REVIEW ARTICLE

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Lambert-Eaton Myasthenic Syndrome and Botulism

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ABSTRACT

PURPOSE OF REVIEW: This article reviews the pathophysiology, epidemiology, clinical features, diagnosis, and treatment of Lambert-Eaton myasthenic syndrome (LEMS) and botulism, presynaptic disorders of neuromuscular transmission in which rapid diagnosis improves long-term outcomes.

RECENT FINDINGS: Therapy for LEMS has seen significant advances in recent years due to the approval of amifampridine-based compounds. LEMS is likely still underdiagnosed, particularly when no underlying malignancy is identified. Clinicians must have a strong suspicion for LEMS in any patient presenting with proximal weakness and autonomic dysfunction. Botulism is another rare disorder of presynaptic neuromuscular transmission that is most commonly associated with improper storage or preservation of food products. Over the past 2 decades, wound botulism has been increasingly reported among users of black tar heroin. A high degree of clinical suspicion and electrodiagnostic studies can be beneficial in distinguishing botulism from other acute neurologic disorders, and early involvement of state and federal health authorities may assist in confirming the diagnosis and obtaining treatment. When botulism is suspected, electrodiagnostic studies can provide clinical evidence of disordered neuromuscular transmission in advance of serologic confirmation, and providers should not wait for confirmation of the diagnosis to initiate treatment.

SUMMARY: A targeted clinical history and a thorough neurologic examination with support from serologic and electrodiagnostic studies are key to early diagnosis of LEMS and botulism. Early diagnosis of both conditions creates opportunities for therapy and improves outcomes.

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Raja discusses the unlabeled/investigational use of immunomodulatory and immunosuppressant therapies for the treatment of Lambert-Eaton myasthenic syndrome and monoclonal antibodies for the treatment of botulism.

INTRODUCTION

Presynaptic disorders of neuromuscular transmission are a rare group of diseases characterized by weakness and autonomic dysfunction. Recognition of presynaptic neuromuscular transmission disorders is important, as recent advances have occurred in the management of these disorders, specifically in Lambert-Eaton myasthenic syndrome (LEMS) and botulism. This article will assist neurologists in identifying and managing these rare disorders of neuromuscular transmission.

LAMBERT-EATON MYASTHENIC SYNDROME

LEMS is an autoimmune disorder of the presynaptic neuromuscular junction. This section will describe the pathophysiology, epidemiology, clinical features, diagnosis, and treatment options of LEMS.

Pathophysiology

Neuromuscular transmission occurs at the neuromuscular junction when calcium influx via a voltage-gated calcium channel (VGCC) triggers release of vesicles containing acetylcholine (ACh). These vesicles travel across the synaptic cleft to bind to ACh receptors on the postsynaptic membrane, thus triggering depolarization and muscle contraction (FIGURE 2-1[1]). LEMS is a presynaptic disorder characterized by the dysfunctional release of ACh vesicles at the neuromuscular junction due to the presence of antibodies to the pore-forming α1A subunit of the P/Q-type VGCC. This then impairs ACh vesicle release through a variety of mechanisms that affect the active zone of a neuromuscular junction: downregulation of presynaptic P/Q-type VGCCs, disorganization of vesicle release sites, and upregulation of alternative calcium channels.[2,3] Variable release of ACh results in failure of neuromuscular transmission, manifesting as weakness, autonomic dysfunction, or both.

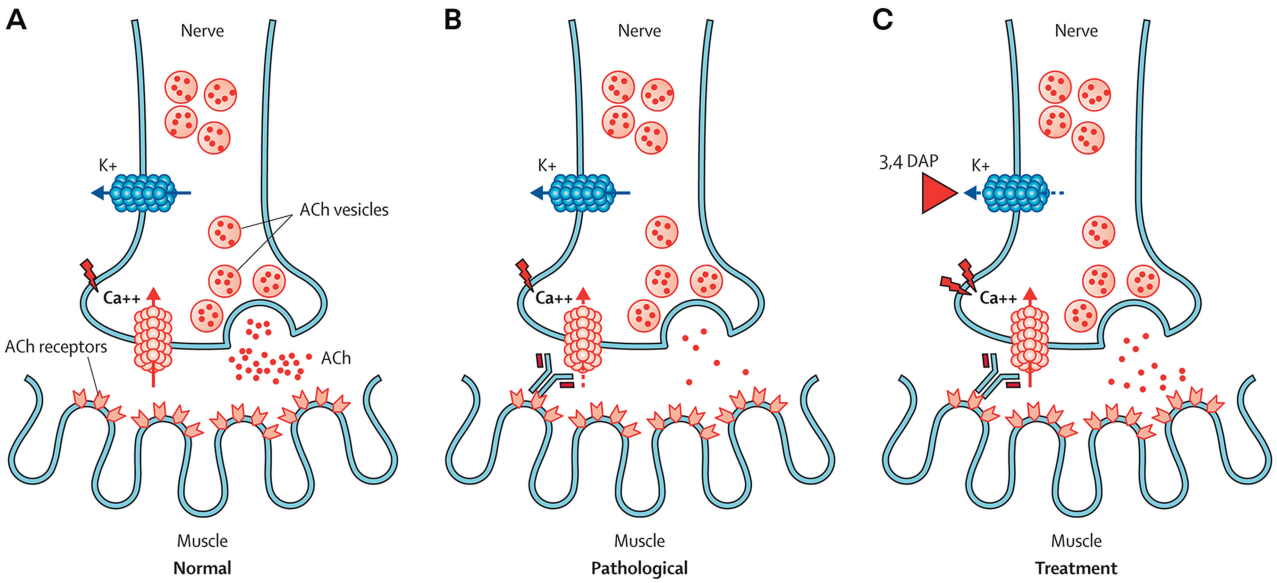

FIGURE 2-1

Pathophysiology of Lambert-Eaton myasthenic syndrome. *A*, Normal depolarization of the presynaptic nerve terminal by ion channels leads to influx of calcium ions and subsequent release of acetylcholine (ACh)–containing vesicles; ACh binds to the ACh receptor, leading to depolarization of the postsynaptic synapse and ultimately to muscle contraction. *B*, In Lambert-Eaton myasthenic syndrome, voltage-gated calcium channel antibodies block calcium influx, leading to reduced ACh vesicle release from the presynaptic membrane; therefore, reduced ACh is available to bind to postsynaptic ACh receptors. *C*, Treatment with 3,4-diaminopyridine (3,4-DAP; *red triangle*) blocks the efflux of potassium ions, prolonging the duration of depolarization. Longer depolarization keeps the pathologically affected calcium channels open longer, increasing calcium ion influx and intracellular calcium concentration and thereby improving the ability of the ACh vesicles to fuse and release neurotransmitter.

