased. Because quantal release of ACh depends on intracellular calcium, release of ACh is also increased. Amifampridine phosphate/3,4-DAP improve symptoms of weakness and autonomic dysfunction in approximately 85% of patients.[16] Although efficacy of 3,4-DAP was first reported in the 1980s, two phase 3 clinical trials, one using the base formulation and the other using the phosphate salt formulation, demonstrated efficacy in LEMS.[16,30] The base is refrigerated and the phosphate salt formulation is stored at room temperature. Amifampridine phosphate was approved by the US Food and Drug Administration (FDA) in late 2018 for the treatment of adult patients with LEMS.[33] 3,4-DAP received FDA approval in mid-2019 for treatment of LEMS in children aged 6 up to 17.[34]

Amifampridine phosphate and 3,4-DAP are dosed similarly, except that amifampridine has a lower maximum dose of 80 mg/d in the FDA's labeling. Patients are typically started on a dose of 15 mg/d to 30 mg/d divided into three or four doses. The dose is increased gradually by 5 mg/d every 3 to 14 days to a maximum total daily dose of 80 mg/d to 100 mg/d. A single dose typically does not exceed 20 mg. Patients with hepatic or renal dysfunction should start at the lower end of the dosing range. Side effects are typically minimal and include digital and perioral paresthesia. Patients have experienced seizures with higher doses or when used in combination with drugs that can lower the seizure threshold. Therefore, amifampridine phosphate/3,4-DAP should be used with caution or avoided in patients with a history of seizures. Of note, the FDA labeling for amifampridine phosphate includes seizures as an absolute contraindication for prescribing and a maximum daily dose of 80 mg/d.[33]

Pyridostigmine, an acetylcholinesterase inhibitor, can be added to amifampridine phosphate/3,4-DAP for the treatment of LEMS. Pyridostigmine alone does not typically result in significant improvement of weakness[11]; rather, it can augment or prolong the benefit of amifampridine phosphate/3,4-DAP. By increasing oral secretions, it also treats dry mouth.[23]

Symptomatic therapies are started while the workup for possible malignancy is ongoing. If symptoms do not improve or are severe, IV immunoglobulin (IVIg) or plasma exchange can also be used in this period. The author typically refrains from adding immunosuppressive therapy until the initial malignancy evaluation is complete and the underlying cancer, if found, is treated for two reasons. First, treating the cancer alone may improve the symptoms of LEMS. Second, concern exists about the potential adverse effect of most immunosuppressive therapies on immunologic control of malignancy and interactions with planned anticancer therapies.

Immunosuppressive therapies, including glucocorticoids and steroid-sparing agents, are second- and third-line therapies. In the VA study population, patients received the following therapies, in combination with symptomatic therapy or as independent therapy: glucocorticoids (35%), IVIg (27%), plasma exchange (12%), and other (10%, including azathioprine, mycophenolate mofetil, and rituximab). Of the treatments used, 3,4-DAP showed the highest percentage of symptom resolution and improvement. However, the study was retrospective and too small to assess comparative efficacy. Additionally, the frequent use of glucocorticoids may reflect this population's limited access to 3,4-DAP (used in 38% of patients) during the study period.[11]

Treatment of potential autonomic symptoms warrants additional attention clinically. For orthostatic hypotension, symptomatic therapy with fludrocortisone or midodrine, or both, can be added. If orthostatic symptoms are

severe or functionally limiting, the author adds IVIg/plasma exchange, corticosteroids, or an immunosuppressive therapy.[35]

Avoiding or using medications cautiously that can impair neuromuscular transmission is as important in LEMS as it is in MG, and the list of medications is the same for both disorders. A concise and relevant list was included as an appendix in the 2016 open access international consensus guidance statements for management of MG.[17] An updated list is also referenced on the website of the Myasthenia Gravis Foundation of America.[36] This issue is particularly relevant in LEMS because patients may require surgery for the management of coincident malignancy. Surgery often occurs early in the disease when LEMS is undiagnosed or untreated. Although prolonged muscle weakness and postoperative respiratory failure are uncommon, exposure to neuromuscular blocking agents increases this risk; therefore, they should be avoided or used with caution.[37] Heat and acute febrile illness can also worsen symptoms.[23]

Trends

The landscape of treatment for LEMS in the United States is in flux. For several decades, patients received 3,4-DAP through compounding pharmacies or a compassionate use program through individual Investigational New Drug (IND) programs at low or no cost to patients. However, the recent FDA approvals of amifampridine phosphate and, subsequently, 3,4-DAP have raised uncertainty and discussion about how access to and cost of treatment will be affected.[38] The annual costs to patients and insurers for the required doses of medication is unknown at this time.

