Clinical Features

Approximately 50 to 60% of patients with LEMS have an associated SCLC; other tumors have been described, including adenocarcinoma and breast cancer, and some may be unrelated to cancer (68). The disorder can thus be divided into two groups based on the presence of a cancer (68). Those without a tumor are generally of younger age, although most patients with LEMS are over age 40 at the onset of symptoms. Male sex is more common in the group with tumors.

The most common symptoms of LEMS are proximal leg and truncal weakness; ptosis and bulbar muscle weakness are less common. Respiratory failure is rare but can occur (68). Some patients have the warming up phenomena where by the first portion of a repetitive movement is more difficult than later ones. This may be apparent clinically with manual muscle testing that culminates in near-normal strength despite easily fatigability. Tendon reflexes may be absent with first testing and later normal after a brief agonist muscle contraction. Autonomic symptoms are common but may be overlooked and can include impotence in men, dry mouth, constipation, and urinary retention.

Natural History

The symptoms of LEMS can begin insidiously and can go undiagnosed for months to years. The most common initial diagnosis is MG (68). Among those with an associated tumor, the prognosis is largely determined by tumor progression and response to tumor treatment. In one series (68), three quarters of patients with a cancer died within a year compared with 80% of patients without a tumor who were alive 7 years after diagnosis. The cancer in LEMS may be inapparent for up to 4 years after onset of neurologic symptoms. Accordingly, it is important to differentiate between MG and LEMS and to perform an evaluation for occult SCLC if LEMS is diagnosed. This should include a history for cancer risk factors, a thorough medical evaluation, and CT of the chest with yearly repeat evaluations for the first 5 years after initial detection.

Pathophysiology

The disorder is due to autoantibodies directed against presynaptic voltage-gated calcium channels (VGCC) or related structures. This affects the regulation of channels in both those with and without an associated cancer (69,70). The antibodies are of the IgG class and are heterogeneous in their specificity against the several types of calcium channels (71). The etiology of antibodies in patients without an associated cancer is unclear, but there is likely antigenic similarity between presynaptic VGCC and those on tumors cells (72). In patients with an SCLC, antibody production is probably triggered by the tumor (73). These antibodies reduce the influx of calcium into the presynaptic terminal and reduce the amount of ACh released, in turn decreasing the size of EPPs and the likelihood of reaching threshold for a given muscle fiber AP (Table 7). The result is a low CMAP amplitude in most muscles that is also a measure of the severity of NMJ blockade (72). Similar calcium channels present on autonomic presynaptic nerve parasympathetic and sympathetic terminals account for the autonomic symptoms.

<table>
<thead>
<tr>
<th>Stimulus number</th>
<th>ACh pool</th>
<th>Available ACh quanta</th>
<th>ACh quanta released</th>
<th>Resultant EPP amplitude* (mV)</th>
<th>Action potential threshold reached</th>
</tr>
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<tr>
<td>Before exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>80</td>
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<td>&gt;640</td>
<td>&gt;128</td>
<td>&gt;30</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Top of table shows the effects of reduced influx of calcium leading to a small number of ACh released. This results in lower amplitude EPPs that fail to elicit muscle fiber action potentials. Bottom of table shows how increased ACh released through enhanced calcium influx will facilitate transmission to normal. Numbers representing ACh quanta are approximate.

*In this model, the EPP amplitude must be greater than 30 mV to reach threshold for generation of a muscle fiber action potential.

NMJ, neuromuscular junction; LEMS, Lambert-Eaton myasthenic syndrome; ACh, acetylcholine; EPP, end plate potential.
Diagnosis

Electrodiagnostic testing is important in identifying LEMS and distinguishing it from MG. A low CMAP amplitude, often less than 10% of the lower limit of normal and in a diffuse distribution, is an important electrodiagnostic clue (Fig. 7). Repetitive motor nerve stimulation at rates of 2 to 4 Hz may show a decrement as in MG; however, the distinguishing feature of LEMS is a marked facilitation after 10 seconds of exercise or with high-frequency stimulation at 50 Hz. The degree of facilitation depends on the size of the first CMAP but will generally restore the CMAP amplitude to normal. The increment after high-frequency activation may reach 10,000-fold if the first CMAP is extremely small (68).

