LAMBERT EATON SYNDROME AND LESS COMMON DISORDERS OF NEUROMUSCULAR TRANSMISSION 2017

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I. Lambert Eaton Myasthenic Syndrome. LEMS is a presynaptic disease characterized by chronic fluctuating weakness of proximal limb muscles. Symptoms include difficulty walking, climbing stairs, or rising from a chair. In LEMS there may be some improvement in power with sustained or repeated exercise. In contrast, eyelid ptosis, diplopia, dysphagia, and respiratory failure are far less common. In addition, LEMS patients often complain of myalgias, muscle stiffness of the back and legs, distal paresthesias, metallic taste, dry mouth, impotence, and other autonomic symptoms of muscarinic cholinergic insufficiency. LEMS is rare compared to MG, which is about 100 times more common. About half of LEMS patients have an underlying malignancy that is usually small-cell carcinoma of the lung. In patients without malignancy, LEMS is an autoimmune disease and can be associated with other autoimmune phenomena. In general, patients over age 40 are more likely to be men and have an associated malignancy whereas younger patients are more likely to be women and have no neoplasm malignancy. LEMS symptoms can precede detection of the malignancy by 1 to 2 years. Of all patients with small cell lung cancer 4% have LEMS.

The examination typically shows proximal lower extremity weakness, although the objective bedside assessment may suggest relatively mild weakness relative to the patient's history. The muscle stretch reflexes are absent. On testing sustained maximal grip there is a gradual increase in power over the initial 2 to 3 seconds (Lambert's sign).

The **diagnosis** is confirmed with EMG studies, which typically show low amplitude of the compound muscle action potentials and a decrement to slow rates or repetitive stimulation. Following brief exercise, there is marked facilitation of the compound motor action potential (CMAP) amplitude. At high rates of repetitive stimulation, there may be an incremental response. SFEMG is markedly abnormal in virtually all patients with LEMS. The pathogenesis involves auto-antibodies directed against voltage-gated calcium channels at cholinergic nerve terminals. These IgG antibodies also inhibit cholinergic synapses of the autonomic nervous system. Over 90% of LEMS patients demonstrated these antibodies to voltage-gated calcium channels in serum, providing another essential diagnostic test. Regarding the question of associated cancer in a patient newly diagnosed with LES a potential new serological indicator of associated small cell lung cancer is the SOX1 antibody. SOX1 antibodies were detected in 64 percent of patients with LEMS with SCLC, but in none of 50 patients with non-paraneoplastic LEMS.

Treatment.

1. In patients with associated malignancy, successful treatment of the tumor can lead to improvement in the LEMS symptoms if the malignancy is successfully treated.
2. Symptomatic improvement in neuromuscular transmission may occur with the use of CEIs such as pyridostigmine.
3. 3,4-Diaminopyridine (DAP) increases ACh release by blocking voltage dependent potassium conductance and thereby prolonging depolarization at the nerve terminal and enhancing the voltage dependent calcium influx. 3,4-DAP has been shown to clearly improve most patients with LEMS with relatively mild toxicity and is becoming increasingly available, such that it represents first-line symptomatic therapy for LEMS. The typical beginning dose is 10 mg every 4 to 6 hours with gradual

increase as needed up to a maximum of 100 mg per day. 3,4 DAP base and 3,4 DAP phosphate salt (amifampridine) two preparations.

4. Immunosuppressive therapy is used in patients with disabling symptoms. Long-term high-dose corticosteroids, plasma exchange, and IVIG have all been used with moderate success. In general, the use of these therapies should be tailored to the severity of patient's symptoms.