BOTULISM

Botulism is a paralytic illness caused by the toxin produced by the bacterium *Clostridium botulinum* (types A and B) and sometimes by strains of *Clostridium butyricum* and *Clostridium baratii* (type F). *C. botulinum* is an anaerobic gram-positive spore-forming bacillus. Botulism spores are ubiquitous but need a low-acid, anaerobic environment to germinate. Clinical disease is caused by one of the subtypes of botulinum toxin (A, B, C, D, E, F, G). Human botulism is most commonly caused by toxin types A, B, E, and F, whereas types C and D mainly affect animals.[39,40]

Pathophysiology

Botulism can be contracted by a variety of mechanisms that have considerable geographic variability. These include home canning, inadequately refrigerated or cooked food, injection drug use (wound botulism), honey (infant botulism), iatrogenic causes, and adult intestinal colonization.

Honey is the only known food cause of infant botulism. Spores from honey germinate in the large intestine, producing botulinum neurotoxin (BoNT), which is absorbed in the bloodstream.[41] Infant botulism can also be related to inhalation of spores from dust and other environmental exposures.

BoNT inhibits neurotransmitter release by interfering with proteins involved in ACh vesicle fusion at the presynaptic nerve terminal. Symptoms of food botulism typically appear within 12 to 36 hours after toxin ingestion, although earlier symptoms or delayed manifestations up to 10 days have been observed.[40] The toxin requires a four-step mechanism to enter and inhibit neurons. First, BoNT binds to the neuronal membrane and is internalized and translocated. Then, it cleaves one of three soluble *N*-ethylmaleimide–sensitive factor

KEY POINTS

- The Triple Timed Up and Go test is a reliable and validated outcome measure that can be easily performed in clinic and is used to monitor disease severity in clinical trials of patients with LEMS.
- Amifampridine phosphate and 3,4-diaminopyridine are the primary symptomatic therapies for LEMS. Immunosuppressive therapies are second- or third-line therapies.
- Botulinum neurotoxin is produced by an anaerobic gram-positive spore-forming bacillus. The toxin inhibits presynaptic acetylcholine release in motor and autonomic nerves.

attachment protein receptor (SNARE) proteins, which normally regulate ACh vesicle fusion and release. Toxin types A and E cleave synaptosomal associated protein of 25 kDa (SNAP-25), whereas types B, D, F, and G affect synaptobrevin and type C affects syntaxin and SNAP-25. The result is reduced presynaptic ACh release and, thus, impaired transmission in both motor and autonomic nerves.[40]

Epidemiology

The Centers for Disease Control and Prevention (CDC) publishes a surveillance report annually, categorizing human botulism cases into four transmission routes: foodborne, wound, infant, and other (which includes iatrogenic).[42] All types can be caused by botulinum toxin types A and B. In 2016, type A was the most common toxin in the United States, with about 102 patients affected. Type E can cause infant and foodborne botulism, whereas type F can also cause adult intestinal colonization. The annual incidence stayed relatively constant between 2005 and 2016. In 2016, 205 cases were confirmed in the United States. Of these, infant botulism was the most common with 150 cases (73%), followed by foodborne botulism with 29 cases (14%), wound botulism with 24 cases (12%), and three cases (1%) of unknown etiology. Ten additional probable cases were reported (8 of the 10 were foodborne). Of the infant botulism cases, 32% occurred in California; the mean age was 4 months (range 0 to 10 months), and no infants died. California also typically reports the highest number of wound botulism cases, mostly related to "skin popping" of black tar heroin. The location of food outbreaks is variable.[42] Recent sources in these outbreaks have included fermented fish/seal,[43,44] seal oil, improperly refrigerated or canned foods, and alcohol made from potatoes in prisons.[45] Foodborne botulism is rare in the winter, and deaths are rare overall, typically fewer than 5 people per year.[42]

Clinical Features

Symptoms of botulism include weakness of cranial nerve innervated and limb, axial, and respiratory muscles. Patients typically present with blurred vision, diplopia/ophthalmoplegia, facial weakness, dysarthria, and dysphagia (FIGURE 13-3).[46] Weakness descends, and then patients lose head control because of neck weakness and develop limb and respiratory weakness, usually in a proximal to distal pattern. Autonomic features such as fixed and dilated pupils, dry mouth, nausea, constipation, diarrhea, ileus, and abnormalities in heart rate and blood pressure may also be present. Importantly, however, dilated pupils are present in less than half of patients with botulism and therefore should not be used as a reliable distinguishing feature. Mental status is typically normal. Deep tendon reflexes are variable, ranging from absent to hyperactive, and are normal in about 50% of patients.[40,47] Fever

