Lambert-Eaton Myasthenic Syndrome

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ABSTRACT

Lambert-Eaton myasthenic syndrome (LEMS) is an idiopathic or paraneoplastic syndrome producing antibodies against presynaptic voltage-gated P/Q calcium channels. This decreases calcium entry into the presynaptic terminal, which prevents binding of vesicles to the presynaptic membrane and acetylcholine release. LEMS is most often associated with small cell lung cancer, although idiopathic presentations comprise ~40% of the cases. The most common initial complaint is proximal muscle weakness involving the lower extremities more than the upper extremities. Depressed deep tendon reflexes and autonomic dysfunction are frequently present. Involvement of the bulbar or respiratory muscles is rare. Diagnosis is confirmed by electrophysiological testing, which demonstrates small compound muscle action potentials and facilitation with exercise or 20-Hz repetitive stimulation. A serum test for voltage-gated calcium channel antibodies is commercially available. Treatment involves removing the cancer associated with the disease. If cancer is not found, immunosuppressive medications and acetylcholinesterase inhibitors are used with moderate success. Patients with idiopathic LEMS should be screened every 6 months with chest imaging for cancer.

KEYWORDS: Lambert-Eaton myasthenic syndrome, paraneoplastic syndrome, voltage-gated P/Q calcium channels

Objectives: On completion of this article, the reader will have an understanding of the pathophysiology, clinical presentation, diagnosis, and treatment of the Lambert-Eaton myasthenic syndrome.

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Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disease producing antibodies against presynaptic voltage-gated calcium channels. It can occur sporadically or as a paraneoplastic syndrome, most often associated with small cell carcinoma of the lung. The clinical presentation may be mistaken for myasthenia gravis, as there are some similarities in their pathophysiology.[1]

Lambert and colleagues first described weakness due to neuromuscular transmission deficiency in association with malignancy in the 1950s.[2] In the 1970s, an autoimmune etiology was suggested in LEMS seen in association with other autoimmune disorders.[3] The autoimmune theory was confirmed in the early 1980s by a series of studies resulting in normal rats developing LEMS after injecting them with immunoglobulin G

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(IgG) antibodies from diseased rats.[4] Antibody blockage of the P/Q voltage-gated calcium channels was identified in the 1990s as the major etiology of the disease process of LEMS.[5]

PATHOPHYSIOLOGY

The normal neuromuscular junction is comprised of the presynaptic neuronal membrane, the synaptic cleft, and the postsynaptic muscle membrane (Fig. 1). As a wave of depolarization arrives at the nerve terminal, voltage-gated calcium channels allow calcium to enter the presynaptic nerve terminal. Calcium is necessary for the vesicles containing quanta of acetylcholine (Ach) to bind to the presynaptic membrane.[6] The vesicles bind in specific regions of the presynaptic membrane called "active zones." Once the quanta are released, Ach crosses the cleft and binds to the postsynaptic receptors on the muscle membrane. The Ach binding causes an end-plate potential, a graded depolarization of the muscle membrane. If the end-plate potential reaches threshold to cause an action potential, muscle fiber contraction occurs.[7]

In 1956, Lambert and colleagues described patients with weakness and fatigue associated with a malignancy.[2] These symptoms were thought to be an indirect effect of the malignancy, or a paraneoplastic syndrome. Although spontaneous release of Ach is not affected, Ach release from presynaptic vesicles following neuronal depolarization is defective.[8] Production of antibodies against presynaptic voltage-gated calcium channels was the presumed cause. With the voltage-gated calcium channels blocked by antibodies, calcium is not able to flow into the nerve terminal when depolarization occurs and Ach cannot be released.[6] Passive transfer of the disease from diseased rats to unaffected rats via serum has been demonstrated. The normal animals developed the disease process after transfusion with both physical and electrophysiological signs, supporting the theory of an autoimmune process.[9,10] There are many subtypes of calcium channels, all determined by the α_1 subunit of the calcium channel. Early reports implicated the L- and N-type calcium channels.[8] However, the antibodies were eventually shown to be associated with the P/Q subtype of the voltage-gated calcium channel.[11] The antibodies not only block the voltage-gated calcium channels at the neuromuscular junction but also block them at muscarinic receptors, thus creating autonomic insufficiency and autonomic symptoms.[1]

The number of active zones, areas where vesicles attach to the presynaptic membrane to release Ach, have also been shown to be reduced in LEMS through techniques of freeze fracture and electron microscopy.