There is a serum assay for antibodies reactive to P/Q- and N-type VGCCs that are detected infrequently except in LEMS or in the context of other paraneoplastic neurologic disorders (70). There is an association between LEMS and both organ-specific and nonorgan-specific autoantibodies in patients with LEMS (20,68). The discovery of VGCC antibodies in a clinically affected patient should prompt a search for occult SCLC; generally, a chest CT or magnetic resonance image will suffice.

Treatment

Many of the same drugs and procedures used to treat MG are also effective in LEMS; however, there are drugs that specifically enhance presynaptic function that are unique to the treatment of LEMS. A laboratory measure that can be used to quantify therapeutic response and has predictive value is the amplitude of the CMAP at the start of therapy; a very low CMAP amplitudes generally suggests a poorer outcome with therapy (73).

Patients with LEMS may benefit from AChE drugs in doses used for MG, although the improvement in strength is likely to be mild. A trial of plasmapheresis may be effective, with rapid improvement in most patients (74,75), and the response may be sustained without an associated cancer. The IgG fraction collected from the plasma separation has been used to transfer symptoms of LEMS to experimental animals (75). IVIg in doses of 2 g/kg over 2 days was temporarily effective in a placebo-controlled crossover trial in LEMS patients without cancer (76). Prednisone was effective in small cohorts with or without cancer (77,78). Azathioprine was tried in patients with LEMS but usually in conjunction with other drugs; accordingly, its effectiveness was difficult to assess (75). There is concern that treatment of patients without an associated cancer could precipitate the development of a later cancer. In one study, several patients treated with azathioprine later showed evidence of SCLC, but several arguments suggest that azathioprine was not the cause. First, it is generally associated with the development of lymphoid tumors, not SCLC. Second, the time interval between initiation of azathioprine and development of cancer in the LEMS patients was 2 to 3 years, a

FIG. 7. Responses to repetitive stimulation in LEMS. Top: Left trace shows low amplitude response to 3-Hz repetitive stimulation; right trace shows 245% facilitation after 10 seconds of maximal muscle activation. Bottom: Facilitation of the response to 50-Hz repetitive stimulation with a 750% increase in amplitude.
period during which malignant cell changes could progress to a radiographically detectable lesion (68).

3,4-Diaminopyridine enhances synaptic transmission and increases ACh release by blocking potassium channels that prolongs nerve APs and in turn prolongs the activation of VGCC (79). In a double-blinded, placebo-controlled, crossover study, 3,4-Diaminopyridine doses of 25 mg orally four times daily significantly improved strength in patients with LEMS, with or without cancer (80). The drug remains effective after several years of follow-up. Mild side effects include perioral and acral paresthesias, epigastric distress, and rarely seizures. 3,4-Diaminopyridine is an orphan drug. It is not approved and is available in the United States at only a few institutions, such as the Mayo Clinic in Rochester, Minnesota, and Duke University in Durham, North Carolina. Availability outside of the United States is unknown.

Treatment of the underlying SCLC is an option with chemotherapy, radiation therapy, and rarely surgery. The response to primary treatment of the cancer has been variable but most show some initial improvement (73). Apparent cures of the cancer and LEMS after 7 years of follow-up have been reported. In some the cancer may respond but the symptoms of LEMS remained unchanged, whereas others have had initial improvement of their weakness but with later relapse.

CONCLUSION

The diagnosis and management of NMJ disorders is ever challenging. It requires understanding of the anatomy, physiology, pathology, immunology, and pharmacology of the motor unit. Diagnostic errors can be reduced by viewing disorders of the NMJ as a family of diseases, in which systematic electrophysiologic studies separate presynaptic from postsynaptic disorders. A battery of serologic, radiographic, and genetic studies provide support to the exact etiologic diagnosis. When thoughtful evaluation and management principles are followed, it will be apparent that each patient is unique, and some patients will continue to challenge the most experienced clinicians.

REFERENCES