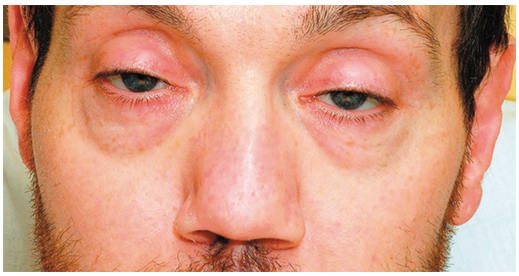

FIGURE 13-3
Ptosis and extraocular muscle and facial weakness in wound botulism.
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is usually absent, unless present from secondary infection. CSF and imaging studies are typically normal.

An infant with botulism commonly presents as an acutely "floppy baby" with a weak cry, feeding difficulties, constipation, and preserved deep tendon reflexes at presentation. The differential diagnosis of infant botulism includes spinal muscular atrophy and metabolic or other infectious etiologies. Nearly 50% of patients with infant botulism require intubation and often less than 24 hours after presentation.[39]

Diagnosis

The differential diagnosis of adult botulism includes Guillain-Barré syndrome (especially the Miller Fisher and pharyngeal-cervical-brachial variants because of the pattern of descending weakness), MG, tick paralysis, diphtheria, and brainstem stroke. The acute and descending presentation and lack of sensory symptoms distinguish botulism from most other entities. When botulism is suspected, a careful examination of the patient's skin and hair should be performed. This can uncover a wound or drug injection site that may be the source of botulism and exclude the presence of an attached tick that might implicate tick paralysis instead of botulism as the cause of acute weakness.

Detecting BoNT in serum, stool, or a suspected food or wound source confirms the diagnosis. The test is performed using an enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR) technique. The CDC conducts laboratory testing for botulism in the United States in collaboration with state health departments. Both serum and stool are typically tested to increase sensitivity, but in infant botulism and in adults affected by intestinal botulism, a stool sample is the preferred method of detection.[47] If a wound is a suspected source, a swab from the wound should be obtained, if possible. Given the time it may take to obtain results and the potential low sensitivity of the assay resulting in false negatives, treatment with antitoxin is started while waiting for results.

ELECTRODIAGNOSTIC STUDIES. Electrodiagnostic studies may also be used to provide additional support for the diagnosis of botulism before the serologic and stool samples return. Normal electrodiagnostic studies, however, do not exclude the diagnosis, particularly when performed early in the disease, and treatment should not be delayed until electrodiagnostic studies are performed. As a presynaptic neuromuscular junction disorder, botulism shares many electrodiagnostic features with LEMS. Cardinal abnormal features include reduced CMAP amplitudes and facilitation after exercise or high-frequency repetitive stimulation. Sensory and motor latencies and conduction velocities are normal. Normal nerve conduction velocities, however, do not fully exclude Guillain-Barré syndrome, since these may be normal in axonal variants or in the early days of acute inflammatory demyelinating polyradiculoneuropathy (AIDP).

Several important differences between LEMS and botulism are seen. Only about 60% of adult patients with botulism exhibit significant postexercise facilitation. The amount of postexercise CMAP amplitude facilitation is typically less in botulism than in LEMS (30% to 100% versus >100%). Additionally, posttetanic facilitation in botulism typically lasts for several minutes, whereas it typically lasts for less than 1 minute in LEMS and is followed by postexercise exhaustion.[26]

KEY POINTS

- Cases of botulism are categorized into one of four major transmission categories: foodborne, wound, infant, and other (which includes iatrogenic).
- Botulism presents as acute descending flaccid weakness and respiratory and autonomic dysfunction. Botulism is considered in the differential diagnosis for the acutely "floppy baby" under 1 year of age.
- Physicians should notify the state or other relevant health department to obtain treatment and work to isolate a source as soon as botulism is suspected.

Concentric needle EMG may be normal or may demonstrate short-duration low-amplitude motor unit potentials. Although typically not needed for diagnosis, single-fiber EMG shows increased jitter. Stimulated single-fiber EMG may be appealing for the diagnosis of infant botulism. Age-adjusted normal values are important to reference. Infants with botulism typically have markedly abnormal jitter with blocking in more than 10% of pairs.[48,49]

Treatment

Patients with suspected botulism should be hospitalized. Monitoring for respiratory and autonomic dysfunction is critical, and early intubation should be considered. Supportive therapy in the intensive care unit is the foundation of care.

