Review Article

The Eaton-Lambert syndrome

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Summary

The Eaton-Lambert syndrome is a non-metastatic manifestation of oat-cell carcinoma of the bronchus, although it has been reported in patients with carcinoma at other sites. The clinical picture is usually one of subacute muscular fatiguability with weakness and wasting affecting the proximal parts of the limbs and trunk, but occasionally the external ocular and bulbar muscles are involved. The weakness is often myasthenic, but it has been observed that muscle power may in fact increase after brief exercise. The pathogenesis, diagnosis, electrophysiological features and some aspects of therapy are reviewed.

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The association of bronchogenic carcinoma with peripheral neuropathies or myasthenia gravis was recognized in the early 1950s.[1] In 1956 Eaton and Lambert[2] from the Mayo Clinic outlined the clinical, pharmacological and electrophysiological abnormalities in this new syndrome. These authors distinguished the syndrome from myasthenia gravis, placed the defect at the level of the neuromuscular junction, and stressed the association with malignant neoplasm of the lung.

Clinical features

The main clinical features of the Eaton-Lambert syndrome are: (*i*) weakness of proximal limb and girdle muscles; (*ii*) reduced rested muscle strength, a temporary increase in strength in response to voluntary exercise of a few seconds' duration, and weakness after prolonged physical effort; (*iii*) decreased or absent deep tendon reflexes; (*iv*) associated neoplasms of the lung in approximately two-thirds of patients; (*v*) dryness of the mouth or dysgeusia; (*vi*) loss of potency, peripheral paraesthesiae and (very rarely) cerebral ataxia; and (*vii*) a relatively poor response to neostigmine and good or very good response to guanidine, with marked sensitivity to D-tubocurarine.

Weakness in the muscles of the proximal limb and girdle is usually the initial symptom, giving the patient a feeling of tightness around the hips and shoulders manifested clinically by difficulty in rising from a chair, climbing stairs or elevating the arms. Neurological examination usually reveals proximal weakness in all limbs, particularly in the lower limbs. In the early stages of the disease proximal leg weakness is usually the most important neurological finding, and the only subjective complaints may be related to it. Some difficulty in speaking or swallowing or some temporary double vision may be noted by about one-third of patients. However, involvement of extraocular, facial and bulbar muscles is not severe. Weakness of the distal parts of the limbs is also mild and uncommon.

Reduced rested muscle strength, temporarily increased strength following a few seconds of exercise, and weakness after prolonged physical effort are other clinical features which distinguish the syndrome from myasthenia gravis. On clinical examination, after a few attempts at voluntary contraction, power of contraction rises in the muscles that were weak initially, such as those of the thigh and maybe the shoulder muscles. This is probably why there is sometimes an apparent discrepancy between the patient's severe disability and relatively slight weakness on strength testing. Deep tendon reflexes are lessened or absent, in contrast to the intact deep reflexes in myasthenia gravis.

Malignant pulmonary tumours are present in about 70% of patients with the Eaton-Lambert syndrome,[3] small-cell carcinoma of the bronchus being by far the most common associated tumour.

Loss of potency and peripheral paraesthesiae are other clinical features of the Eaton-Lambert syndrome, and may be considered clinical manifestations of 'paraneoplastic neuromyopathy'.

Pharmacological responses in the syndrome are fairly typical; neostigmine or edrophonium produce at most only slight improvement in strength, a response quite different from that in patients with myasthenia gravis, which improves after anticholinergic medication. Guanidine produces only a slight improvement in strength in myasthenia gravis but decided improvement in the Eaton-Lambert syndrome.

The incidence and prevalence of the syndrome are unknown. Herrmann[4] estimated that the syndrome occurs in slightly less than 1% of cases of primary cancer of the lung. The syndrome is commoner after the age of 40. Men are four times more frequently affected than women, but this is probably changing because of the rising incidence of lung cancer in women.