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LEMS can occur as a paraneoplastic syndrome associated with malignancy (cancer-associated LEMS) or as an autoimmune phenomenon in the absence of malignancy (nontumor LEMS). Between 50% and 60% of all LEMS cases are associated with malignancy, particularly small cell lung carcinoma (SCLC), although LEMS has been described in individuals with non–small cell and mixed cell lung carcinomas, neuroendocrine tumors such as prostate cancer, thymoma, and lymphoproliferative disorders.[4] The exact etiology of nontumor LEMS remains elusive; however, some evidence suggests that the presence of comorbid autoimmune disease may increase the risk of developing LEMS.[5]

Epidemiology

The epidemiology of LEMS has been well described in cohorts from the United States and the Netherlands. Within the United States, the population is best described by the 2017 population study of LEMS by the Department of Veterans Affairs (VA).[6] This study assessed the time interval from 1999 to 2013 to estimate a point prevalence of 2.6 confirmed cases per million that was expanded to 3.3 per million with inclusion of probable cases. The findings within this VA patient population are consistent with those from 1990 to 1999 in the Dutch population that reported a prevalence of 2.32 cases per million and worldwide estimates of 2.8 per million.[7,8]

CASE 2-1

A 47-year-old woman presented with a 31-year history of progressive bilateral lower extremity weakness and associated falls. She reported gradual-onset weakness that slowly impaired her ability to run, climb stairs, and stand up from a squatting position. At the onset of her symptoms at age 16, she underwent extensive evaluation including a muscle biopsy that did not reveal any specific etiology. She went on to have 2 uneventful pregnancies. Between ages 30 and 35, she developed ptosis and dysphagia, for which glucocorticoids were initiated, with some improvement in dysphagia. Repeat electrodiagnostic evaluation revealed postexercise facilitation of 114% in the trapezius with a 37.5% decrement on 2-Hz repetitive nerve stimulation, a 600% compound muscle action potential (CMAP) increment following 10 seconds of brief exercise on routine nerve conduction in the abductor digiti quinti, and pseudomyopathic changes on EMG. Antibody testing revealed borderline positive P/Q-type voltage-gated calcium channel antibodies. A diagnosis of Lambert-Eaton myasthenic syndrome was established, and evaluation for malignancy was unrevealing. Therapy with mycophenolate mofetil was initiated with improvement in weakness.

COMMENT

This case illustrates the challenge of diagnosing Lambert-Eaton myasthenic syndrome in patients who have focal symptoms without clear autonomic dysfunction. Although the patient reported onset at age 16, it took an additional 31 years to obtain a diagnosis and initiate therapy. Electrodiagnostic studies proved essential in establishing the diagnosis because of the characteristic pattern observed.

LEMS typically affects adults in the sixth and seventh decades. Cancer-associated LEMS is more commonly identified in males, and nontumor LEMS has a similar prevalence in males and females.[9] Diagnosis is often delayed, particularly with nontumor LEMS, in which the median duration of disease before diagnosis was found to be 17 months, compared with 3.5 months in cancer-associated LEMS.[10] The LEMS and malignancy diagnoses are often made simultaneously, with a diagnosis of LEMS leading to rapid workup for identification of malignancy.[11] The diagnostic delay is more pronounced in patients with nontumor LEMS, although screening for malignancy is recommended at regular intervals during the first 2 to 4 years after diagnosis.[12] As illustrated by CASE 2-1, LEMS diagnoses are likely underreported given that over 58% of people with LEMS are initially misdiagnosed as a result of limited access to neurologic care, greater attribution of weakness and fatigue to underlying malignancies, a paucity of clinical examination findings, and confusion with congenital muscular dystrophies and inflammatory myopathies by clinicians.[10]

Long-term prognosis and survival for LEMS depend on whether an associated malignancy is identified and the extent of clinical disease at the time of diagnosis. In cases of LEMS associated with SCLC, studies have indicated a median survival of 18 months versus only 9.5 months in patients without neurologic disease.[13] Nontumor LEMS is not associated with reduced survival but does negatively affect quality of life and worsen overall disability.[14] Clinical disease severity, as assessed by manual muscle testing, is the best predictor of long-term prognosis, and over 70% of patients experience clinical improvement through such therapies as immunomodulation and immunosuppression, potassium channel antagonists such as amifampridine phosphate, and acetylcholinesterase inhibitors such as pyridostigmine.[4,6]

It is also important to recognize that LEMS may present in the pediatric population; approximately 15 cases are reported in the literature, of which only 3 were associated with malignancy.[15] Pediatric LEMS is most often confused with muscular dystrophy and is frequently observed in conjunction with other autoimmune diseases of childhood.

Clinical Features

Clinical presentation of LEMS is variable, with the triad of proximal muscle weakness, autonomic dysfunction, and areflexia/hyporeflexia most commonly observed. Milder involvement of oculobulbar muscles and axial muscles can be observed, and respiratory muscle weakness is rare. Clinical symptoms and distribution progress with increasing time since symptom onset (FIGURE 2-2[1]).

Patients with LEMS are most likely to report symptoms of lower extremity weakness, manifesting as abnormal gait and difficulty ascending and descending stairs, rising from the floor or standard-height chairs and toilets, and reaching for overhead objects. Brief activity may improve strength, and some patients report improvement in symptoms late in the day. Motor examination may reveal such features as a waddling gait that improves with increased distance and mild proximal upper extremity weakness that improves with repeated testing. When LEMS is suspected, it is particularly important to assess reflexes before and after manual muscle testing, as brief exercise may improve previously diminished or absent tendon reflexes. In a patient who is unable to sufficiently activate a muscle, repeated percussion of a tendon may elicit a similar response.

Thorough questioning regarding autonomic symptoms is a critical component of evaluation for LEMS, as demonstrated in CASE 2-2. In addition to a general

KEY POINTS

- Lambert-Eaton myasthenic syndrome is associated with pathogenic P/Q-type voltage-gated calcium channel antibodies that impair the release of acetylcholine vesicles at the presynaptic neuromuscular junction.
- Presynaptic defects of neuromuscular transmission can cause weakness and autonomic dysfunction.
- Malignancy, particularly small cell lung cancer, is identified in over 50% of patients with Lambert-Eaton myasthenic syndrome.
- Lambert-Eaton myasthenic syndrome is a rare disease with worldwide prevalence of approximately 2.8 cases per million individuals.
- Misdiagnosis of Lambert-Eaton myasthenic syndrome is frequent because of the lack of awareness and confusion with other more common diseases.
- Lambert-Eaton myasthenic syndrome is a treatable condition, and most patients improve with appropriate therapy.
- Lambert-Eaton myasthenic syndrome is characterized by a clinical triad of proximal muscle weakness, autonomic dysfunction, and areflexia/hyporeflexia.

