

Clinical Reasoning: A 48-year-old woman with generalized weakness

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SECTION 1

A 48-year-old woman was referred to the neuromuscular clinic because of progressive generalized weakness for 4 months. Her symptoms started after she had a thyroidectomy and radioactive iodine treatment for a thyroid papillary carcinoma.

She had proximal arm weakness when washing her hair and had trouble climbing steps and getting out of her chair without using her arms. About 2 months later, she developed fluctuating bilateral ptosis and blurred vision. Her symptoms were associated with episodes of transient horizontal binocular diplopia that would last for a couple of minutes and get worse by the end of the day. She also had dry eyes and mouth. A month later, she started having episodes of transient dysarthria. At that time she was found to have a low AM cortisol level by the medical team while being evaluated for her symptoms. She was treated with a hydrocortisone taper which partially improved her weakness and a follow-up cortisol level suggested resolution of the adrenal insufficiency. The patient was on levothyroxine with normal thyroid gland function. She smoked 1 or 2

cigarettes daily for 10 years. She denied head drop, shortness of breath, lightheadedness, constipation, or weight loss.

Her general examination, including orthostatic blood pressure, was normal. Her mental status was normal; visual acuity could be corrected to 20/20. Her pupils were symmetric with a sluggish response to light. Extraocular movements were intact and there was no ocular misalignment on alternate cover testing. There was no lid-twitch. She had mild right ptosis that worsened with sustained upgaze. Facial sensation was intact. There was no facial weakness, dysarthria, or dysphagia. The palate was midline and elevated symmetrically. The tongue movements were normal. No fasciculations were observed. Her strength was 4/5 in both biceps and psoas, which improved on repeated testing. The remaining neurologic examination, including deep tendon reflexes and sensory testing, was normal.

Question for consideration:

1. What is your differential diagnosis at this stage?

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SECTION 2

This patient has subacute onset of proximal limb weakness associated with fluctuating ocular and bulbar symptoms, which suggests a myasthenic syndrome. The differential diagnosis includes myasthenia gravis (MG) or Lambert Eaton myasthenic syndrome (LEMS). Congenital myasthenic syndromes typically present in childhood and patients with botulism intoxication have a rapid descending weakness that develops over hours to days, which is not the case here. Patients with MG most commonly present with double vision and ptosis. They may report blurred vision instead of diplopia but this resolves while covering either eye. Patients with LEMS complain of blurred vision because of dry eyes, difficulty with accommodation, or both.

The pupillary reflex to light, while normal in MG, is usually sluggish in LEMS. Other signs of dysautonomia found in LEMS but not in MG include dry mouth and skin, constipation, and orthostasis.

Unilateral ptosis and ptosis fatigability are, however, more characteristic of MG. Patients with LEMS almost always present with limb weakness, especially in the proximal lower extremities, and commonly have normal facial and extraocular muscles. The improvement of this patient's proximal weakness on repeated testing is characteristic of LEMS. Reflexes, while normal or brisk with MG, are usually weak or absent in LEMS, and can reappear after sustained contraction of the specific muscle. The improvement of the patient's weakness with steroids is nonspecific as both MG and LEMS are autoimmune conditions.

In our patient, acetylcholine receptor (AChR) binding antibodies were positive (1,040 nmol/L), but voltage-gated calcium channel (VGCC) antibodies were negative.

Question for consideration:

1. Does the serology confirm the diagnosis of MG and rule out LEMS?

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SECTION 3

Antibodies (Abs) that bind AChR proteins are specific serologic markers for acquired MG. AChR-binding Abs are detected in 85% of patients with generalized MG and have very high specificity for MG (>97%).¹ Testing for AChR modulating Abs, blocking Abs, and anti-muscle-specific receptor tyrosine kinase Abs (anti-MuSK) are helpful in patients with generalized MG when they test negative for AChR Abs.² Anti-MuSK-positive patients often have bulbar dysfunction, shoulder girdle weakness, and respiratory symptoms. Note that elevated titers of AChR Abs can also be found in patients with thymoma without MG, systemic lupus erythematosus, amyotrophic lateral sclerosis, inflammatory neuropathy, rheumatoid arthritis on D-penicillamine, and in normal relatives of patients with MG. They can also be seen in patients with LEMS.^{3,4} Thus, relying only on the serology to diagnose MG can be misleading. In this patient in particular, the complaints related to the autonomic nervous system and strength improvement on repetitive testing are unusual for MG.