Botulism is treated with either human botulism immunoglobulin intravenous (BIG-IV) or heptavalent antitoxin, which both block the action of toxin circulating in the blood and have been shown to reduce mortality. As soon as a physician suspects the diagnosis, he or she should begin the process to obtain antitoxin or BIG-IV from the state health department in the United States or the appropriate source internationally. The BIG-IV and heptavalent antitoxin are most effective when used early in the patient's illness because they can neutralize the botulinum toxin before extensive binding to nerve terminals. Early administration (within 3 days of admission) can shorten length of hospital stay compared to later administration, and the goal is administration within 24 hours.[41]

The type of antitoxin used depends on the age of the patient, geographic location, and type of botulism suspected. BIG-IV is given to pediatric patients younger than 1 year of age to treat infant botulism with botulinum toxin A or B. This is typically well tolerated. Equine-derived heptavalent botulinum antitoxin (contains antitoxin against subtypes A through G) is used for all other forms of botulism in the United States (ie, types C through G in infants, and all patients older than one year of age). Patients receiving heptavalent antitoxin are carefully monitored for hypersensitivity reactions, which occur in approximately 10% of patients. Symptoms include pyrexia, rash, chills, nausea, and edema, although anaphylaxis has not been reported.[50]

Botulism is a condition that requires public health notification. In the United States, contacting the state's health department starts the process to get antitoxin. State public health officials can then reach the CDC's clinical emergency botulism service for consultation.[51] Health Canada's Special Access Program regulates antitoxin administration in Canada. Antibiotics and wound debridement may be recommended for wound botulism; antibiotics are not part of routine treatment for other types of botulism. Identification and treatment of other individuals who may have been exposed is helped by early reporting.

Outcomes

Respiratory failure is the primary cause of death in botulism. While antitoxin can reduce the length of hospital stay and length of mechanical ventilation by several weeks, recovery remains slow and is expected over weeks to months. Recovery of strength results from development of new neuromuscular junctions, which takes time. Most patients with infant botulism make a complete recovery. The worldwide mortality rate of infant botulism is 1.1%. The mortality overall from all botulism types in the United States is 5%.[51]

Trends

Most cases of botulism are preventable by using proper food storage and canning techniques and refraining from feeding honey to infants younger than 1 year of age. However, several methods of transmission may be growing. Although such cases of botulism are rare, clinicians must consider the possibility of iatrogenic botulism with inappropriately high doses of commercially available botulinum toxin types A and B. Additionally, electromyographers contend with the influence of botulinum toxin routinely. With growing cosmetic and medical use of botulinum toxin injections for conditions including dystonia, migraine, sialorrhea, and spasticity, it is not uncommon for patients undergoing electrodiagnostic studies to have received injections. Needle EMG in a muscle that has received therapeutic doses of botulinum toxin can have abnormal spontaneous activity and either short-duration, low-amplitude motor unit potentials with early recruitment or long-duration, tall motor unit potentials with reduced recruitment. Motor unit potentials are frequently unstable, particularly if injections were recent. Findings of increased neuromuscular jitter can be seen in muscles remote to the site of injection and may persist for months to years.[52] With this limitation, it is challenging to confirm the diagnosis of seronegative MG in patients who have received botulinum toxin injections (CASE 13-2). Before performing single-fiber EMG studies, the author routinely asks about botulinum toxin injection history.

Wound botulism is part of the opioid epidemic. Injection of black tar heroin in particular has been linked to cases of botulism and may pose increased risk compared to other forms of heroin.[53] Black tar heroin often contains additives to increase bulk, or soil contaminants from transport. Cooking black tar heroin before injection does not destroy *C. botulinum* spores, which survive high heat and germinate to produce BoNT. Injecting subcutaneously instead of into a vein, known as *skin popping*, creates an anaerobic area of necrotic tissue and leads to abscesses and scarring (FIGURE 13-4).[54] In this environment, BoNT can be easily formed and released. As such, a thorough drug injection history in patients with suspected botulism is necessary. Additionally, it is important to inform patients of this potentially lethal consequence of drug injection and notify patients' communities when cases of wound botulism are identified.[53]

KEY POINTS

- Electrodiagnostic studies are critical in helping narrow the differential diagnosis and may demonstrate the presynaptic abnormalities of botulism. However, normal studies do not exclude the diagnosis of botulism, especially early in disease.
- Early public health notification of the suspected botulism diagnosis allows for early treatment with human botulism immunoglobulin intravenous (BIG-IV) or antitoxin, which improves outcomes.
- Mortality from botulism is low; however, recovery can be protracted.