KEY POINTS

- **Patients may not voluntarily disclose autonomic symptoms, particularly dry mouth, orthostatic hypotension, constipation, and erectile dysfunction.**
- **Symptoms of Lambert-Eaton myasthenic syndrome are often disproportionate to clinical examination abnormalities.**

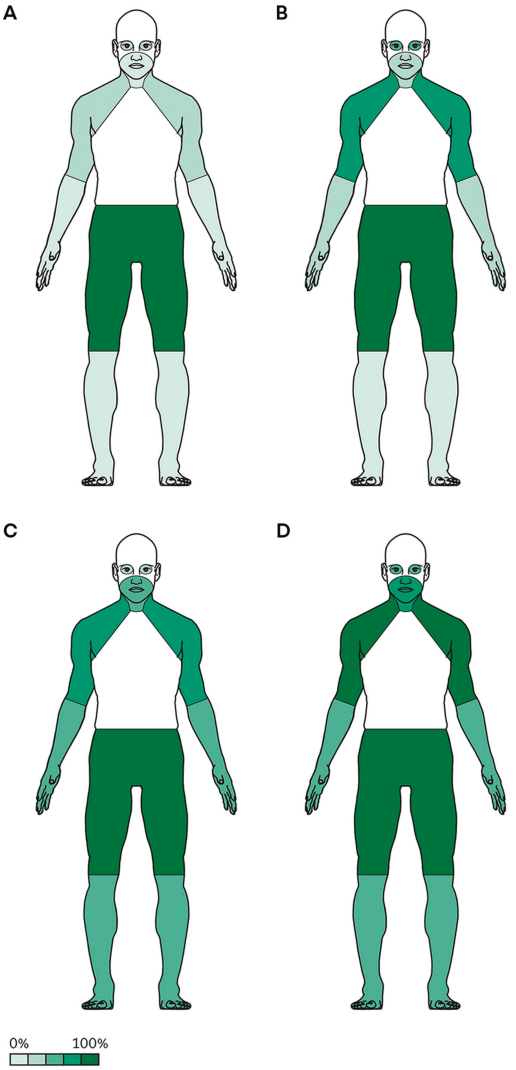

FIGURE 2-2
Spreading of symptoms in patients with nontumor Lambert-Eaton myasthenic syndrome and small cell lung carcinoma Lambert-Eaton myasthenic syndrome. Frequency of symptoms at 3 months (*A*) and 12 months (*B*) in patients with nontumor Lambert-Eaton myasthenic syndrome, and frequency of symptoms at 3 months (*C*) and 12 months (*D*) in patients with small cell lung carcinoma Lambert-Eaton myasthenic syndrome. The percentages indicate the approximate proportion of patients who have that symptom within the given time frame.
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review of systems, the clinician must directly question the patient about dry eyes, dry mouth, orthostatic hypotension, urinary incontinence (more common in females), constipation, and erectile dysfunction (in males). In some cases, patients are unlikely to volunteer these symptoms, and careful observation may assist in diagnosis. Frequent sips of water between sentences, constant sucking of hard candies or lozenges, and slow position changes during examination are commonly observed. TABLE 2-1 highlights the key musculoskeletal, autonomic, and clinical examination findings of LEMS. It is important to note that the symptoms are often more prominent than the clinical signs on examination.

Significant ataxia on clinical examination should raise concern for LEMS with paraneoplastic cerebellar degeneration, which is associated with reduced P/Q-type VGCCs in the molecular layer of the cerebellum and is diagnosed in approximately 10% of patients with LEMS and SCLC.[16,17] Careful evaluation of gait and targeted cerebellar functions such as coordination of fine motor functions, dysdiadochokinesia, and dysmetria can reveal subtle cerebellar dysfunction in patients with LEMS, although care must be taken to distinguish these findings from those of peripheral neuropathy–associated ataxias.

Diagnosis

Diagnosis of LEMS requires multiple modalities including clinical history and examination, a search for pathogenic autoantibodies, and electrodiagnostic studies.

SEROLOGIC TESTING. Autoantibodies targeting the P/Q-type VGCC are most commonly identified in patients with LEMS (FIGURE 2-1), although approximately 10% to 15% of patients do not have antibodies.[3] N-type and L-type antibodies to VGCCs have been identified in smaller proportions of patients with LEMS but have not been shown to confer the same pathogenic effect as the P/Q-type VGCC and are nonspecific.[18-21] Thus, while individuals who test positive for P/Q-type VGCCs may also have antibodies to N-type and L-type VGCCs, the presence of N-type and L-type VGCCs in the absence of P/Q-type VGCCs should not be considered supportive of a LEMS diagnosis. Evaluation for LEMS thus should always include serologic testing for P/Q-type VGCCs, other paraneoplastic syndromes, and myasthenia gravis. P/Q-type and N-type VGCCs are occasionally present in individuals without LEMS, so careful attention to

CASE 2-2

A 65-year-old man presented for neurologic evaluation with a 3-month history of proximal lower leg weakness. He revealed additional symptoms of dry mouth, dry skin, dry eyes, reduced appetite, and impotence. Three months before symptom onset, he developed sharp, lancinating pain in the right lung apex, and he was subsequently diagnosed with stage IIIA small cell carcinoma.

Neurologic examination revealed dry mucous membranes and skin, atrophy of the knee extensors bilaterally, and a waddling gait pattern. Cranial nerve examination revealed no abnormalities, but there was 4/5 weakness of the shoulder and hip girdle muscles with preservation of strength in the distal limbs. Reflexes were absent on initial testing but were present in the lower limbs after ambulation. Sensory examination revealed no abnormalities to pinprick, temperature, vibration, or joint position sense. Electrodiagnostic evaluation demonstrated 100% compound muscle action potential (CMAP) facilitation in the abductor digiti quinti following 10 seconds of brief exercise and a decrement of 47% on 3-Hz repetitive nerve stimulation followed by postactivation facilitation of 83%. Autonomic studies revealed panautonomic failure at the level of the ganglia. Serologic evaluation revealed high-titer P/Q-type voltage-gated calcium channels. A diagnosis of Lambert-Eaton myasthenic syndrome was established based on clinical presentation, electrodiagnostics, and serology. He was subsequently treated with conventional chemotherapy and radiation. Mild improvement in strength occurred; however, he continued to experience xerosis and proximal weakness restricting mobility. The patient began 3,4-diaminopyridine and pyridostigmine therapy 2 years later with improvement in residual symptoms.

