Lambert-Eaton Myasthenic Syndrome

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Introduction

Background

Lambert-Eaton myasthenic syndrome (LEMS) is a rare condition in which weakness results from an abnormality of acetylcholine (ACh) release at the neuromuscular junction. LEMS results from an autoimmune attack against voltage-gated calcium channels (VGCC) on the presynaptic motor nerve terminal.

Cancer is present when the weakness begins or is later found in 40% of patients with LEMS. This is usually a small cell lung cancer (SCLC), although LEMS has also been associated with non-SCLC, lymphosarcoma, malignant thymoma, or carcinoma of the breast, stomach, colon, prostate, bladder, kidney, or gallbladder.

Clinical manifestations frequently precede cancer identification. In most cases, the cancer is discovered within the first 2 years after onset of LEMS and, in virtually all cases, within 4 years.

Pathophysiology

Physiological studies of neuromuscular transmission demonstrate that ACh release from the motor nerve terminal is impaired in the LEMS muscle. The effect of ACh on the postsynaptic muscle membrane is normal.

The following clinical observations suggest autoimmune etiology: LEMS is frequently associated with known autoimmune diseases. Prednisone, plasma exchange (PEX), and intravenous hyperimmune human gamma globulin (IVIg) are effective treatments. Patients with LEMS but without cancer frequently have elevated serum levels of organ-specific autoantibodies.

More direct evidence has been accumulated supporting the autoimmune etiology of LEMS. Active zone particles (AZP), which represent the VGCCs, are normally arranged in regular parallel arrays on the presynaptic muscle membrane. In patients with LEMS and in mice injected with LEMS immunoglobulin G (IgG), divalent antibodies against the VGCC cross-link the calcium channels, disrupting the parallel arrays. Ultimately, the AZPs cluster and decrease in number.

SCLC cells originate from neuroectoderm, share a number of antigens with peripheral nervous system tissue, and contain high concentrations of VGCC. Calcium influx into these cells is inhibited by LEMS IgG. Antibodies to VGCC are found in the serum of most LEMS patients. These observations suggest that VGCC antibodies down-regulate VGCC in LEMS.

In patients with LEMS who have SCLC or other cancer, cancer cells presumably contain antigens that mimic VGCC and induce production of VGCC antibodies. In patients with LEMS but no cancer, VGCC antibodies are probably produced as part of a more general autoimmune state. In patients with LEMS without cancer, an antibody response to domain IV of the 1A subunit of P/Q-type VGCC is more common then in LEMS with cancer.

VGCC antibody levels do not correlate with disease severity among patients with LEMS. However, antibody levels do fall in individual patients if the disease improves after cancer therapy or immunosuppression.

Frequency

United States

An estimated 3% of patients with SCLC have LEMS. The prevalence of SCLC is 5 cases per million population in the United States. Only half of patients with LEMS have a tumor, so total prevalence is at least double this figure (1 case per 100,000 population). Because in many patients LEMS is undiagnosed, the true incidence is probably higher.

Mortality/Morbidity

Morbidity and mortality correlate with the morbidity and mortality of the underlying SCLC.

Sex

In earlier reports, LEMS occurred in males more frequently than females by a ratio of almost 2:1. However, more recent studies show that the sex incidence is almost equal.

Age

LEMS usually begins in later adulthood; it can occur in children, but rarely.

Clinical

History

Symptoms usually begin insidiously. Many patients have symptoms for months or years before the diagnosis is made. Weakness is the major symptom, with proximal muscles more affected than distal muscles (especially in the lower limbs).

- The typical patient with LEMS presents with slowly progressive proximal leg weakness.
    - Weak muscles may ache and are occasionally tender.
    - Oropharyngeal and ocular muscles may be mildly affected.
    - Respiratory muscles are not usually affected, but cases with severe respiratory compromise have been reported.
- Most patients have a dry mouth, which frequently precedes other symptoms of LEMS. Many do not mention this unless specifically questioned.
    - Many patients report an unpleasant metallic taste.
    - Some patients have other manifestations of autonomic dysfunction, including impotence in males and postural hypotension.
- LEMS may be discovered first when prolonged paralysis follows the use of neuromuscular blocking agents during surgery.
- Exacerbation of weakness has been described following administration of aminoglycoside or fluoroquinolone antibiotics, magnesium, calcium channel blockers, and iodinated intravenous contrast agents.
- Relationship between cancer and LEMS
    - Smoking and age at onset are major risk factors for cancer in patients with LEMS.
    - Duration of symptoms is a factor.
    - If a tumor is not found within the first 2 years after symptom onset, cancer is unlikely. For example, a patient younger than 50 years at onset who does not have a tumor discovered after 2 years of close follow-up is unlikely to have an underlying cancer. On the other hand, a long-term smoker with LEMS onset after age 50 years probably has underlying lung cancer.