IMMUNE CHECKPOINT INHIBITOR–RELATED DISORDERS OF NEUROMUSCULAR TRANSMISSION

Immune-related MG is a syndrome of a postsynaptic disorder of neuromuscular transmission in patients who have received an immune checkpoint inhibitor for cancer. Neurologists are increasingly caring for these patients in emergency departments, on inpatient services, and in subspecialty outpatient clinics. As such, familiarity with the drugs and the disorders of neuromuscular transmission that can follow their administration is important.

Since 2011, six immune checkpoint inhibitors have been approved by the FDA and fall into three drug classes: anti-CTLA4 (ipilimumab), anti-PD1 (nivolumab, pembrolizumab), and anti-PDL1 (atezolizumab, avelumab, durvalumab). Initially approved for metastatic melanoma, they now have a range of cancer indications both as monotherapy and in combination. These monoclonal antibodies exert their anticancer effect by releasing the normal inhibitory signals on T-cell activation.[55] Side effects, termed *immune-related adverse events*, can affect any organ or tissue.[56]

Pathophysiology

In normal immune function, PD1 and CTLA4 are inhibitors that contribute to the prevention of B-cell–mediated autoimmune disease and maintenance of self-tolerance. Polymorphisms in PD1 and CTLA4 are associated with various autoimmune conditions.[57] As in other immune-related adverse events, the pathophysiology of immune-related MG has not been fully defined, and it is unknown how much the pathophysiology overlaps with idiopathic MG. Some proposed mechanisms for immune-related adverse events in general include the following:

- Increased T-cell activity against antigens that are present in tumors and healthy tissue
- Increased levels of preexisting autoantibodies
- Increased inflammatory cytokines
- Enhanced complement-mediated inflammation due to direct binding of an antibody against CTLA4 with CTLA4 expressed on normal tissue

CASE 13-2

A 30-year-old woman presented with a 6-month history of bilateral ptosis, diplopia, intermittent mild dysphagia, and neck "heaviness." Symptoms started several weeks after she had botulinum toxin injections for migraine. Examination was notable for asymmetric mild bilateral ptosis, diplopia with left and right gaze, moderate eye closure weakness, and 4+/5 neck flexion and triceps strength.

Creatine kinase level was normal, and acetylcholine (ACh) receptor, muscle-specific tyrosine kinase, and lipoprotein receptor–related protein 4 antibodies were negative. Routine nerve conduction studies, needle EMG, and repetitive nerve stimulation studies were normal. Single-fiber EMG of the frontalis and extensor digitorum communis muscles revealed abnormally increased jitter with increased fiber density. Mediastinal imaging revealed no evidence for thymoma.

Pyridostigmine resulted in notable improvement in her ocular symptoms. Repeat ACh receptor antibody testing 6 months later showed elevated ACh receptor binding and modulating antibodies. A diagnosis of seropositive generalized myasthenia gravis was made. The patient had some residual functionally limiting weakness, and immunosuppressive therapies were started with a plan for thymectomy.

COMMENT

This patient likely had underlying myasthenic weakness that presented in the setting of receiving botulinum toxin injections. Because she was initially seronegative and had just received botulinum toxin injections, the results of the single-fiber EMG alone were inconclusive and could not confirm the diagnosis. However, her pattern of neck flexion and triceps weakness was consistent with myasthenia gravis, and pyridostigmine resulted in improvement. She had a positive ACh receptor antibody titer upon retest 6 months later, confirming the diagnosis.

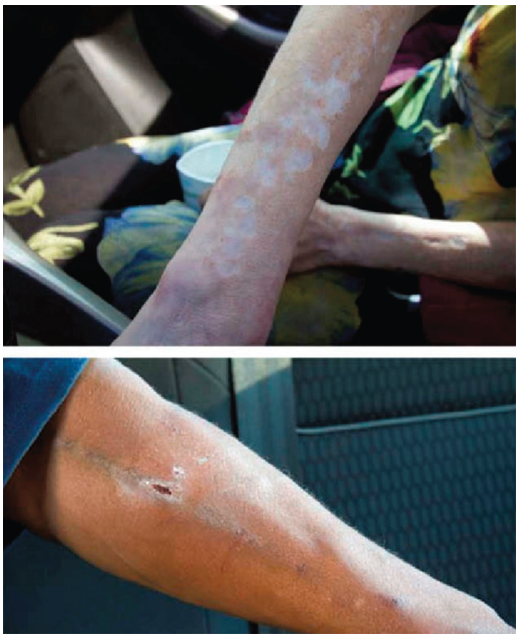

FIGURE 13-4
Scars from long-term "skin popping" of black tar heroin.
Reprinted with permission from Mars SG, et al, J Psychoactive Drugs.[54] © 2016 Taylor & Francis.