Pathology and pathogenesis

The most common tumour associated with the Eaton-Lambert syndrome is the bronchogenic small-cell or oat cell carcinoma, but other pulmonary tumours such as squamous cell carcinoma have also been associated with it. There have been reports of the syndrome occurring in patients with lymphosarcoma,[5] Sjögren's syndrome[6] and sarcoidosis.[7]

The defect in the Eaton-Lambert syndrome is a functional block of neuromuscular transmission. *In vitro* intracellular recordings from intercostal muscle specimens taken from patients with the syndrome showed that miniature end-plate potentials produced by an evoked response are diminished. This phenomenon may be caused by a decrease in the number of packets of acetylcholine being released from the nerve terminals with the nerve impulse. A similar abnormality in neuromuscular transmission is produced by botulism and by neomycin and other antibiotics. Takamori *et al.*[8] have postulated that there is a

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defective calcium-dependent acetylcholine release by nerve impulses that can be partially corrected by calcium and adrenaline. McQuillen and Johns[9] carried out electrophysiological studies of the function of various levels of motor units in the Eaton-Lambert syndrome and concluded that the basic defect lies in a dysfunction of neuromuscular transmission and not in the nerves or muscles. Engel and Santa[10] have described an overdevelopment of the postsynaptic or secondary synaptic region in the motor end-plate of patients with the syndrome quite different from that seen in myasthenia gravis.

Diagnosis

The study of the effects of repetitive stimulation of a muscle through its peripheral nerve is of great assistance in establishing the diagnosis. The response to a single stimulus is abnormally small, and if the nerve is stimulated at a slow rate (1 - 2 Hz) there is a progressive reduction in size of the evoked muscle potentials. On the other hand, with rapid rates of stimulation there is a progressive increase in the size of the potentials. This phenomenon is the electrophysiological translation of the temporary increase in muscle strength in response to voluntary exercise of a few seconds' duration. Single-fibre electromyographic studies showed an increase in 'jitter' impulse blocking and improvement of neuromuscular transmission with high rates of innervation frequency. This method, however, provides little additional information for the diagnosis of the syndrome compared with the regular recording of compound muscle action potentials at different stimulus frequencies.

Muscle biopsy is not diagnostic of the syndrome as it shows atrophy of type II muscle fibres.

Differential diagnosis

The syndrome should be differentiated from myasthenia gravis clinically and electrophysiologically (Table I). Myasthenic syndromes associated with antibiotic administration have been reported, the first reported being neomycin. Myasthenic syndromes have also been reported in hypo- and hyperthyroidism, acute leukaemia, lupus erythematosus and the use of trimethadione. All these syndromes respond to discontinuation of the drugs that induce them or to treatment of the underlying disease causing the myasthenic condition.

Treatment

The first aim in the treatment of the syndrome is detection of any underlying malignant lesion. In some patients symptoms improve after treatment of the carcinoma, while in others weakness is not relieved by these measures. Anticholinesterase medication provides mild or no improvement of strength. Guanidine hydrochloride was initially found to be helpful in the treatment of mysthenia gravis and has subsequently been recognized as the drug of choice in the Eaton-Lambert syndrome. It has a good influence on the fatigue and weakness of patients with the syndrome, and the characteristic electrophysiological findings are significantly improved. The daily dose varies from 20 to 30

TABLE I. DIFFERENTIATION OF MYASTHENIC SYNDROME FROM MYASTHENIA GRAVIS

	Myasthenic syndrome	Myasthenia gravis
Symptoms	**Weakness in walking, rising, climbing; double vision; difficulty in speaking and swallowing**	**Double vision; drooping eyelids; difficulty in speech, swallowing and chewing**
Distribution of weakness	**Weakness of proximal limb and girdle muscles common in thigh and pelvis; weakness of cranial nerve muscles less common and mild**	**Ophthalmoparesis and ptosis; variable weakness of jaw closers, tongue neck flexors, proximal and distal muscles**
Tendon jerks	**Hypo-active to absent**	**Intact**
Age of onset	**⩾ 40 years**	**Either sex, any age**
Sex distribution	**5 men to 1 woman**	**4 women to 3 men**
Associated neoplasm	**Lung carcinoma 70%**	**Thymoma 15 - 20%**
Rested muscle strength	**Reduced**	**Normal or mildly reduced**
Effects of repeated voluntary activity	**Strength initially improves and later declines**	**Strength declines**
Nerve muscle stimulation		
Single stimulus in rested muscle	**Muscle action potential and contraction reduced**	**Muscle action potential about normal**
Slow repetitive stimulation (1-3/s)	**Muscle action potential declines**	**Muscle action potential declines**
Rapid repetitive stimulation	**Muscle action potential improved**	**Muscle action potential declines**
Postactivation facilitation	**Present**	**Present**

mg/kg body weight, given in dividend doses. Unfortunately the drug causes several serious side-effects such as atrial fibrillation, bone marrow depression, renal tubular necrosis and liver toxicity. Germine-3-acetate has been tried with some success, but its association with numerous sensory symptoms has led to its discontinuation.

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