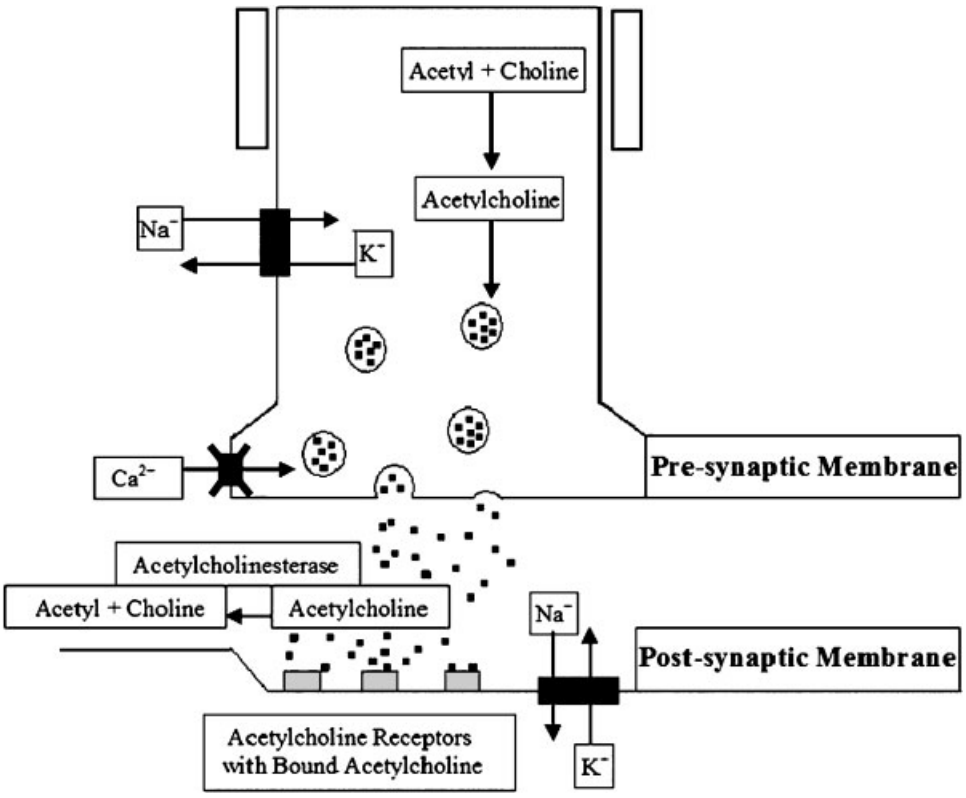

Figure 1 The neuromuscular junction is comprised of the presynaptic membrane, synaptic cleft, and postsynaptic membrane. Antibodies in Lambert-Eaton myasthenic syndrome are directed against the voltage-gated calcium channels in the presynaptic membrane, indicated by the X.

Active zones include particles that align the quanta into units.[9] It is hypothesized that the IgG antibodies responsible for blocking the voltage-gated calcium channels also link to these particles that align the vesicles in the active zone. This active linking groups the particles together and then decreases the number of particles associated with active zones. This would decrease the number of vesicles binding to active zones.[7,9]

