Diagnosis and Treatment of Lambert-Eaton Myasthenic Syndrome

Recognition of this rare immune-mediated disorder of the neuromuscular junction is critical for treatment, including of potential associated malignancy.

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Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune presynaptic disorder of the neuromuscular junction (NMJ) associated with weakness, reduced or absent muscle stretch reflexes, and autonomic dysfunction. Awareness of the clinical features, diagnostic evaluation, malignancy workup, and management of LEMS, as well as a high index of suspicion, are important for timely diagnosis and proper treatment.

Pathophysiology
The NMJ connects the terminal end of a motor nerve to a muscle and permits neuromuscular transmission. An action potential resulting in depolarized membrane potential causes opening of the voltage-gated calcium channel (VGCC), influx of calcium, and a sequence of events that culminates in the release of vesicles containing acetylcholine (ACh) into the synaptic space. Under physiologic conditions, ACh binds to its receptors located on the postsynaptic membrane, which results in propagation of the electrical impulse along the surface of the muscle membrane to the sarcoplasmic reticulum and excitation–contraction coupling.

LEMS is a presynaptic NMJ disorder in which ACh release is impaired. This most often is caused by autoantibodies against the P/Q-type VGCC, with impaired release of ACh from the presynaptic membrane resulting in transmission failure and the clinical symptoms of weakness and autonomic dysfunction. The relevant structures of the NMJ in the context of LEMS are illustrated in Figure 1.

LEMS is a rare autoimmune disease that is considered to be idiopathic or part of a paraneoplastic syndrome associated with a malignancy. Up to 60% of LEMS diagnoses are paraneoplastic in the context of an either known or undiagnosed malignancy. Small cell lung carcinoma (SCLC) is the most common associated malignancy, although non–small cell lung carcinoma, prostate carcinoma, and lymphoproliferative disorders have been described to be less commonly associated with LEMS. With tumor-associated LEMS, symptoms of LEMS typically precede the cancer diagnosis by up to 2 years.

Epidemiology
LEMS has an estimated prevalence of 10 per million. However, epidemiologic studies indicate that LEMS is approximately 50 times less common than myasthenia gravis (MG), and another study estimated a prevalence of 2.6 to 3.3 per million individuals. Tumor-associated LEMS more commonly affects men, with a 1 LEMS series showing 70% male prevalence, whereas non–tumor-associated LEMS affected slightly more women than men. Age at onset varies with LEMS type, with tumor-associated LEMS having a median age at onset of 58 to 60 years and non–tumor-associated LEMS having a median age at onset of 50 to 54 years. Non–tumor-associated LEMS has 2 peak median ages at onset: a peak at 35 years and another peak that overlaps with the median age at onset of tumor-associated LEMS.

Prognosis varies depending upon the underlying cause. Individuals with non–tumor-associated LEMS have a normal life expectancy but experience chronic symptoms that impair functional abilities and affect quality of life. Muscle strength at initial evaluation is the only factor that can predict long-term disease control. Individuals with tumor-associated LEMS have a poor long-term survival rate as a result of the associated malignancy. In the context of LEMS associated with SCLC, the median survival is approximately 18 months. Median survival in individuals with SCLC and LEMS is better than those with only SCLC (median survival...
of 17 vs 7 months). This longer survival was seen in both limited SCLC (median survival of 19 vs 12.1 months) and extensive SCLC (13 vs 4.9 months). Individuals with non–tumor-associated LEMS have a similar life expectancy to the general population.

**Clinical Features**

The primary clinical presentation of LEMS is the triad of muscle weakness, reduced or absent reflexes, and autonomic dysfunction. Weakness is most prominent in the proximal legs and arms, with other muscle groups being less severely affected. In contrast with MG, in LEMS, weakness of oculobulbar and axial muscles is generally mild or absent, and respiratory weakness is rare. Autonomic dysfunction is another common feature of LEMS. As such, the clinician will inquire about lightheadedness with position changes, dry mouth, constipation, urinary symptoms, and erectile dysfunction. Muscle weakness in LEMS starts in the proximal limbs, particularly the lower extremities and spreads from proximal to distal muscles.

A thorough neuromuscular examination should be completed in all individuals suspected of having LEMS. When LEMS is suspected based on the presenting symptoms, muscle stretch reflexes should be tested first, to avoid exercise-induced reflex facilitation. Muscle stretch reflexes are often reduced or absent, but will improve in about half of LEMS cases after brief exercise. This postexercise facilitation can be assessed by evaluating reflexes before and after manual muscle testing or by a 10-second exercise test. Muscle strength examination reveals proximal weakness and in advanced cases distal weakness. A thoughtful cerebellar examination should also be completed. Ataxia, dysmetria, or dysdiadochokinesias on examination may suggest the presence of paraneoplastic cerebellar degeneration, which can be seen in up to 10% of people with LEMS and SCLC.