COMMENT

This case highlights the importance of a detailed clinical history with careful attention to autonomic symptoms. This patient experienced some improvement in proximal strength following the treatment of his malignancy and then further improvement following the initiation of symptomatic therapy with a potassium channel antagonist and a cholinesterase inhibitor.

supporting clinical features and electrodiagnostic studies is paramount.[21] In patients with persistently positive serologic findings and no clinical or electrodiagnostic features, malignancy screening may be appropriate.

ELECTRODIAGNOSTIC STUDIES. Thoughtful electrodiagnostic studies can provide evidence of neuromuscular transmission disorders and narrow the differential diagnosis. In the author's practice, a complete electrodiagnostic evaluation for LEMS must include routine nerve conduction studies, concentric needle EMG, and 2-Hz to 3-Hz repetitive nerve stimulation. Performance of routine nerve conduction studies and EMG is necessary to exclude other etiologies of proximal weakness, most commonly myopathies and radiculopathies. Routine studies should be performed at a minimum of 32 °C (89.6 °F) to ensure accurate latencies, amplitudes, and conduction velocities. Routine needle EMG studies may reveal pseudomyopathic changes, specifically shortened motor unit potential duration and amplitude with normal recruitment, in clinically weak muscles.[22,23]

TABLE 2-1 Symptoms and Clinical Examination Findings of Patients With Lambert-Eaton Myasthenic Syndrome

Muscle weakness

- Gait dysfunction
- Double vision
- Dysphagia
- Slurred speech

Autonomic features

- Dry eyes[a]
- Dry mouth
- Palpitations
- Orthostatic hypotension
- Urinary incontinence[a]
- Constipation
- Erectile dysfunction

Clinical examination findings

- Proximal > distal weakness of lower > upper extremities
- Ptosis
- Ophthalmoparesis
- Diminished or absent reflexes
- Poorly reactive pupils
- Dry mouth and caries
- Irregular heart rate

[a] Less commonly reported symptoms

COMPOUND MUSCLE ACTION POTENTIAL INCREMENT. One of the most common findings on routine studies is the widespread observation of a low compound muscle action potential (CMAP) amplitude on initial stimulation of a motor nerve. Often with repeated stimulation at the same intensity, the CMAP amplitude is variable and increases following brief exercise, demonstrating the characteristic postactivation facilitation.

2-HZ TO 3-HZ REPETITIVE NERVE STIMULATION. Low-frequency (2-Hz to 3-Hz) repetitive nerve stimulation is ideally performed at a higher temperature of 34°C (93.2°F) and typically produces a decrement of greater than 10% in patients with disorders of neuromuscular transmission.[24] Following maximal voluntary contraction (at least 10 seconds), 2-Hz to 3-Hz repetitive nerve stimulation should be repeated at intervals of 30 seconds for at least 3 to 5 minutes to capture postexercise facilitation of at least 100%. Ideal muscles are distal and innervated by a single nerve: abductor pollicis brevis (median), adductor digiti minimi (ulnar), extensor digitorum communis (radial), and extensor digitorum brevis (fibular [peroneal]) muscles. The combination of 10 seconds of exercise and repeated trains for 5 minutes maximizes sensitivity for detection of facilitation of greater than 100%, depending on the patient and the muscle tested. In rare circumstances, particularly when patients are unable to voluntarily activate, high-frequency (50-Hz) repetitive nerve stimulation will also demonstrate increment, but this is often unnecessary. When assessing muscles, it is crucial to remember that not every muscle will demonstrate an abnormality. For this reason, it is important to test multiple muscles, as only 41% of patients with LEMS demonstrated a minimum 100% facilitation in three of three tested muscles, but 88% met this criterion in at least one muscle.[25,26]

SINGLE-FIBER EMG. Jitter studies using single-fiber EMG techniques are even more sensitive for the detection of LEMS and correlate with clinical severity.[27] Jitter studies are most useful in patients who have normal routine conduction studies and 2-Hz to 3-Hz repetitive nerve stimulation studies but clear signs and symptoms of LEMS.

Recommended Workup

As noted above, evaluation of a patient for LEMS is a multimodality process requiring a high level of suspicion based on clinical history and examination. It is supported by electrodiagnostic findings. The differential must be broad enough to exclude alternative causes of proximal muscle weakness and autonomic dysfunction. Common pathologies such as myasthenia gravis, myopathies, lumbosacral radiculopathies, and cancer cachexia or therapy are important considerations for weakness, and acquired autonomic dysfunction due to diabetes mellitus or other autoimmune disorders should be excluded through an individualized workup. The following paradigm is recommended by the author:

- **Serologic testing: VGCC (P/Q- and N-type) antibodies and paraneoplastic panel that includes ACh receptor antibodies (nicotinic and ganglionic)**
- **Testing for creatine kinase with or without aldolase**
- **Electrodiagnostic studies: routine and specialized (2-Hz to 3-Hz repetitive nerve stimulation with or without jitter studies)**

KEY POINTS

- **Routine nerve conduction studies and EMG are necessary to narrow the differential diagnosis of Lambert-Eaton myasthenic syndrome.**
- **Electrodiagnostic features of Lambert-Eaton myasthenic syndrome include low-amplitude compound muscle action potentials with incremental increases with repeated stimulation and facilitation following 10 seconds of maximal exercise on 2-Hz to 3-Hz repetitive nerve stimulation.**

- If the diagnosis is confirmed by the above, it is important to ensure that age- and sex-appropriate malignancy screening is up to date. Routine chest, abdomen, and pelvis CT should be performed, and a positron emission tomography (PET) CT is recommended if the initial CT is negative for mass lesions.
- Repeat malignancy screening at 3- to 6-month intervals for the first year following diagnosis and then periodic screening (annual) until 2 years after the initial LEMS diagnosis.[28] Consider more aggressive screening for SCLC in patients who score ≥4 on the clinical Dutch-English LEMS Tumor Association Prediction (DELTA-P) score.[29] This is a six-item scale with equal weighting for six features: bulbar weakness, erectile dysfunction, weight loss of 5% or greater, tobacco use at onset, age at onset of 50 years or older, and Karnofsky performance score.