With the voltage-gated calcium channels blocked, there is a decrease in calcium influx during depolarization of the presynaptic membrane. The vesicles containing Ach cannot bind to the presynaptic membrane and less Ach is released into the synaptic cleft. In addition, the decrease in active zones further reduces the amount of Ach released. Therefore, fewer end-plate potentials will reach threshold, resulting in fewer action potentials and reduced number of muscle fibers contracting or no muscle fiber contraction. This is reflected electrophysiologically as small compound muscle action potential (CMAP) amplitudes.[7] After a short duration of exercise (10 seconds), nerve conduction studies demonstrate an increase in CMAP amplitudes. Short duration of contraction causes the nerve terminal to depolarize repeatedly. This allows calcium to enter and accumulate in the nerve terminal more quickly than it can be cleared. Due to the increase in calcium, more vesicles are able to attach to the presynaptic membrane and release more Ach. This leads to a normal or near-normal muscle contraction and motor nerve conduction amplitudes. This effect is short-lived as the calcium is quickly removed from the nerve terminal by the mitochondria.[7]

Muscle biopsies have been done in LEMS patients to try to differentiate the disease process further. In these cases, type 2 muscle fiber predominance has been noted. This finding is more likely due to the decrease in muscle activity experienced during the disease process, leading to the conversion from type 1 (slow twitch) fibers to type 2 (fast twitch) fibers, rather than the disease process itself.[10]

CLINICAL PRESENTATION

LEMS usually presents in adulthood, usually over 40 years of age, although it can present at any age.[4] Due to similarities in clinical presentation, LEMS can be easily mistaken for myasthenia gravis (MG). Wirtz and colleagues examined the patterns of weakness between MG and LEMS and found that MG involved ocular muscles and bulbar muscles more prominently than LEMS. In addition, all LEMS patients in their study had lower extremity involvement, although the lower extremities were spared in a significant proportion of MG patients.[12]

Proximal muscle weakness, greater in the lower extremities than in the upper extremities, is the typical clinical presentation.[4] The weakness is exacerbated by exercise and heat. Rarely, cranial nerve symptoms such as ptosis, difficulty swallowing, and double vision may also be present. However, if ocular weakness is the only finding, then another diagnosis should be considered.[12] Respiratory failure is rarely the presenting symptom in LEMS patients, although it can develop later in the disease process.[13] Autonomic dysfunction, including dry mouth, blurred vision, constipation, and orthostatic hypotension, occurs in up to 75% of patients (Table 1).[9] To direct muscle strength testing, the patient may seem minimally weak. This is due to the nearly continuous influx of calcium and its buildup in the presynaptic nerve terminal with exercise.[14] Initially, calcium is blocked from entering the presynaptic terminal due to the voltage-gated calcium channel antibodies. Less Ach is released and the muscle contraction is decreased. With continuous contraction from strength testing, calcium accumulates faster than it can be removed by the mitochondria. This buildup of calcium allows more vesicles to attach to the nerve membrane and release Ach, producing a normal or near-normal contraction for the short time that strength is tested in any particular muscle.[7] This is referred to as Lambert's sign when the grip becomes more powerful over several seconds of strength testing.[1]

On examination, most LEMS patients also have depressed muscle stretch reflexes.[4] The stretch reflex causes a muscle contraction. Briefly exercising the muscle involved in the stretch reflex and then rechecking the reflex results in a normal or near-normal muscle stretch reflex. This finding is again a result of the calcium entry

Table 1 Signs and Symptoms of Lambert-Eaton Myasthenic Syndrome

Symptoms
Proximal limb weakness
Legs > arms
Fatigue or fluctuating symptoms
Difficulty rising from a sitting position, climbing stairs
Metallic taste in mouth
Autonomic dysfunction
Dry mouth
Constipation
Blurred vision
Impaired sweating
Signs
Proximal limb weakness
Legs > arms
Weakness on exam is less demonstrable than patient's level of disability
Hypoactive or absent muscle stretch reflexes
Lambert's sign (grip becomes more powerful over several seconds)
Sluggish pupillary reflexes

into the presynaptic terminal with exercise enhancing the muscle contraction.[7] Autonomic dysfunction is evidenced by complaints of dry mouth and findings of sluggish pupils and orthostasis.[1,4] This is also attributable to the decrease in the number of vesicles of Ach binding to the presynaptic membrane and being released at the muscarinic receptors.