These processes may be involved in isolation or in combination, depending on the tissue, drug, and tumor type.[58] Some patients likely have preexisting undiagnosed MG, and in some, immune-related MG is likely a de novo presentation following treatment with an immune checkpoint inhibitor.[59]

KEY POINT

- A myasthenic syndrome is now associated with immune checkpoint inhibitor therapy for cancer. It frequently overlaps with other neurologic and non-neurologic immune-related adverse events.

Epidemiology

Neurologic immune-related adverse events are rare, affecting approximately 1% to 3% of patients treated with immune checkpoint inhibitors. They are variably classified and likely underdiagnosed. However, along with cardiac toxicities, they have some of the highest fatality rates of the immune-related adverse events.[60] The peripheral nervous system appears to be affected twice as often as the central nervous system.[56] Epidemiologic data on immune-related MG are limited. Studies have been retrospective and disproportionately included patients who had ACh receptor antibody–positive MG.[59]

Clinical Features

Immune-related MG resembles its idiopathic counterpart. However, early or disproportionately severe bulbar weakness or respiratory involvement, or both, may be present. It is unclear whether this is due to concurrent inflammation of bulbar and respiratory muscles or disordered neuromuscular transmission. A fatigable component to weakness may be present or absent by history and on examination. Immune-related MG can overlap with myositis, myocarditis, or thyroiditis (FIGURE 13-5). Symptoms typically present within one to four cycles of immune checkpoint inhibitor treatment. Fulminant symptoms may present after just one cycle, or symptoms may present more indolently.

Diagnosis

Currently, no distinct definition exists for immune-related MG. When patients present with a combination of ocular, bulbar, facial, limb, axial, and respiratory weakness after immune checkpoint inhibitor therapy, the differential diagnosis includes myositis (including orbital myositis), polyradiculoneuropathy with or without immune-mediated leptomeningeal involvement, myocarditis, and a direct effect of the cancer (CASE 13-3). The workup includes CK, ACh receptor binding and modulating panel with antistriated muscle antibodies, antinuclear antibody, thyroid-stimulating hormone (TSH) and free T4, and troponin and