Antibodies against the P/Q-type VGCC are found in more than 90% of patients with LEMS.^{4,5} In addition, VGCC Abs are found in less than 5% of patients with MG, and they may be found in patients with paraneoplastic cerebellar degeneration associated with small cell lung cancer.^{4,5} Our patient tested negative for VGCC Abs. But VGCC Abs may rapidly fall to zero after initiation of steroid therapy, which might have been the case in our patient.⁴ The presence of these Abs, in the correct clinical setting, confirms the diagnosis of LEMS but does not indicate the risk for cancer. Antibodies against SOX1, however, are highly associated with small cell lung cancer in patients with LEMS.⁶ PET studies are necessary to screen for cancer in patients with LEMS. If PET scan is negative, patients should have a chest MRI and be monitored for malignancy—mainly small cell lung carcinoma—since they can have LEMS several months before the manifestation of the cancer.

Question for consideration:

1. What is the role of electrodiagnostic testing?

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SECTION 4

Electrodiagnostic studies are essential to differentiate between LEMS and MG,¹ and the physician should not rely solely on the serology. In LEMS, the CMAP amplitudes are generally reduced and decrement further at low frequencies of repetitive nerve stimulation (RNS at 2 Hz to 3 Hz). Voluntary isometric muscle contraction for 10 seconds (or high-frequency RNS at 50 Hz) will result in a facilitation of CMAP amplitude, usually by higher than 100% in LEMS. In MG, low frequency RNS causes progressive decrement in the CMAP amplitude of at least 10%. In ocular MG, the sensitivity of RNS is low (about 30%).¹ If the RNS is normal and a high suspicion for a neuromuscular junction (NMJ) disorder exists, single fiber EMG (SFEMG) should be performed. SFEMG is very sensitive for detection of a defect in NMJ, and its sensitivity allows for demonstration of abnormalities in clinically unaffected muscles. The SFEMG specificity is, however, very low, and it does little in helping to differentiate LEMS from MG or another NMJ process such as an immature NMJ junction from acute neuropathy with resprouting. As