Physical

Weakness is usually mild compared to the patient's reports.

- Strength is usually reduced in proximal muscles of the legs and arms, producing a waddling gait and difficulty elevating the arms.
- Some degree of eyelid ptosis or diplopia, usually mild, is found in 25% of patients. Occasionally, difficulty chewing, dysphagia, or dysarthria is present.
- Most patients have a dry mouth, eyes, or skin.
- In some patients, strength may improve after exercise and then weaken as activity is sustained. This is demonstrable in approximately half of all patients with LEMS.
- Tendon reflexes are reduced or absent but can frequently be provoked or increased by activating the appropriate muscles or by repeatedly tapping the tendon.

- Sensory examination is normal unless a coincident peripheral neuropathy is present, which is not uncommon in patients with underlying cancer.
- Tensilon or pyridostigmine may improve strength, but this is rarely as dramatic as in myasthenia gravis (MG).

Causes

All patients with LEMS who have associated SCLC have a history of long-term smoking. Only half of patients with autoimmune LEMS are long-term smokers.

Differential Diagnoses

Acute Inflammatory Demyelinating Polyradiculoneuropathy
Chronic Inflammatory Demyelinating Polyradiculoneuropathy
Dermatomyositis/Polymyositis
Inclusion Body Myositis
Myasthenia Gravis
Spinal Muscular Atrophy

Other Problems to Be Considered

Cachexia
Paraneoplastic neuropathy

Workup

Laboratory Studies

- Voltage-gated calcium channel antibodies
  - VGCC antibodies have been reported in 75-100% of patients with Lambert-Eaton myasthenic syndrome (LEMS) who have SCLC and in 50-90% of patients with LEMS without underlying cancer.
  - They are also found in fewer than 5% of patients with MG, in up to 25% of patients with lung cancer without LEMS, and in some patients who do not have LEMS but have high levels of circulating immunoglobulins (eg, systemic lupus erythematosus, rheumatoid arthritis).
  - Sensitivity and specificity of the VGCC assay are affected by the source of antigen and the specific laboratory measuring the antibody.
  - Reports suggest that SOX1, an immunogenic tumor antigen in small cell lung cancer, may play a role in identifying LEMS patients with lung cancer.[1]