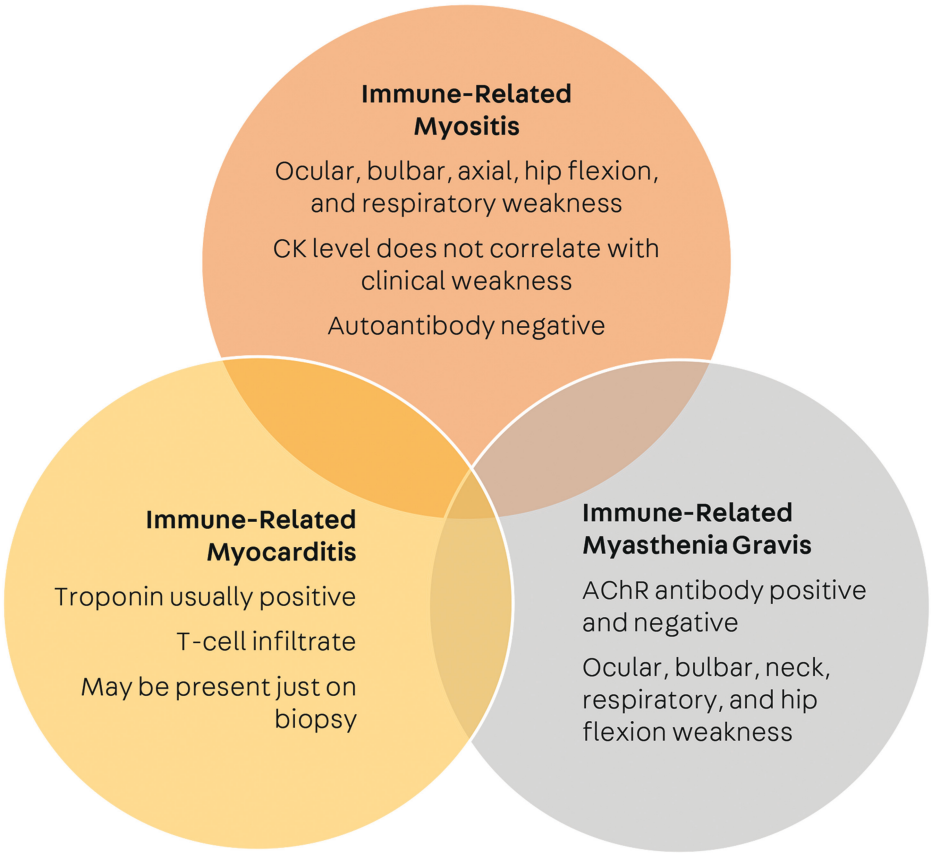

FIGURE 13-5
Overlap of immune-related myasthenia gravis with myositis and myocarditis after immune checkpoint inhibitor therapy.
AChR = acetylcholine receptor; CK = creatine kinase.
Modified from Moreira A, et al, Eur J Cancer.[62] © 2018 Elsevier Ltd.

ECG to screen for concurrent myocarditis. If ACh receptor binding antibodies are negative, muscle-specific tyrosine kinase and lipoprotein receptor–related protein 4 should be checked. If troponin is elevated, additional cardiac evaluation and cardiology consultation are warranted.[61]

Electrodiagnostic studies should be performed to provide further insight into the pathophysiology of the patient's symptoms. This is important for several reasons. First, in this population, ACh receptor antibody positivity may be nonspecific. The presence of ACh receptor binding antibodies may not mean the patient has an active disorder of neuromuscular transmission, and a higher proportion of patients with immune-related MG and weakness outside of the ocular region (ie, generalized myasthenia) do not have MG-specific autoantibodies.[62] These are features which distinguish immune-related MG from idiopathic MG. Second, overlap syndromes are common. Electrodiagnostic studies evaluate for concurrent myositis, polyneuropathy, or sensory neuronopathy. If the evaluation is unremarkable or inconclusive, single-fiber EMG and/or muscle biopsy are performed.[61]

Treatment and Outcomes

Although several guidelines address the management of immune-related adverse events, the most recent and relevant for immune-related MG was published by

CASE 13-3

A 60-year-old man with metastatic melanoma presented to the emergency department with shortness of breath and trouble walking, which began after completion of two cycles of pembrolizumab (anti-PD1). He noted dysphagia and myalgia in his lower back and thighs.

Examination demonstrated mild bilateral nonfatigable ptosis, diplopia with sustained right and left gaze, eye closure weakness, and mild weakness of cheek puff and tongue opposition into his cheek. He had mild neck flexion and extension weakness and 4/5 hip flexion weakness bilaterally. Sensation, coordination, and reflexes were normal. His negative inspiratory force was 35 cm H_2O, and his vital capacity was 1.8 liters.

Laboratory evaluation was notable for a creatine kinase level of 800 U/L and an elevated thyroid-stimulating hormone (TSH) level. Troponin was elevated, and an ECG demonstrated new-onset atrial fibrillation. Acetylcholine receptor binding antibodies were negative. Striated muscle antibodies were present in a high titer. CT of his chest showed no thymoma.

Electrodiagnostic studies showed low-amplitude lower extremity compound muscle action potentials (CMAPs) without facilitation and normal sensory nerve action potentials (SNAPs). An abnormal 15% decrement was seen on 3-Hz repetitive nerve stimulation of the facial-nasalis and spinal accessory-trapezius nerve-muscle combinations. Concentric needle EMG demonstrated abnormal spontaneous activity in thoracic paraspinal muscles and the deltoid and vastus lateralis muscles. A cardiac MRI was consistent with myocarditis.

COMMENT

This patient has immune-related myasthenia gravis with myocarditis and likely myositis after anti-PD1 therapy. Additional evaluation for immune checkpoint-related thyroiditis is warranted given possible new-onset hypothyroidism. Treatment would focus on holding the pembrolizumab and treating with pyridostigmine and corticosteroids. In this case, given the respiratory and cardiac involvement and dysphagia, the author would begin with methylprednisolone 1 g IV for 3 days followed by prednisone 60 mg/d and a taper. If the patient worsens or does not respond, IV immunoglobulin (IVIg) or plasma exchange should be added. This strategy is different from idiopathic myasthenia gravis, in which IVIg or plasma exchange would be used first, followed by oral corticosteroids, and IV corticosteroids are often avoided. If the patient responds to steroids, rapid improvement over a few days can be expected. In the author's experience, shortness of breath and hip flexion weakness take longer to improve. Skeletal muscle biopsy could be helpful to confirm myositis in this case but would not likely change management.

the American Society of Clinical Oncology.[56] The mainstay of treatment for immune-related adverse events and immune-related MG is holding or discontinuing immune checkpoint inhibitor therapy or adding corticosteroids, or both. In patients who have incomplete benefit or who have severe bulbar or respiratory weakness, either IVIg or plasma exchange should be quickly added or started concurrently. If patients are antibody negative and have no history of MG symptoms, corticosteroids are weaned more rapidly than in idiopathic disease, over approximately 4 to 6 weeks.[56] If preexisting MG is suspected or if the patient has ACh receptor antibodies, the author typically weans more slowly. While corticosteroids given afterward do not "undo" the effect of immune checkpoint inhibitor treatment, debate exists regarding whether higher or prolonged doses of corticosteroids or immunosuppressant therapies have adverse effects on the oncologic prognosis.[63] No data exist regarding the potential for transient early steroid-associated worsening in patients with immune-related MG.