Assessing Disease Severity and Response to Therapy

Measuring disease severity and response to therapy are critical aspects of disease management. Recent clinical trials have used a variety of measures as primary endpoints, including the Quantitative Myasthenia Gravis (QMG) score, a Subject Global Impression score, and the Triple Timed Up and Go (3TUG) test.[30,31] Of these measures, only the 3TUG test has been shown to be reliable in patients with LEMS and specifically validated as a measure of disease severity.[32,33] The 3TUG test is a simple, noninvasive test that is easily performed in a typical outpatient clinic using a standard-height, armless, straight-backed, hard chair. As shown in FIGURE 2-3, in this test the patient stands up from a seated position, walks approximately 3 meters (10 feet), turns around, walks back to the chair, and sits back down. This procedure is repeated for two more laps, and the individual lap times are averaged. By assessing individual lap time, the examiner can assess fatigability or improvement. Although other measures such as the QMG score have been used in clinical studies and recommended for use in the postsynaptic disorder myasthenia gravis, the QMG score is not always appropriate for patients with LEMS because it includes more measures of ocular and bulbar function that are often absent to minimal in LEMS.

Treatment

Treatment of LEMS should be individualized to the symptoms and situation of each patient. Symptomatic therapies can address symptoms of weakness or autonomic dysfunction. Amifampridine phosphate or the base formulation of amifampridine, 3,4-diaminopyridine (3,4-DAP), is a potassium channel antagonist that blocks presynaptic potassium efflux to prolong depolarization by maintaining calcium influx through functional VGCCs and optimize ACh release (FIGURE 2-1C). Amifampridine phosphate or 3,4-DAP has been used to treat LEMS since the 1980s when it was reported as effective in a series of 3 patients and in an additional series of 12 patients.[34,35] Recent phase 3 randomized controlled trials of amifampridine phosphate and 3,4-DAP demonstrated efficacy in up to 85% of patients.[30] The

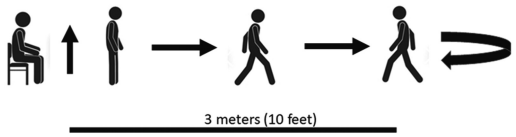

FIGURE 2-3

The Timed Up and Go test. The Timed Up and Go test is performed using a standard-height, armless, straight-backed, hard chair. The patient rises from a seated position, walks forward for 3 meters (10 feet), turns around, returns to the chair, and sits back down. A single lap is assessed from when the patient's buttocks rise to when the back touches the chair back as the patient sits. This is repeated for two more laps, and the times of the three laps are averaged to provide a Triple Timed Up and Go test score.

phosphate salt was approved by the US Food and Drug Administration (FDA) in 2018 for the treatment of adult patients (age >17 years) with LEMS.

Typical dosing of amifampridine phosphate or 3,4 DAP starts at 15 to 30 mg/d (lower range for renal and hepatic impairment) divided into three to four oral doses with increases to a maximum daily dosage of 80 mg for amifampridine phosphate and 100 mg for 3,4-DAP.[36] The most common side effects observed in phase 3 trials included perioral and acral paresthesia; seizures have been reported in patients receiving higher doses or using concomitant drugs that lower seizure thresholds.[30,31]

The acetylcholinesterase inhibitor pyridostigmine can be a useful adjunct to amifampridine phosphate or 3,4-DAP, as it can prolong the effect of the potassium channel agonist as well as improve oral secretion production to treat dry mouth. Therapy for other associated autonomic dysfunction is individualized to the target symptom. The author uses fludrocortisone, midodrine, and compression devices for orthostatic symptoms and osmotic laxatives for the management of constipation. Phosphodiesterase 5 inhibitors can also be used in patients with erectile dysfunction if they are appropriate candidates based on concomitant medications and cardiovascular risk factors.

IV immunoglobulin (IVIg) and therapeutic plasma exchange can be used to control severe disease that is not responsive to symptomatic therapy prior to malignancy workup. Caution should be exercised when using IVIg in patients with suspected malignancy because of the risk of thrombotic events. Therapeutic plasma exchange via peripheral veins is preferred in the author's practice to reduce the risk of infection and bleeding associated with central catheters.

In patients with malignancy, the underlying malignancy should be treated in accordance with the recommended guidelines. Aggressive treatment for malignancy may reduce or eliminate symptoms of LEMS, and the use of immunosuppressive or immunomodulatory therapies may affect the progression of malignancy or be contraindicated with concomitant malignancy therapies.

Immunosuppressive and immunomodulatory agents such as corticosteroids (prednisone, prednisolone), azathioprine, mycophenolate, and rituximab may be used with great caution in this population only after malignancy has been ruled out and if symptomatic therapy with amifampridine and cholinesterase inhibitors is ineffective. A summary of these therapeutic options is shown in TABLE 2-2.

Avoidance of medications with neuromuscular blockade properties is also critical to the management of patients with LEMS. The most common offending agents include neuromuscular blockade agents used in general anesthesia, macrolide and quinolone antibiotics, and immune checkpoint inhibitors (in patients with malignancy). A complete list of therapies to be used with caution can be viewed on the website of the Myasthenia Gravis Foundation of America (see Useful Websites section at the end of this article), and the author recommends that patients with LEMS keep this list on their person at all times to share with other providers.[37] Although the overall risk of prolonged postoperative muscle weakness and respiratory failure is low, this is most likely to occur in patients with malignancy who undergo surgical procedures before achieving symptomatic disease control.[38]

Trends

The past 5 years have seen tremendous progress in the development of therapies for LEMS with the approval of amifampridine phosphate for this condition.

KEY POINTS

- Malignancy screening should be performed for a minimum of 2 years after diagnosis of Lambert-Eaton myasthenic syndrome.
- Symptomatic therapies are first line for Lambert-Eaton myasthenic syndrome and include forms of amifampridine.
- Pyridostigmine augments the effects of amifampridine and may improve some autonomic symptoms.
- IV immunoglobulin and therapeutic plasma exchange can be used in severe cases of Lambert-Eaton myasthenic syndrome that are unresponsive to symptomatic therapy.
- Treatment of underlying malignancy reduces symptoms in cancer-associated Lambert-Eaton myasthenic syndrome.
- Immunosuppressive and immunomodulatory therapies such as corticosteroids, azathioprine, and mycophenolate can be used in patients with nontumor Lambert-Eaton myasthenic syndrome who have inadequate control with symptomatic therapies.

Prior to this approval, 3,4-DAP was available only through compounding pharmacies or a compassionate use program requiring individual Investigational New Drug programs. Since the approval of amifampridine phosphate, concern regarding access and drug pricing has raised many questions about the "financial toxicity" of drugs and their role in the management of rare diseases such as LEMS.[39,40] This is increasingly a concern as historically established, previously compounded entities are approved for disease-specific indications as trademarked products.

BOTULISM

Botulism is an acquired disorder of presynaptic transmission mediated by botulinum neurotoxin. The following section describes the pathophysiology, epidemiology, clinical features, diagnosis, and treatment of botulism.