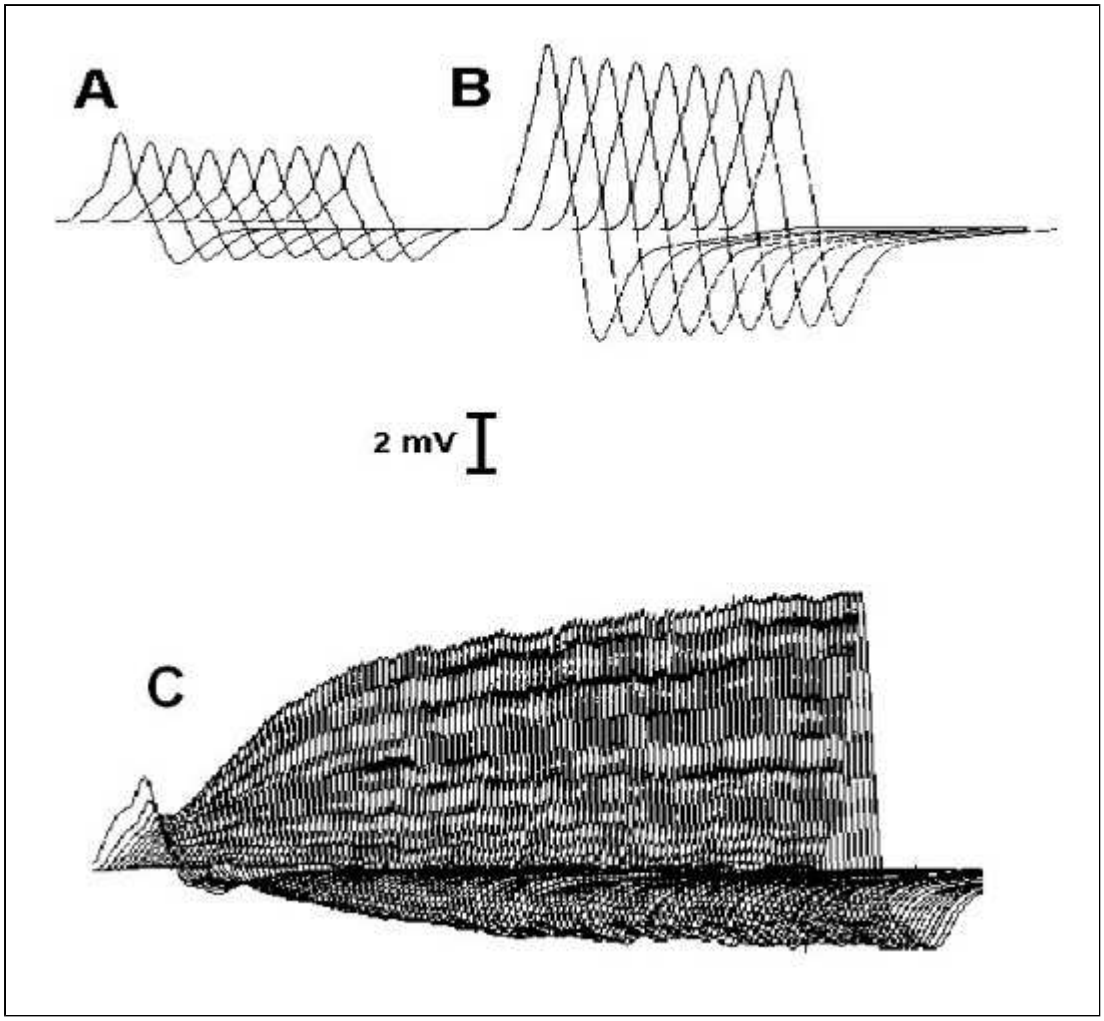
Imaging Studies

- CT scanning or MRI of chest
  - SCLC is the malignancy most frequently associated with LEMS.
  - In all adult patients with LEMS, imaging studies of the chest for cancer detection should be performed. If imaging findings are negative in a patient with a substantial risk of having lung cancer, bronchoscopy should be performed. If both imaging and bronchoscopy results are initially negative and risk factors for lung cancer are present, positron emission tomography (PET) scanning should be considered. If all imaging study results are negative in such patients, periodic reassessment thereafter is indicated.

Other Tests

- Acetylcholine receptor antibodies
  - ACh receptor (AChR) antibodies are most commonly associated with MG.
  - AChR antibodies are occasionally found in low titers in LEMS.

Procedures

- Repetitive nerve stimulation studies
    - These studies confirm the LEMS diagnosis by demonstrating characteristic findings on electrodiagnostic studies (see image below). Compound muscle action potentials (CMAPs) recorded with surface electrodes are usually small, often less than 10% of normal, and fall during 1- to 5-Hz repetitive nerve stimulation (RNS)
    - 

Characteristic responses to repetitive nerve stimulation in a patient with Lambert-Eaton myasthenic syndrome (LEMS). A: Responses elicited from a hand muscle by stimulation of the nerve at 3 Hz. Amplitude of the initial response is less than normal and the response is decremental. B: Responses as in A, immediately after voluntary activation of the muscle for 10 seconds. Amplitude has increased. C: Responses in a hand muscle elicited by 20-Hz stimulation of the nerve for 10 seconds. Response amplitude is less than normal initially, falls further during the first few stimuli, then increases and ultimately becomes more than twice the initial value.