**Diagnosis**

The diagnosis of LEMS is based on the presence of the typical clinical triad, with support from serology and electrodiagnostic testing. Serologic studies are used to confirm a suspected diagnosis of LEMS, with autoantibodies against the P/Q type VGCC being the most sensitive and specific for LEMS. The majority of people with LEMS are positive for the P/Q type VGCC antibody, with only 10% to 15% being seronegative. Autoantibodies against the N- and L-type VGCC also have been described, and may be seen together with positive P/Q-type VGCC antibody, although their presence is nonspecific and not supportive of a LEMS diagnosis when seen in isolation.

Electrodiagnostic studies may be helpful to exclude other diagnoses and provide additional supportive evidence of a presynaptic NMJ defect. When LEMS is suspected clinically, electrodiagnostic evaluation will consist of nerve conduction studies, needle EMG, slow (2- to 3-Hz) repetitive nerve stimulation (RNS), and either fast RNS (30- to 50-Hz) or assessing compound muscle action potentials (CMAPs) before and after brief exercise. The electrophysiologic triad of LEMS consists of low CMAP amplitude at rest, decrement on slow RNS, and incremental response at 50-Hz stimulation for 1 second or after brief 10-second exercise. As with MG, pathologic decrement is present in LEMS on slow RNS. However, the baseline CMAP amplitudes are preserved in MG.

The most common initial clue for LEMS is diffusely...
reduced CMAP amplitude. Whenever an individual with proximally predominant muscle weakness is noted to have diffusely low CMAP amplitudes, LEMS must be suspected. This is evaluated electrophysiologically by performing either fast RNS or CMAP recordings on several nerves before and after 10 seconds of exercise. CMAP recordings are preferred because they better tolerated. CMAP amplitude after exercise classically increases by 100%, consistent with facilitation, which is often seen on physical examination. Assessing CMAP amplitude before and after 10 seconds of muscle contraction showed facilitation in excess of 100% in 77% of participants when recording at the abductor digiti quinti, with other distal muscles showing lower sensitivity. Slow RNS typically shows decremental response in individuals with LEMS. High-frequency (50-Hz) RNS is also sensitive at showing the incremental response seen with LEMS, but is painful and infrequently utilized. The typical cutoff for a significant incremental response on fast RNS in LEMS is 100% which results in a sensitivity of 85%. Reducing the cutoff to 60% incremental response improves sensitivity to 97% without worsening specificity. Not all muscles show the characteristic electrophysiologic triad, particularly when brief exercise is the method used, likely because of the severity of associated muscle weakness impairing the quality of exercise. In a series including 73 participants consisting of testing involving 3 distal arm or leg muscles or the trapezius after brief exercise for incremental response, 41% of individuals showed 100% facilitation in all 3 muscles, 88% of individuals had 100% facilitation in only 1 muscle, and 13% of individuals had facilitation less than 100% in all muscles tested. A lower threshold for increment of 60% after brief exercise is more sensitive (80%) than 100% increment (60%) while maintaining high specificity. Single-fiber EMG may also be utilized to support a diagnosis of LEMS and is typically reserved for when there is strong suspicion for LEMS despite negative serology and nerve conduction studies. Single-fiber EMG is sensitive in the context of LEMS and correlates with clinical severity. Figure 2 illustrates a typical repetitive nerve stimulation pattern in the abductor pollicis brevis muscle in LEMS. Additional radiologic testing is mandatory in LEMS based on the strong association with malignancy, particularly SCLC. The DELTA-P (Dutch-English LEMS Tumor Association Prediction) score is helpful in predicting risk for future malignancy development and assists in modulating the frequency of imaging studies and other methods to evaluate for SCLC. Repeat screening for cancer every 3 to 6 months is recommended for at least 2 years after the diagnosis of LEMS.

**Conclusion**

LEMS is a rare autoimmune disease of the NMJ that is characterized by the clinical triad of proximal muscle weakness, dysautonomia, and hyporeflexia. There is a strong association with cancer, with more than half of LEMS cases being paraneoplastic in etiology, which renders serial cancer screening of critical importance. Diagnosis is based on history and examination findings, and is supported by serology (Continued on page 47)
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and an electrophysiologic triad. Treatment consists of management of the underlying cancer in paraneoplastic cases, symptomatic therapy with 3,4-DAP, and consideration of intravenous immunoglobulin, plasma exchange, or immunosuppression in severe or refractory cases. A high clinical suspicion and familiarity with LEMS are required as the symptoms may mimic other disorders and go unrecognized, leading to diagnostic and treatment delays.


Disclosures

Dr. Varon reports no disclosures.

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