Pathophysiology

Botulism is a disorder of neuromuscular transmission characterized by afebrile, symmetric descending weakness, respiratory failure, and autonomic dysfunction.[41] The disorder is caused by intoxication with one of seven botulinum neurotoxin (BoNT) serotypes (A, B, C, D, E, F, G), all of which are produced by *Clostridium* species.

TABLE 2-2 Therapeutic Options for Patients With Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) (symptomatic therapies)

- **Weakness**
  - Amifampridine phosphate
  - IV immunoglobulin (IVIg)
  - Therapeutic plasma exchange (severe cases only)
- **Autonomic dysfunction**
  - Pyridostigmine bromide
  - Volume expanders and midodrine
  - Osmotic laxatives
  - Phosphodiesterase 5 inhibitors

Cancer-associated LEMS

- **Malignancy-specific therapy**[a]

Nontumor LEMS[b]

- **Immunosuppression**
  - Prednisone
  - Azathioprine
  - Mycophenolate mofetil

IV = intravenous.
[a] May include conventional chemotherapy, radiation, and immunotherapy.
[b] Immunosuppressive therapies should be offered if the response to symptomatic therapy is inadequate.

BoNT is a 150-kDa zinc endopeptidase that specifically inhibits neurotransmitter release through a multistep process illustrated in FIGURE 2-4.[42,43] BoNT irreversibly binds to the presynaptic membrane, where it is internalized via endocytosis and translocated (step 1). Within the endosomes, it cleaves a soluble *N*-ethylmaleimide–sensitive factor attachment protein receptor (SNARE) protein, an important mediator of ACh vesicle fusion and release (step 2). BoNT types A, C, and E specifically cleave the synaptosomal-associated protein of 25 kDa (SNAP-25), BoNT type C cleaves the proteins syntaxin and SNAP-25, and BoNT types B, D, F, and G cleave synaptobrevin. Cleavage of these key proteins prevents formation of the synaptic fusion complex, which includes the SNARE proteins and a synaptic vesicle containing ACh. The net effect of this process is impaired fusion of the synaptic vesicle to the presynaptic membrane,

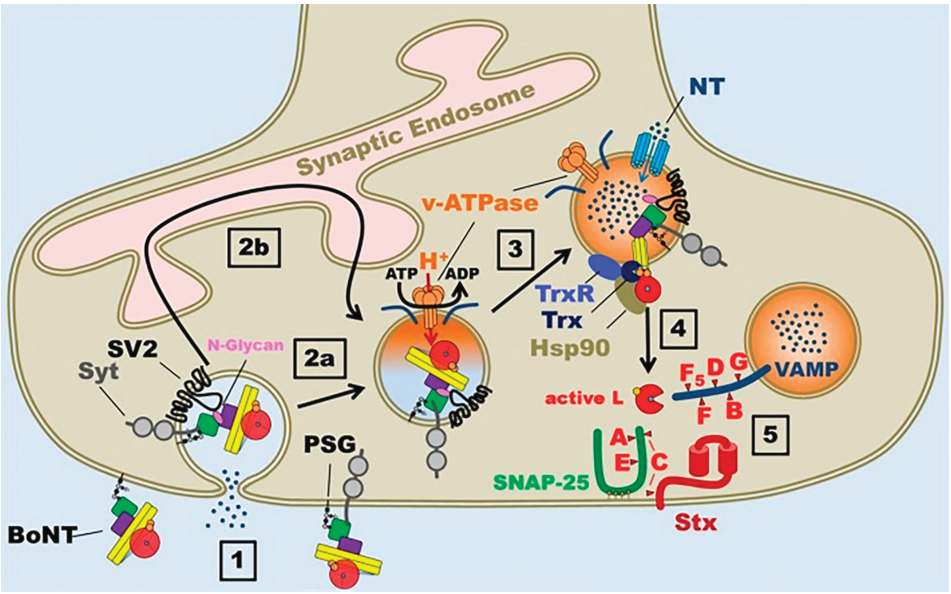

FIGURE 2-4

Mechanism of action of botulinum toxin. The nerve terminal intoxication by botulinum neurotoxins is a multistep process. The first step (*1*) is the binding of the HC domain (*green*) to a polysialoganglioside (PSG) receptor of the presynaptic membrane (*gray and black*), followed by binding to a protein receptor. The currently known protein receptors are (*i*) synaptotagmin (Syt [*gray*]) for BoNT-B1, -DC, and -G; (*ii*) glycosylated synaptic vesicle protein 2 (SV2 [*black*], with its attached N-glycan in *pink*) for BoNT-A1 and -E1. Syt may be located either within the exocytosed synaptic vesicle or on the presynaptic membrane. The BoNT is then internalized inside SVs, which are directly recycled (*2a*) or inside SVs that fuse with the synaptic endosome and reenter SV cycle by budding from this intermediate compartment (*2b*). The acidification (*orange*) of the vesicle, operated by the v-ATPase (*orange*), drives the accumulation of neurotransmitter (*blue dots*) via the vesicular neurotransmitter transporter (*light blue*). The protonation of BoNT leads to the membrane translocation of the L chain into the cytosol (*3*), which is assisted by the HN domain (*yellow*). The L chain (*red*) is released from the HN domain by the action of the thioredoxin reductase–thioredoxin system (TrxR [*blue*] and Trx [*dark blue*]) and Hsp90 (*olive green*), which reduce the interchain disulfide bond (*orange*) and avoid the aggregation of the protease (*4*). In the cytosol, the L chain displays its metalloprotease activity: BoNT-B, -D, -F, -G cleave VAMP (*navy blue*); BoNT-A and BoNT-E cleave SNAP-25 (*green*); and BoNT-C cleaves both SNAP-25 and syntaxin (Stx [*dark red*]) (5). Each of these proteolytic events is sufficient to cause a prolonged inhibition of neurotransmitter release with consequent neuroparalysis.

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KEY POINTS

- **Botulism is characterized by a toxidrome of acute, afebrile, descending weakness and autonomic dysfunction.**
- **Botulinum neurotoxin irreversibly binds to presynaptic neurons and cleaves soluble *N*-ethylmaleimide–sensitive factor attachment protein receptor (SNARE) proteins to prevent formation of the synaptic fusion complex and release of acetylcholine vesicles.**

which leads to failure of release of ACh (step 3), and impaired neuromuscular transmission (step 4) resulting in skeletal muscle and autonomic paralysis.