    - During stimulation at 20-50 Hz, the CMAP increases in size (ie, facilitation) and characteristically becomes at least twice the size of the initial response.
    - A similar increase in CMAP size is seen immediately after the patient voluntarily contracts the muscle maximally for several seconds (see image below).
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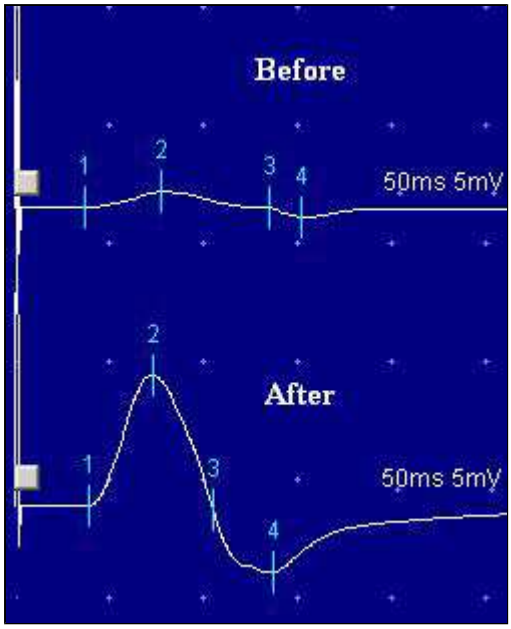

Compound muscle action potentials elicited from a hand muscle before and immediately after maximal voluntary activation of the muscle for 10 seconds. The amplitude is small initially, increasing almost 10 times after activation.

- In virtually all patients with LEMS, a decremental response to low-frequency nerve stimulation is observed in the hand muscles. This finding is not specific to LEMS and can be seen in MG and other neuromuscular diseases.
- In LEMS, the CMAP amplitude is low in most muscles tested. This finding is also nonspecific and is commonly observed in other neuromuscular diseases.
- Facilitation greater than 100% is seen in some but not all muscles (or in all patients) with LEMS. Facilitation greater than 50% in any muscle suggests LEMS. However, these findings might also be observed in MG. If facilitation is greater than 100% in most muscles tested or greater than 400% in any muscle, the patient almost certainly has LEMS. If facilitation is less than 50% in all muscles tested, the patient still may have LEMS, especially if weakness has been present for only a short time or the patient has been partially treated.
- When LEMS is mild, the electromyography (EMG) findings may resemble those of MG, including normal CMAP amplitudes, decremental response to RNS at low rates, and little facilitation. One helpful feature is that in LEMS, the EMG findings are usually more severe than the clinical findings would suggest. The opposite is frequently true in MG.

- Needle electromyography: Conventional needle EMG in LEMS demonstrates markedly unstable motor unit action potentials, which vary in shape during voluntary activation.
- Single-fiber electromyography
  - The jitter and blocking measured by single-fiber EMG is increased markedly in LEMS, frequently out of proportion to the severity of weakness.
  - In many endplates, jitter and blocking decrease as the firing rate increases. This pattern is not seen in all endplates or in all patients with LEMS.
  - Because jitter and blocking may also decrease at higher firing rates in some endplates of patients with MG, this pattern does not confirm an LEMS diagnosis unless it is dramatic and seen in most muscles.
- Bronchoscopy: If risk of lung cancer is substantial and findings on imaging studies are normal, perform bronchoscopy to detect SCLC. If these findings are also normal, consider PET scanning.

Treatment

Medical Care

- Individually tailor therapy on the basis of severity of weakness, underlying disease(s), life expectancy, and response to

previous treatment.

- When the Lambert-Eaton myasthenic syndrome (LEMS) diagnosis is confirmed, extensively search for an underlying malignancy with radiography and CT scanning of the chest, bronchoscopy, and possibly PET scanning.
- Initial treatment should be aimed at the neoplasm because weakness frequently improves with effective cancer therapy. No further LEMS treatment may be necessary in some patients.

- If no tumor is found, periodically search again for occult malignancy. Frequency of these evaluations is determined by the patient's risk of cancer.
  - Patients younger than 50 years without history of long-term smoking have a low risk of associated malignancy, especially if evidence of coexisting autoimmune disease is present. Extensive surveillance for cancer may not be necessary for such patients.
  - Patients older than 50 years with history of long-term smoking almost certainly have underlying small cell lung cancer (SCLC).