A wide spectrum of severity in cases of immune-related MG exists. In the author's experience, some cases have been mild, monophasic, and extremely steroid responsive, even if the initial presentation included notable generalized weakness. Other cases have been surprisingly severe, rapidly progressive, and even fatal. The author agrees with others who have observed that patients with concurrent myositis or myocarditis appear to have a more aggressive course of immune-related MG.[57] Generally, however, the author initially treats immune-related MG aggressively even in patients with advanced cancers. At the author's institution, the experience has been that that most patients do experience significant improvement in myasthenic weakness, and improvement can be rapid over days to weeks.[62] Some patients, however, have permanent disability.[62]

Trends

Increased rates and recognition of immune-related MG are expected as the use of immune checkpoint inhibitors continues to grow. Immune checkpoint inhibitors were recently added to the Myasthenia Gravis Foundation of America's list of medications to use with caution in patients with MG.[36] Experience is needed regarding the outcome of patients with preexisting autoimmune diseases, including MG, who are treated with immune checkpoint inhibitors. Additional data are needed on what is effective in treating immune-related MG that is refractory to steroids and when/if patients with immune-related MG can be safely treated again with an immune checkpoint inhibitor.

One case of LEMS after immune checkpoint inhibitor therapy has been reported in a patient with squamous cell lung cancer who was treated with nivolumab.[64] VGCC antibodies were present, and electrodiagnostic studies showed a presynaptic neuromuscular junction abnormality, consisting of low-amplitude CMAPs with facilitation, and decrement on slow repetitive nerve stimulation. Additional reports of immune-related LEMS are expected in the future with increased use of immune checkpoint inhibitors.

CONCLUSION

The history and examination together with supporting laboratory and electrodiagnostic testing make the diagnosis in cases of LEMS, botulism, and

immune checkpoint inhibitor–associated MG. More than half of patients with LEMS have an underlying small cell lung cancer. If an initial malignancy screen is negative, additional screening should be performed for up to 2 years after LEMS diagnosis. Most patients with LEMS present with proximal lower extremity weakness, autonomic symptoms, and P/Q-type VGCC antibodies. Electrodiagnostic confirmation of a presynaptic disorder of neuromuscular transmission is often warranted even in patients who are antibody positive. Amifampridine phosphate and 3,4-DAP are the most effective symptomatic treatments in LEMS, and immunosuppression is typically reserved for nonparaneoplastic disease that does not respond.

Early diagnosis and treatment of botulism has the potential to improve outcomes. Consideration of botulism on the differential diagnosis of acute descending weakness is needed, particularly with risk of wound botulism during the opioid epidemic.

MG and LEMS have been reported after immune checkpoint inhibitor therapy for cancer, likely due to worsening of existing disease and de novo disease. Immune-related MG frequently overlaps with myositis and myocarditis. Holding or discontinuing the immune checkpoint inhibitor, or early treatment with steroids, or both, is currently first-line therapy. Additional research into the pathophysiology and best treatments for this growing subset of patients with neuromuscular junction disease is anticipated to refine our approach in the future.

KEY POINT

- **Currently, treatment of immune-related myasthenia gravis from immune checkpoint inhibitor therapy first involves treatment interruption and often corticosteroids.**

USEFUL RESOURCES

CENTERS FOR DISEASE CONTROL AND PREVENTION
To obtain consultation on an adult patient with suspected botulism or diphtheria and obtain botulinum antitoxin or diphtheria antitoxin, physicians should contact the Centers for Disease Control and Prevention Emergency Operations Center.
770-488-7100 or 1-800-232-4636
For botulinum antitoxin: *cdc.gov/laboratory/drugservice/formulary.html#bat*

HEALTH CANADA'S SPECIAL ACCESS PROGRAMME
Information regarding botulism reporting and testing and access to antitoxin in Canada can be found through Health Canada's Special Access Programme.
canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/botulism-guide-healthcare-professionals-2012.html

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