Clinically, 50 to 70% of LEMS patients will have associated cancer as was originally described by Lambert and colleagues.[2] Small cell lung carcinoma is most commonly associated with LEMS.[2,4] The cancer cells have proteins that have been demonstrated to match proteins found in the P/Q_voltage-gated calcium channels, thus stimulating an autoimmune response.[15] LEMS may precede the diagnosis of cancer by ~2 years.[4] In addition to carcinomas, LEMS can be associated with other autoimmune disorders, such as hypothyroidism, pernicious anemia, celiac disease, and juvenile-onset diabetes mellitus.[3,4]

DIAGNOSIS

The most common differential diagnoses for LEMS are MG and myopathy. Distinguishing clinical features such as autonomic symptoms and depressed reflexes help to differentiate these. Electrophysiological testing also has distinctive features. A serological test for voltage-gated calcium channel antibodies is positive in 85% of patients with LEMS.[1]

With electrophysiological testing, CMAP amplitudes are small but latencies and conduction velocities are normal. Repetitive stimulation at 2 Hz may produce a decrement in CMAP amplitudes. This decrement is a normal physiological function amplified by the disease. With slow repetitive stimulation (less than 5 Hz), the amount of readily available Ach is depleted after each stimulation, releasing less Ach each time. This lasts for the first few stimuli, at which point mobilization of stored Ach occurs. In normal patients, the amount of Ach released with each stimulus is still enough to reach action potential threshold, despite the decrease in amount released. In LEMS, the amount released does not reach threshold for all the action potentials to occur, resulting in a decrement in amplitude of the first few CMAPs. This is also seen in MG. After exercise for 10 seconds or with repetitive stimulation exceeding 20 Hz for 10 seconds, the CMAP amplitude will immediately increase by greater than 200%[7] (Figs. 2, 3). In

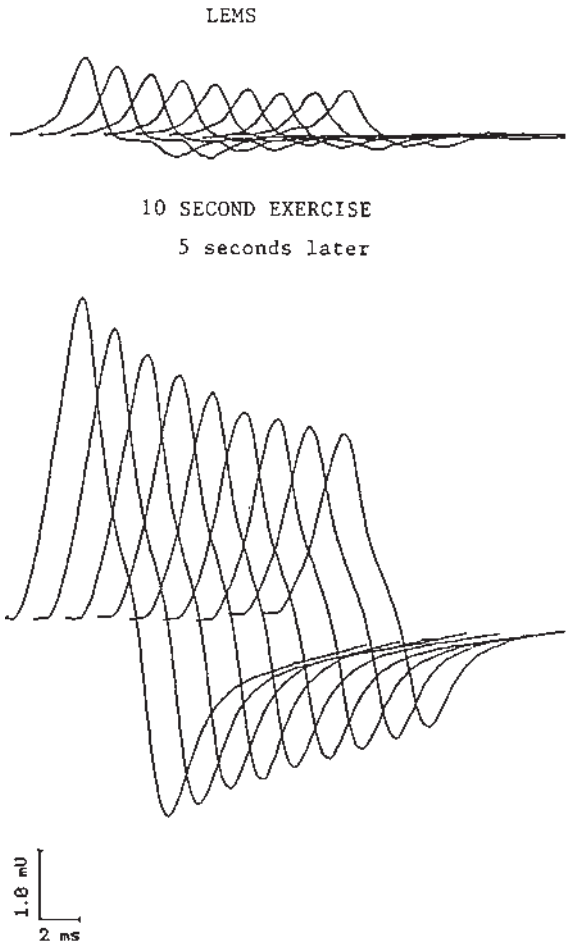

Figure 2 Decrement is seen in 2-Hz repetitive stimulation. Postexercise facilitation after 10 seconds of exercise is seen with a greater than 200% increment in compound motor action potential amplitude.