- In patients with cancer, LEMS is usually not the major therapeutic concern. The initial concern is the cancer.
  - Immunotherapy of LEMS without effective treatment of the underlying cancer usually produces little or no improvement in strength. A theoretical concern is that the immunosuppression may reduce immunologic suppression of tumor growth.
  - In patients with LEMS who do not have cancer, aggressive immunotherapy is justified more readily.

Consultations

Appropriate consultations include a neurologist and may include an oncologist and a physical medicine specialist.

Medication

The initial pharmacotherapy of LEMS is with agents that increase the transmission of ACh across the neuromuscular junction, either by increasing the release of ACh or by decreasing the action of acetylcholinesterase. Treatment of the associated cancer may also decrease the weakness and other symptoms.

If these treatments are not effective and the patient has relatively mild weakness, determine if aggressive immunotherapy is justified. When such therapy is warranted, PEX or high-dose IVIg may be used initially to induce rapid, albeit transitory, improvement. Immunosuppressants should be added for more sustained improvement, although a theoretical concern exists that immunologic suppression of tumor growth may thereby be reduced in paraneoplastic LEMS.

Prednisone and azathioprine, the most frequently used immunosuppressants, can be used alone or in combination. Cyclosporine may benefit patients with LEMS who are candidates for immunosuppression but cannot take or do not respond well to azathioprine. Improvement may be seen within 1-2 mo after beginning cyclosporine, while the maximum response is usually observed in 3-4 mo.

PEX produces improvement in many patients with LEMS. Improvement is temporary unless the patient is also receiving immunosuppression. Response to PEX in patients with LEMS is often more gradual than in those with MG. Maximal response may take several weeks. Repeated courses of PEX may be necessary to maintain improvement. PEX may be performed 4-6 times over 7-10 d, as described in standard protocols. Potential complications include autonomic instability, hypercalcemia, and bleeding due to depletion of clotting factors.

IVIg, given in a course of 2 g/kg over 2-5 d, also induces clinically significant temporary improvement in many patients. The frequency of improvement in response to repeated courses of treatment has not been determined.

Neuromuscular agents

These agents produce symptomatic improvement in strength, autonomic symptoms, or both in some patients with LEMS.

Pyridostigmine bromide (Mestinon)

Acetylcholinesterase inhibitors do not usually produce dramatic improvement in LEMS, but they may provide relief from

weakness or dry mouth in some patients. Pyridostigmine is the preferred agent and should be administered for several days before assessing response.

Dosing

Adult

30 or 60 mg PO q4-6h

Pediatric

Not established

Interactions

Complements beneficial actions and adverse GI effects of 3,4-diaminopyridine; increases effects of depolarizing neuromuscular blockers; increases toxicity of edrophonium

Contraindications

Documented hypersensitivity; GI or GU obstruction

Precautions

Pregnancy

A - Fetal risk not revealed in controlled studies in humans

Precautions

Individually determine dose for each patient; an excessively high dose may cause diarrhea, abdominal cramping, or increased weakness; beneficial and adverse actions of these medications complement those of 3,4-diaminopyridine

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3,4-Diaminopyridine (DAP)

Aminopyridines improve neuromuscular transmission by facilitating release of ACh from the motor nerve terminal. They act by presynaptic potassium channel blockade, prolonging action potentials and extending activation of VGCC. For >20 y, has been used to improve strength and autonomic function in patients with LEMS. Effect begins about 20 min after a PO dose. Each dose lasts about 4 h, and maximum effect of a given dosage may not be observed for 2-3 d. Patients with or without underlying cancer benefit from DAP. In the authors' experience, >80% of patients with LEMS have significant clinical benefit; in over half of these, improvement is marked. Not approved for clinical use in the United States, but available on a compassionate-use basis for individual patients. In most patients, pyridostigmine enhances and prolongs duration of action, permitting lower doses.
Obtain application process information from
Jacobus Pharmaceutical Co., Inc.
Princeton, NJ
Fax # 609-799-1176