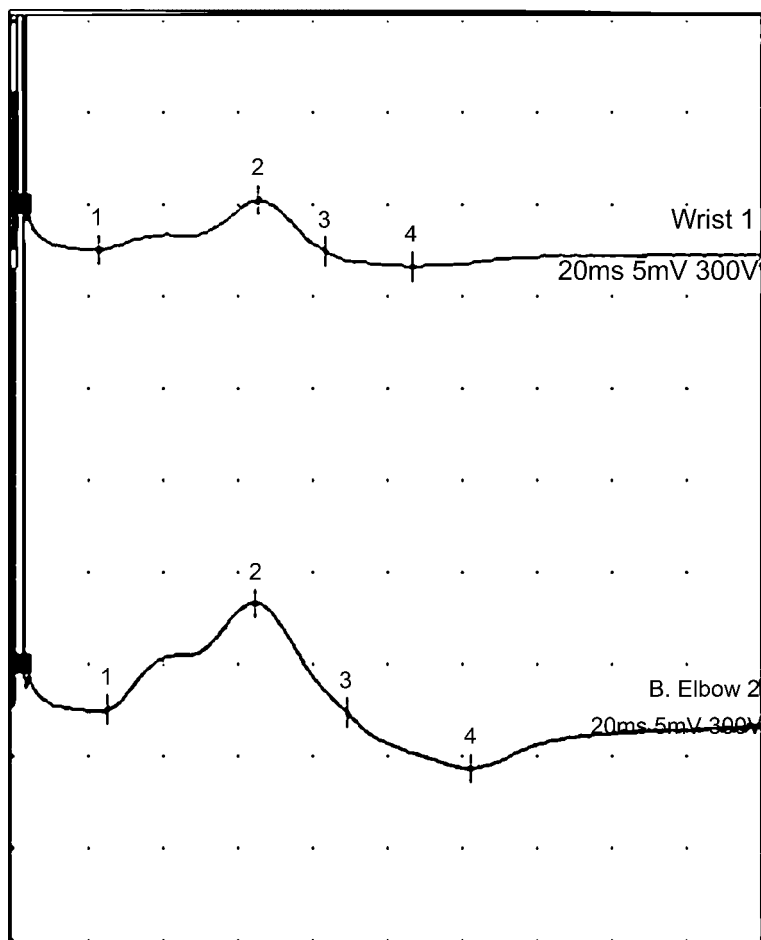
in MG, SFEMG in LEMS and other NMJ processes shows marked motor unit instability (increased jitter and impulse blocking) in most muscles tested. In LEMS, with increased rates of voluntary activation or stimulation, the jitter and blocking may decrease at some endplates.²

In our patient, the right median sensory and ulnar motor conduction velocities were normal. The right median and ulnar motor response amplitudes were reduced (3.1 and 2.8 mV). Immediately following 15 seconds of maximal exercise, there was a 110% increment in the CMAP amplitudes (figure). The right spinal accessory muscle motor response amplitude was normal. RNS of the right median nerve and spinal accessory nerve at 3 Hz showed no significant decrement. Needle EMG in limb muscles showed no spontaneous activity at rest. Motor unit potentials durations were normal except for long duration potentials in the right psoas muscle.

DISCUSSION In this patient, the autonomic symptoms suggested LEMS. In LEMS, VGCC Abs block the release of acetylcholine vesicles from the presynaptic endplate and affect not only the NMJ, but also the synapses between axons of the autonomic system. In MG, the AChR Abs block the nicotinic receptors, but do not affect the muscarinic ones, hence the absence of autonomic symptoms. In our patient, brief exercise caused significant facilitation in the CMAP amplitudes, which is consistent with a presynaptic NMJ disorder. The NMJ safety factor (SF) is the difference between the end plate and threshold potentials (EPP and TP) for initiating an action potential (AP). EPP is generated when acetylcholine binds to its receptor on the postsynaptic membrane. In intact NMJs, the SF is high and an AP is always achieved, even after RNS. In MG, fewer receptors are present, which results in reduced EPP and, as a result, a low SF. Slow RNS causes a decrement in the EPP, which becomes subthreshold, resulting in no AP in some muscle fibers. In LEMS, the baseline EPP is low and with slow RNS, there is also further decrement of the EPP and CMAP, as in MG. In rapid RNS and brief exercise, however, there is accumulation of calcium in the presynaptic end plate, resulting in a facilitation and incremental response in the CMAP.

Our patient had LEMS, which was suggested by the autonomic symptoms and strength improvement on repetitive testing, and confirmed by the increment in the CMAP amplitudes after rapid brief exercise. The ophthalmoparesis and normal reflexes are, however, more characteristic of MG and the AChR Abs are more than 97% specific for MG.¹ One⁷ may conclude that this is a case of concomitant

Figure Pre-exercise (top) and 15 seconds postexercise (bottom) compound muscle action potential of the ulnar nerve



LEMS and MG, while others³ would argue that the presence of AChR in this patient might reflect a “nonpathogenic epiphenomenon.”

DISCLOSURE

Dr. Karam serves on the editorial team for the *Neurology*[®] Resident and Fellow Section. Dr. Scelsa reports no disclosures.

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