II. Congenital myasthenia represents a group of rare hereditary disorders of the neuromuscular junction. The patients tend to have lifelong relatively stable symptoms of generalized fatigable weakness. These disorders are nonimmunologic, without ACh receptor antibodies, and therefore patients do not respond to immune therapy (steroids, thymectomy, and plasma exchange). Most of these patients improve on CEI. Even though there are many established subtypes of congenital myasthenia gravis, several are worth noting due in part to specific therapeutic implications. The **fast channel congenital myasthenic syndrome** tends to be static or slowly progressive, but usually very responsive to combination therapy with 3,4-diaminopyridine (enhances release of ACh) and pyridostigmine (reduces metabolism of ACh). **Slow channel congenital myasthenic syndrome** typically worsens over years as the endplate myopathy progresses. Although CEIs typically worsen symptoms, quinidine and fluoxetine, which reduce the duration of ACh receptor channel openings, are both effective treatments for slow channel syndrome. **The congenital myasthenic syndrome associated with ACh receptor deficiency** tends to be relatively nonprogressive and may even improve slightly as the patient ages. The disorder typically responds to symptomatic therapy with pyridostigmine and/or 3,4-diaminopyridine. Ephedrine produces benefit in some cases. **Patients with endplate AChE deficiency** usually present in infancy or early childhood with generalized weakness, underdevelopment of muscles, slowed pupillary responses to light, and either no response or worsening with CEIs. No effective long-term treatment has been described for congenital endplate AChE deficiency. A homozygous mutation of **Dok-7** is responsible for a form of congenital myasthenia characterized by weakness in limbs and trunk but largely sparing the face, eyes, and oropharyngeal muscles. The formation of neuromuscular synapses requires the muscle-specific receptor tyrosine kinase (MuSK). Dok-7 is necessary and sufficient for the activation of MuSK. Albuterol was effective in treating patients with **endplate acetylcholinesterase deficiency** and also **Dok-7** forms of congenital myasthenia.

III: Transient neonatal myasthenia occurs in 10 to 15% of babies born to mothers with autoimmune MG. Within the first few days after delivery the baby has a weak cry or suck, appears floppy, and on occasion, requires mechanical ventilation. The condition is caused by maternal antibodies that cross the placenta late in pregnancy. As these maternal antibodies are replaced by the baby's own antibodies the symptoms gradually disappear, usually within a few weeks, and the baby is normal thereafter. Infants with severe weakness are treated with oral pyridostigmine 1-2 mg/kg every 4 hours.

IV: Non-physiological myasthenia: Pseudo-myasthenia: Patients with psychological ocular symptoms include not only those with ptosis but also those with impairment of extraocular motility and associated diplopia. Convergence spasm can mimic myasthenic weakness and serve as a source of potential diagnostic error. Inconsistent eye movement findings, resolution with distraction. Volitional ptosis is often associate with lowing of the upper id and raising of the lower lid. Shaky twitchy movements of the lids are unlikely to be related to myasthenia.

Psychiatric disorders in MG are common, especially depression and anxiety. Ybarra observed 26% of MG patients were diagnosed with a depressive disorder and 46 were diagnosed with anxiety. (Ybarra) Management of psychological causes for weakness including those primarily ocular remains challenging as with the spectrum of psychological disorders including, anxiety, depression, conversion, somatization and also those with malingering. (Qiu, Lundeen)

There are four distinct groups of patients that the clinician may face in this clinical context. One group has myasthenia gravis which is producing the primary ophthalmological and neurological symptoms and is treated accordingly. The second group has primarily psychologically sourced symptoms and the management must focus on the behavioral and psychological status of the patient. The third group has both- a combination of organic myasthenic symptoms with superimposed psychological weakness ocular or generalized. This clinician has seen patients with and without underlying myasthenia who have decompensated from a psychological perspective and become hospitalized in the intensive care unit, intubated, mechanically ventilated, and treated with plasma exchange, IVIg, high dose corticosteroids without objective support for their weakness being myasthenic (these patient have had psychological causes for their decompensation). The fourth group represents patient who have

myasthenia gravis. And they have significant stress and psychological conditions that appear to exacerbate their myasthenia. Thus they do not have psychogenic weakness, but they have psychological causes for their myasthenia gravis to worsen. Zou et al established pre-operative anxiety as a risk factor for MG patients developing a post-thymectomy exacerbation of weakness (crisis). (Zou)

Management of these challenging patients requires recognition, consideration of the 4 subtypes, reassurance, and team management utilizing professionals in psychology, psychiatry, and psychotherapy.

V. Hypermagnesemia
VI. Tick Paralysis

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