Dosing

Adult

Optimal dose varies considerably among patients, so tailor dose and dosing schedule for each patient as follows:
10 mg PO tid/qid initial dose; observe response for 2 wk, increase dose in 5-mg increments at 2-wk intervals until maximum benefit obtained; not to exceed 80 mg/d; add pyridostigmine, 30 or 60 mg tid, and note effect on maximum response and on duration of action of each DAP dose; reduce DAP dose in 5-mg decrements until lowest effective dose determined
Optimal dose of DAP may change, so periodically reassess response to medication by slowly reducing dose to redetermine minimum dose that produces maximum response; repeat this procedure at least q12mo

Pediatric

Interactions

In most patients, pyridostigmine enhances and prolongs the duration of action of DAP and permits lower doses; DAP may increase adverse GI effects of pyridostigmine; if this occurs, reduce dose of pyridostigmine

Contraindications

Documented hypersensitivity; history of seizures; cardiac arrhythmia

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Adverse effects minimal, usually limited to brief perioral and digital paresthesias, if dose is >10 mg; GI hyperactivity with cramps and diarrhea may occur when DAP is taken with pyridostigmine; minimize this effect by reducing pyridostigmine dose; seizures may occur at doses >100 mg/d; asthma attacks have been induced in patients with preexisting asthma; theoretically, DAP could cause cardiac arrhythmia, although no such effects have been reported; no known organ toxicity even in patients with LEMS who have taken aminopyridines for >10 y; because clinical experience with these agents is limited, periodically perform blood tests of liver, kidney, and hematologic functions to detect adverse effects; liver function tests, BUN and creatinine, and CBC should be performed q3mo for first year, then q6-12mo

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Guanidine HCl

Increases ACh release and temporarily improves strength in many patients with LEMS.
Maximal effect may take 2-3 d.

Dosing

Adult

5-10 mg/kg/d PO divided throughout waking hours as initial dose; may increase prn, but not more often than q3d; not to exceed 30 mg/kg/d depending on clinical response; adverse effects may be severe at doses > 1 g/d

Pediatric

Interactions

Pyridostigmine enhances therapeutic response to guanidine and permits lower dose

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Use guanidine with extreme caution because of frequent adverse effects, including bone marrow suppression, renal tubular acidosis, chronic interstitial nephritis, cardiac arrhythmia, hepatic toxicity, pancreatic dysfunction, peripheral paresthesias, ataxia, confusion, and mood alterations; perform frequent blood tests of hematologic, hepatic, and renal functions

Blood products

Intravenous immunoglobulin can be an effective treatment for LEMS.

Intravenous immunoglobulin (IVIg)

Features that may be relevant to efficacy include neutralization of circulating antibodies through anti-idiotypic antibodies; down-regulation of proinflammatory cytokines, including IFN-gamma; blockade of Fc receptors on macrophages; suppression of inducer T and B cells and augmentation of suppressor T cells; and blockade of complement cascade.

Dosing

Adult

2 g/kg IV over 2-5 d

Pediatric

Administer as in adults

Interactions

None reported

Contraindications

Documented hypersensitivity; IgA deficiency; anti-IgE/IgG antibodies

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Consider checking serum IgA before IVIg and using IgA-depleted IVIg (G-Gard-SD), if indicated
May increase serum viscosity and thromboembolic events; adverse effects may include migraine attacks; 10% increased risk of aseptic meningitis; increased risk of urticaria, pruritus, or petechiae 2-5 d after infusion (possibly lasting up to 1 mo); increased risk of renal tubular necrosis in older patients and patients with diabetes mellitus, volume depletion, or preexisting kidney disease
Can lead to changes in laboratory values, eg, elevated antiviral or antibacterial antibody titers for 1 mo, 6-fold increased ESR for 2-3 wk, apparent hyponatremia

Follow-up

Prognosis

- Prognosis is largely determined by the presence and type of any underlying cancer, the presence and severity of any associated autoimmune disease, and the severity and distribution of weakness. In addition, patients with rapidly progressive symptoms usually have more severe disease.
- Because Lambert-Eaton myasthenic syndrome (LEMS) may lead to early detection of small cell lung cancer (SCLC), prognosis of SCLC in patients with SCLC-LEMS is better than in SCLC without LEMS. Patients with SCLC who develop LEMS possibly have a more effective immunologic response to the cancer, which results in improved survival.
- When LEMS has been symptomatic for at least 2 years and no underlying cancer has been demonstrated, the LEMS was probably caused by an autoimmune process. At that point, prognosis is determined by severity of dysfunction and the presence and severity of other autoimmune conditions.
- A more rapid clinical course is more frequent in patients with SCLC-LEMS.
    - In most patients, weakness does not severely affect vital muscles.
    - Maximum severity usually becomes established within several months of symptom onset.
    - Without treatment, weakness and dysfunction do not usually vary. Exceptions are during periods of exacerbation induced by intercurrent illness or by medications that impair neuromuscular transmission.