Epidemiology

Botulism is most commonly a foodborne illness caused by consumption of food contaminated with the toxin; it may also result from infection of wounds, ingestion of *Clostridium* species with resultant toxin production in the gut (toxicoinfection), and other causes, specifically iatrogenic chemodenervation.[44,45] The most common types of botulism are caused by serotypes A, B, and E. The US Centers for Disease Control and Prevention (CDC) tracks botulism cases annually, with the last update in 2021 for cases reported in 2018. In that report, a total of 242 cases were documented: 162 cases of infant toxicoinfection (median age, 4 months; 1 death), 61 cases of wound botulism (median age, 46 years; no deaths), 18 cases of foodborne botulism (median age, 55 years; no deaths), and 1 suspected case of adult toxicoinfection (no deaths).[46] Case numbers and etiologies of intoxication varied largely by geographic region and food preparation practices, with the largest number of cases reported in California, New York, Pennsylvania, Texas, Arizona, and Alaska.[46,47] Common sources of intoxication included honey, home-canned foods including vegetables and soups, fermented foods (legumes and seafood), fish/seal oils, and improper food storage.

Clinical Features

Like other disorders of neuromuscular transmission, botulism has a predilection for involvement of cranial nerves but can also affect axial, limb, and respiratory muscles. Symptoms typically manifest 12 to 36 hours after exposure; in rare circumstances, symptoms manifest as early as 6 hours or as late as 10 days after exposure.[48] Cranial nerves are often involved first, with the disorder manifesting clinically as blurred vision, ophthalmoparesis or ophthalmoplegia, droopy facies, dysarthria, and dysphagia. In cases of foodborne BoNT intoxication, gastrointestinal symptoms include nausea, vomiting, abdominal discomfort, pain, and diarrhea followed by severe constipation.[49] Respiratory failure can develop in severe cases and often requires aggressive support. Autonomic symptoms, particularly dry mouth and sore throat mimicking acute pharyngitis, can also be seen early in the disease course, with subsequent development of fixed and dilated pupils, unstable heart rate and blood pressure, and the above-mentioned gastrointestinal symptoms of nausea, diarrhea, ileus, and constipation. Clinical examination reveals intact mental status, weakness in a descending pattern with flaccid tone, and variable reflexes. Individuals with wound botulism are most commonly injection drug users with limited vascular access who use the technique of "skin popping" to deliver drugs subcutaneously. They are more likely to present with symptoms of opiate intoxication that is poorly responsive to reversal agents such as naloxone and features of local or systemic infection, including fever and open wounds or abscesses.[44]

Symptoms may be less obvious in infants, and the clinician should carefully observe the infant for signs of sluggish pupils, reduced facial expression with prominent drooling, weak cry and suck, poor feeding, diminished suck and gag reflexes, generalized hypotonia (the "floppy baby"), and respiratory difficulty (FIGURE 2-5[50]).

FIGURE 2-5

Three-month-old patient with mild infant botulism. Ptosis, an expressionless face, and hypotonia of the neck, trunk, and limbs are evident. The additional bulbar palsies of ophthalmoplegia, weak cry, weak sucking, and dysphagia (drooling) are not apparent in the photograph.

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Diagnosis

Making a diagnosis of botulism requires careful history taking and consideration of a broad differential that includes acute inflammatory demyelinating polyradiculoneuropathy (AIDP), especially the Miller Fisher and pharyngeal-cervical-brachial variants; early chronic inflammatory demyelinating polyradiculoneuropathy (CIDP); other disorders of neuromuscular transmission such as myasthenia gravis or LEMS; tick paralysis; infections such as diphtheria and poliomyelitis; and brainstem strokes. Thorough examination of hair-covered areas and skin is necessary when acute descending paralysis is the presenting symptom to exclude the presence of ticks or wounds. Additionally, the clinician should perform a detailed sensory evaluation, as lack of sensory involvement is a distinguishing feature of botulism. In infants, the differential also includes such conditions as spinal muscular atrophy, metabolic disorders, and infection, particularly involving the central nervous system.

A diagnosis of botulism is confirmed only when botulinum neurotoxin is identified in a clinical or suspected food source. The traditional in vivo mouse lethality bioassay is the choice of public health departments and the CDC but is extremely labor-intensive and can take several days to complete. Modern in vitro techniques for identification of botulinum toxin include enzyme-linked immunosorbent assay (ELISA) and multiplex polymerase chain reaction (PCR) amplification techniques and provide qualitative evidence within a few hours. Public health laboratories including state health departments and the CDC recommend testing at least two sources and specifically stool or gastric aspirates in the case of suspected foodborne toxin or toxicoinfection.[48] When a wound source is suspected, it is important to also test the devitalized tissue. When botulism is suspected, the state health department and CDC should be notified immediately to obtain assistance, and therapy should not be delayed.

ELECTROPHYSIOLOGIC STUDIES. When botulism is suspected clinically, electrophysiologic studies can provide confirmation of disordered neuromuscular transmission before the return of confirmatory study results from public health departments. Electrophysiologic studies may be normal in early cases when the BoNT has not yet penetrated the nerve terminals; thus, normal studies should not justify a delay in therapy when circumstantial evidence for botulism is high. Botulism and LEMS share many electrodiagnostic features such as reduced CMAP amplitudes and facilitation after brief exercise or high-frequency repetitive nerve

KEY POINTS

- **Intoxication with botulinum toxin is most commonly due to serotypes A, B, and E.**
- **Sources of botulinum toxin transmission include food, wounds, toxicoinfection, and others (including iatrogenic).**
- **Early botulism may present with limited symptoms, and it is important to look for signs of clinical weakness involving craniobulbar muscles and autonomic dysfunction.**
- **Infant botulism classically presents as "floppy baby."**
- **An acute, descending paralysis without fever and sensory symptoms should raise suspicion for botulism.**
- **Confirmation of botulism requires identification of the neurotoxin and is performed in collaboration with the Centers for Disease Control and Prevention and state health departments.**
- **Providers should notify state health authorities and the Centers for Disease Control and Prevention immediately when botulism is suspected to assist with source identification, coordination of diagnostic testing, and acquisition of therapeutics.**

stimulation. Both are characterized by normal sensory and motor latencies and conduction velocities, but the electromyographer should be careful to exclude atypical forms of AIDP and CIDP that may be isolated to motor nerves. A side-by-side comparison of electrodiagnostic features in LEMS and botulism is shown in TABLE 2-3. Critical differences include less-apparent, longer-lasting postactivation facilitation on 2-Hz to 3-Hz repetitive nerve stimulation and an absence of postactivation exhaustion in botulism.[51] Jitter studies using single-fiber EMG techniques can be a useful adjunct, particularly when a patient is paralyzed and unable to activate muscles for voluntary repetitive nerve stimulation. This approach can be particularly helpful to identify blocked neuromuscular transmission in infants.

Treatment

The mainstay of treatment for botulism is supportive care. Patients with suspected botulism must be monitored closely in an intensive care unit for signs of respiratory failure, aspiration, and autonomic dysfunction. Because of the risk of rapid respiratory decompensation, early intubation is advised if there is a decline in respiratory parameters.