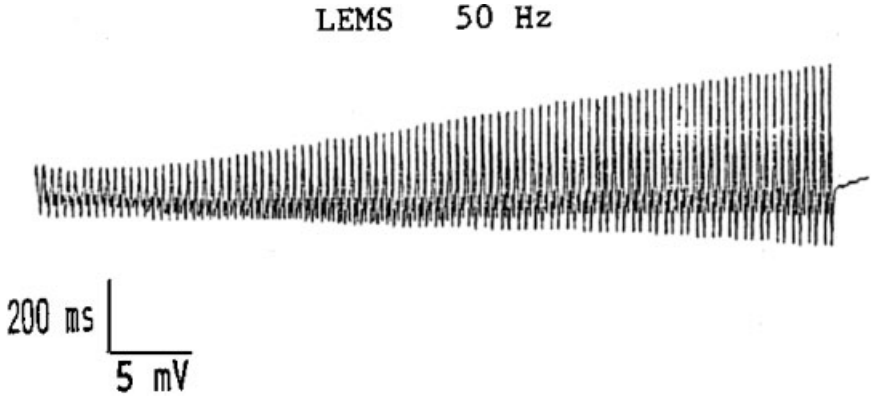

Figure 3 Repetitive stimulation at 50 Hz produces an increase in compound motor action potential amplitudes.

a review of 50 patients, the mean increase in amplitude was 890% after exercise.[4] The initial small CMAP amplitude is due to the decreased influx of calcium due to the voltage-gated calcium channel antibodies. With brief sustained muscle contraction, as described earlier, calcium concentrations are increased in the presynaptic nerve terminal, more Ach is released, and the CMAP amplitude is briefly increased. This can last up to 30 seconds.[7]

Single-fiber examination demonstrates increased jitter, consistent with a neuromuscular junction deficit.[4,7] Blocking may also be seen, demonstrating that either not enough quanta were released to reach threshold or the time to reach threshold was too long and the response was not recorded.[7] Blood work useful in clarifying the diagnosis includes creatine kinase, thyroid functions and calcium channel antibodies.[4] Because of the high incidence of lung cancer associated with LEMS, a chest computed tomography or magnetic resonance to look for cancer needs to be part of the evaluation.[4]

TREATMENT

Treatment of LEMS depends on the etiology of the disease. When associated with cancer, treating the cancer will usually improve symptoms significantly.[1,4] It has been demonstrated that calcium channels in the cancer cells cross-react with the presynaptic voltage-gated calcium channels. Removal of the cancer may reduce the autoimmune response and antibody production.[5,15] Regardless of the presence of cancer, using immunosuppressive drugs such as azathioprine and prednisone are useful but not as helpful when compared with their use in treating other autoimmune diseases.[4] Intravenous immunoglobulin has also been used with some success. Pyridostigmine, an anticholinesterase inhibitor, can also reduce symptoms.[5,16] Inhibition of acetylcholinesterase will decrease the amount of breakdown of Ach, thus increasing the amount found in the synaptic cleft. This increase in Ach concentration allows more end-plate potentials to reach threshold, resulting in a larger number of action potentials and greater muscle contraction. Plasma exchange has been used to filter out the antibodies causing the disease and has been suggested to be the first line of treatment in acute situations. The use of plasma exchange has had limited success because the benefit dissipates more quickly than in other diseases such as MG. It has been suggested that immunosuppressive drugs are needed to maintain the benefits of plasma exchange.[5] Another drug used for the treatment of LEMS is 3,4-diaminopyridine (3,4-DAP). 3,4-DAP is a potassium channel blocker, which helps to maintain depolarization of the nerve terminal by preventing repolarization.[4] This allows more calcium to enter the nerve terminal and release more Ach.

If cancer has not been found in patients presenting with LEMS, they should be screened for small cell lung carcinoma every 6 months with chest imaging for at least 2 years. In addition, evaluation for other autoimmune disorders should be done.[1]

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