Patient Education

For excellent patient education resources, visit eMedicine's Cancer and Tumors Center. For information specific to lung cancer see Lung Cancer.

Miscellaneous

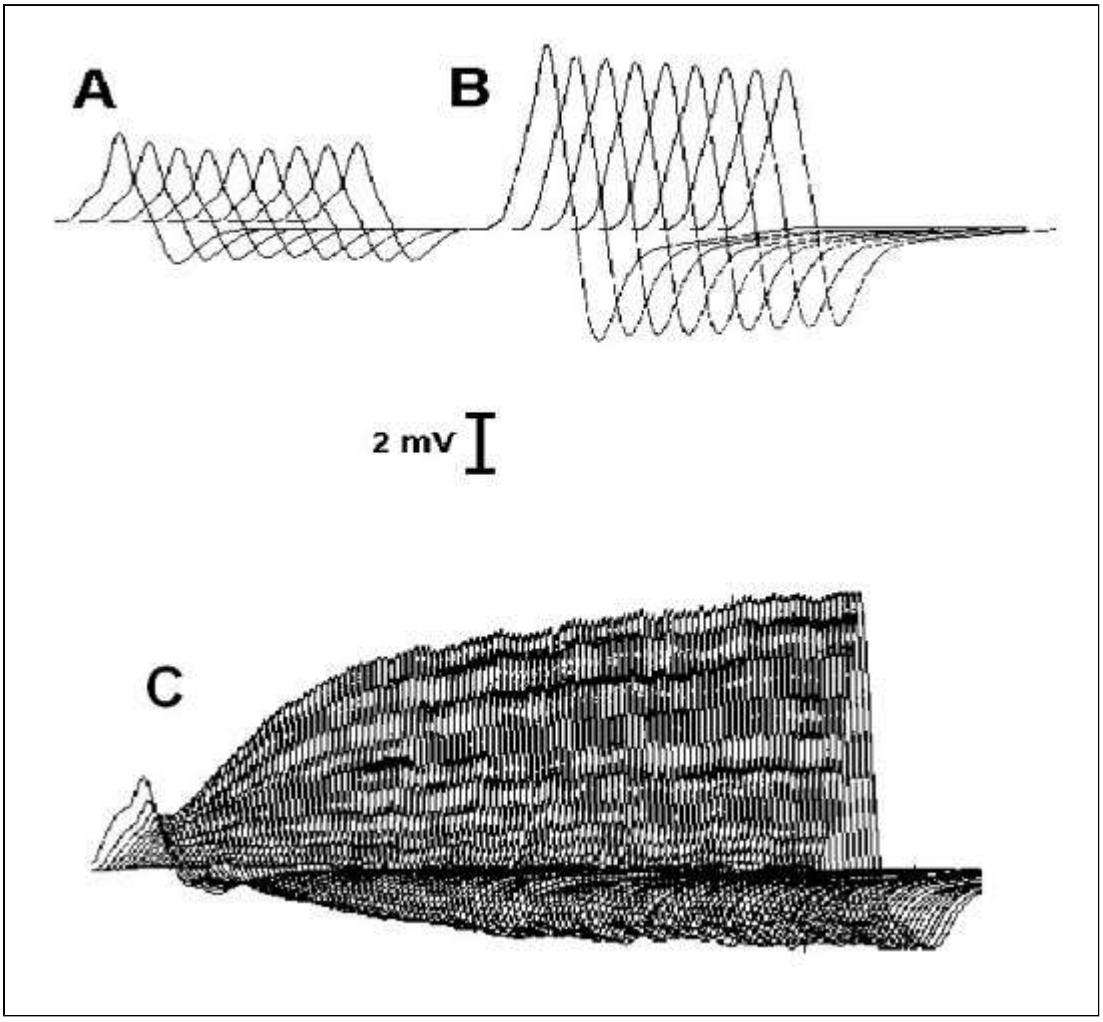
Medicolegal Pitfalls

To avoid possible medicolegal problems, a thorough search for an underlying SCLC should be performed. In addition, drugs that can exacerbate the condition should be avoided if possible.