Patients with botulism are eligible for antitoxin or immunoglobulin therapy that is available through the CDC. Providers suspecting botulism should immediately contact health authorities for guidance on acquiring therapies, as early administration (within 3 days of hospital admission) can neutralize circulating toxin, prevent paralysis, and accelerate recovery.[48] Two therapies are available on request from the CDC: intravenous human botulism immune

TABLE 2-3 **Electrodiagnostic Features of Lambert-Eaton Myasthenic Syndrome and Botulism**

Feature	Lambert-Eaton myasthenic syndrome	Botulism
Routine studies		
Distal latencies and conduction velocities	Normal	Normal
Compound muscle action potential (CMAP) amplitude	Reduced	Reduced
Concentric needle examination	With or without pseudomyopathic changes	With or without pseudomyopathic changes
2- to 3-Hz repetitive nerve stimulation		
Postactivation facilitation	Marked (>100% amplitude) increment	Mild to moderate (30%-100% amplitude) increment
	Duration: <1 minute	Duration: several minutes
Single-fiber		
Jitter studies	Markedly abnormal	Markedly abnormal

globulin for infants (serotypes A and B only), and equine heptavalent botulinum antitoxin which covers serotypes A through G. If a serotype other than A or B is suspected in an infant, heptavalent toxin may also be administered for coverage of all seven serotypes. The equine antitoxin is highly immunogenic, and its use requires close monitoring because of the risk of infusion reactions and hypersensitivity reactions; this risk is greatest in individuals with prior exposure to equine antitoxins. Reactions such as headache, pyrexia, rash, urticaria, chills, nausea, and edema were reported in ≥1% of patients treated with equine antitoxin; although no anaphylactic reactions were reported in the initial studies, cases have been reported during postmarketing surveillance.[52]

Supportive care remains the mainstay of therapy, as recovery from paralysis is a slow process that can take many months because of the irreversible nature of botulinum toxin, requiring regeneration of nerve terminals. Supportive care, particularly respiratory support, and timely administration of antitoxins have reduced mortality from 60% to approximately 3%.[53-57]

Trends

Foodborne transmission and toxicoinfection continue to represent the largest transmission sources of botulism; however, the past decade has seen a rising increase in transmission due to iatrogenic intoxication and wound botulism. Iatrogenic botulism is due primarily to overdose from botulinum toxin use in the treatment of migraines, dystonias, blepharospasm, spasticity, sialorrhea, and cosmetic use. When evaluating for a disorder of neuromuscular transmission, it is particularly important to closely question a patient about prior exposure, as even a single exposure to targeted botulinum toxin can manifest with distant systemic symptoms.[58] EMG signs of prior exposure include abnormal spontaneous activity and short-amplitude, short-duration motor unit potentials with early recruitment or tall, thin, longer-duration motor unit potentials with reduced recruitment. If a study is performed after the recent administration of botulinum toxin, motor unit potentials may be unstable. These features add significant difficulty to the diagnosis of a neuromuscular transmission disorder and often require further evaluation with jitter studies and fiber-density studies to determine the etiology of the disordered motor unit architecture.

In addition to the rising use of botulinum toxin for medical and cosmetic purposes, the past 2 decades have seen an increase in cases of wound botulism that are primarily associated with the use of injectable opiates, particularly black tar heroin, in the setting of the more widespread opioid epidemic. Case numbers were stable in the range of 15 to 25 per year from 2001 to 2017 but rapidly increased to 61 cases, 51 of which were confirmed, in 2018.[46] Most of these cases were identified in users of black tar heroin who employ the technique of skin popping; the areas of injection subsequently become devitalized and a site for the growth of *Clostridium* species. The black tar formulation is less expensive to produce and is frequently adulterated with other compounds, with an average purity of only 27.1%; this form of heroin is also produced in nonsterile environments where there is greater risk of contamination from soil.[59] Providers unfamiliar with wound botulism may not consider this important diagnosis when a patient presents with symptoms of intoxication, which can lead to a delay in treatment with antitoxin. Sepsis due to cellulitis and polymicrobial wounds may also delay diagnosis, and patients may continue to worsen following antibiotic therapy. Clinicians in geographic areas with high IV

KEY POINTS

- **Moderate, long-lasting postactivation facilitation on 2-Hz to 3-Hz repetitive nerve stimulation and an absence of postactivation exhaustion are key electrodiagnostic features of botulism.**
- **A human immunoglobulin is available for infants and equine heptavalent botulinum antitoxin is available for adults through the Centers for Disease Control and Prevention.**

drug use must be aggressive in questioning patients regarding a history of recent drug use and should inform patients of the risks associated with drug use and skin popping.

CONCLUSION

LEMS and botulism are two prototypical disorders of neuromuscular transmission. High clinical suspicion based on a detailed history, thoughtful neurologic examination, and carefully planned serologic and electrodiagnostic studies are essential in making these diagnoses. In individuals with LEMS, evaluation for malignancy is essential, but it is also important to recognize that there is a non–cancer-associated form. Judicious use of symptomatic therapies for LEMS improves quality of life, and the nontumor LEMS subtype may be particularly responsive to long-term immunosuppression and immunomodulation. Although it shares some electrodiagnostic features with LEMS, botulism is due to an irreversible neurotoxin that causes a clinical toxidrome of acute, afebrile, descending paralysis. Electrodiagnostic studies can distinguish LEMS from botulism and other neuromuscular disease; however, the clinician must also be aware of potential exposure to botulinum toxin for medical and nonmedical purposes. Providers suspecting botulism should immediately contact the appropriate health authorities, as early treatment with antitoxin or immunoglobulin improves outcomes.

USEFUL WEBSITES

MYASTHENIA GRAVIS FOUNDATION OF AMERICA–CAUTIONARY DRUGS
The Myasthenia Gravis Foundation of America offers guidance on drugs to avoid in the treatment of patients with myasthenia gravis.

myasthenia.org/MG-Community/Cautionary-Drugs

CENTERS FOR DISEASE CONTROL AND PREVENTION–BOTULISM: INFORMATION FOR HEALTH PROFESSIONALS
The Centers for Disease Control and Prevention has developed clinical guidelines for the diagnosis and treatment of patients with botulism.

cdc.gov/botulism/health-professional.html

BOTULISM–GUIDE FOR HEALTHCARE PROFESSIONALS
The Government of Canada maintains a guide for healthcare professionals on ways to identify and report cases of botulism, how cases are confirmed through laboratory testing, and which treatments are approved in Canada for treating patients with botulism.

canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/botulism-guide-healthcare-professionals-2012

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