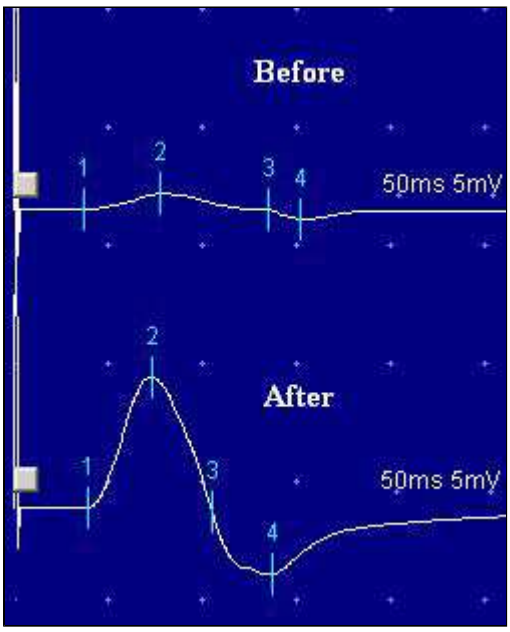
Special Concerns

- Drugs that may exacerbate weakness in LEMS
    - Drugs that compromise neuromuscular transmission frequently exacerbate weakness in LEMS. Competitive neuromuscular blocking agents, such as d-tubocurarine and pancuronium, have an exaggerated and prolonged effect in patients with LEMS.
    - Initial signs of possible LEMS include prolonged weakness or apnea following administration of neuromuscular blocking agents during anesthesia.
    - Some antibiotics, particularly aminoglycosides, fluoroquinolones (eg, ciprofloxacin), and erythromycin, have significant neuromuscular blocking effects. Some antiarrhythmics (eg, quinine, quinidine, procainamide) and beta-adrenergic blocking drugs also worsen myasthenic weakness.
    - Exacerbation of LEMS after administration of any of several other agents, including magnesium and intravenous iodinated radiographic contrast agents, has been reported in isolated cases. In general, patients with LEMS should be observed for clinical worsening after initiating any new medication.
    - Unless absolutely necessary, avoid drugs that are known to impair neuromuscular transmission. In such cases, a thorough knowledge of their potential deleterious effects is required.
- Elevated temperature
    - Weakness of LEMS may be worse when the ambient temperature increases or when the patient is febrile.
    - Patients should avoid hot showers or baths.
    - Systemic illness of any sort may cause transient worsening of weakness.

Multimedia



Media file 1: Characteristic responses to repetitive nerve stimulation in a patient with Lambert-Eaton myasthenic syndrome (LEMS). A: Responses elicited from a hand muscle by stimulation of the nerve at 3 Hz. Amplitude of the initial response is less than normal and the response is decremental. B: Responses as in A, immediately after voluntary activation of the muscle for 10 seconds. Amplitude has increased. C: Responses in a hand muscle elicited by 20-Hz stimulation of the nerve for 10 seconds. Response amplitude is less than normal initially, falls further during the first few stimuli, then increases and ultimately becomes more than twice the initial value.



Media file 2: Compound muscle action potentials elicited from a hand muscle before and immediately after maximal voluntary activation of the muscle for 10 seconds. The amplitude is small initially, increasing almost 10 times after activation.

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Keywords

Lambert-Eaton myasthenic syndrome, LEMS, acetylcholine release, ACh release, neuromuscular transmission, small cell lung

cancer, SCLC, non-SCLC lung cancer, non–small cell lung cancer, lymphosarcoma, malignant thymoma, carcinoma of the breast, carcinoma of the stomach, carcinoma of the colon, carcinoma of the prostate, carcinoma of the bladder, carcinoma of the kidney, carcinoma of the gallbladder

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