# Lambert–Eaton myasthenic syndrome

## Introduction

Lambert–Eaton myasthenic syndrome, like myasthenia gravis, is an autoimmune disorder of neuromuscular transmission. This article presents a case of Lambert–Eaton myasthenic syndrome and discusses its pathophysiology, diagnosis and management.

## Discussion

There are two main subtypes of Lambert–Eaton myasthenic syndrome:

1. Paraneoplastic – occurring as a remote, non-metastatic complication of cancer (especially small cell lung cancer) which accounts for about 60% of cases
2. Sporadic – no underlying cancer (Palace and Hilton-Jones, 2004).

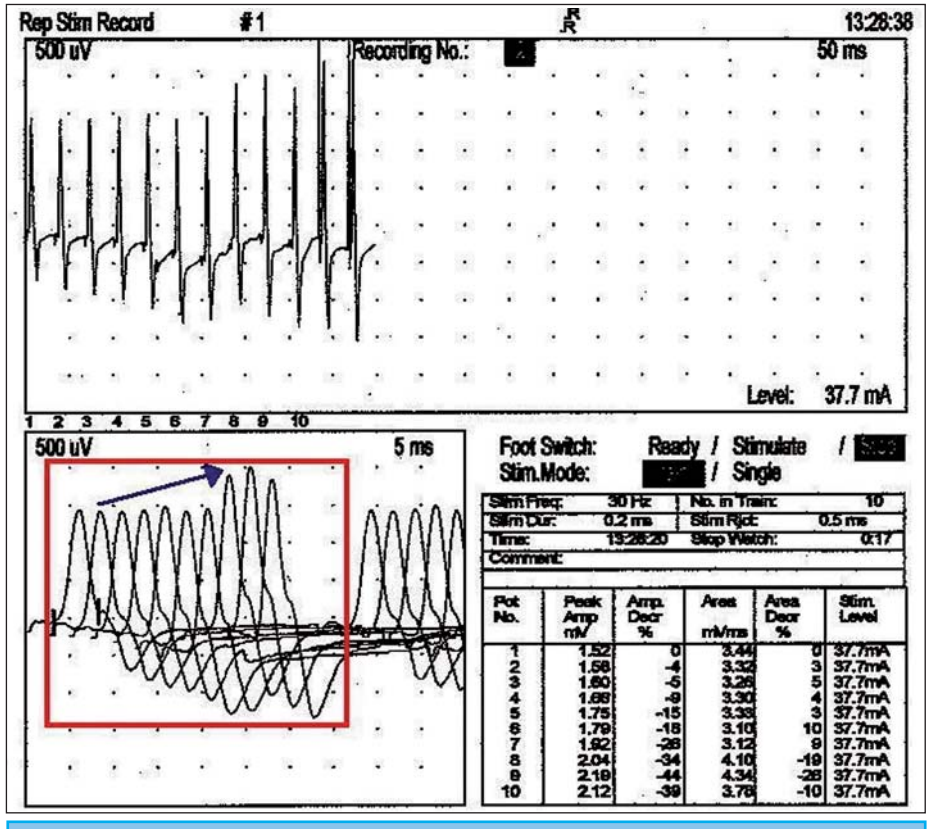
Lambert–Eaton myasthenic syndrome is caused by autoantibodies to presynaptic neurone P/Q type voltage-gated calcium channels (Fukunaga et al, 1983; Lennon et al, 1995). This reduces calcium entry into the nerve terminal and results in reduced acetylcholine release (*Figure 3*).

Typically, Lambert–Eaton myasthenic syndrome presents with fatigable weakness of the proximal lower limbs that later ascends to the proximal upper limb muscles. *Table 1* shows the main differential diagnoses for acquired proximal muscle weakness. Sustained muscle use results in fatigable weakness, but the first few seconds of a maximum voluntary muscle contraction paradoxically increases muscle strength (augmentation) and can restore tendon reflexes (post-tetanic potentiation) temporarily by provoking the release of calcium stored in the sarcoplasmic reticulum within the nerve terminal (Meriggioli and Sanders, 2005). Following this, calcium stores are rapidly depleted and weakness ensues.

Ocular and bulbar muscle weaknesses can occur, but are usually mild. Autonomic problems (dry mouth, dry eyes, impotence, constipation, urinary incontinence) are common (Palace and Hilton-Jones, 2004). Aches and other abnormal sensations can occur in the weak muscles. At rest, reflexes are reduced or absent. *Table 2* shows key differences between myasthenia gravis and Lambert–Eaton myasthenic syndrome.

Serum voltage-gated calcium channels antibodies and neurophysiological studies – particularly repetitive nerve stimulation – are the two most important investigations. A raised voltage-gated calcium channels antibody titre is both sensitive and specific for Lambert–Eaton myasthenic syndrome, particularly in the paraneoplastic variant where almost all patients are antibody-positive (Palace and Hilton-Jones, 2004). SOX1 antibodies have been identified as a possible marker for paraneoplastic

***Figure 1. Compound muscle action potentials during repetitive nerve stimulation at high frequency (30 Hz).***




## Case Report

A 64-year-old man presented with proximal lower limb muscle weakness that had ascended over 3 months to involve the upper limb, bulbar and periocular muscles. In addition, he had muscle aches, dry eyes and mouth, with 10 kg of weight loss. He was an ex-smoker of 50 pack-years.

On examination, he had mild dysarthria, bilateral ptosis and proximal muscle weakness (MRC power 4/5) in all limbs that improved transiently after muscle use. All limb tendon reflexes were absent at rest but returned after sustained muscle contraction for 10 seconds.

The serum voltage-gated calcium-channel antibody titre was 237 pmol/litre (normal <45 pmol/litre). High frequency repetitive nerve stimulation (*Figure 1*) produced a successive increase in compound muscle action potential amplitude, confirming the diagnosis of Lambert–Eaton myasthenic syndrome. On spiral computed tomography there was a pretracheal mass extending into the right paratracheal region (*Figure 2*). Tissue biopsy confirmed small cell lung carcinoma.

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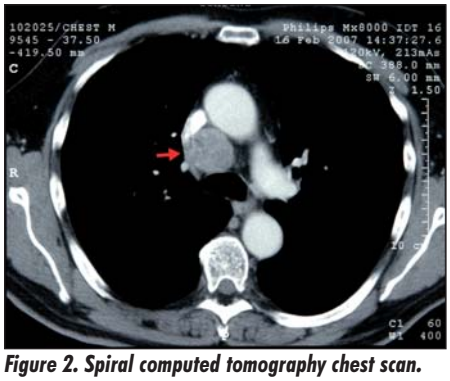

*Figure 2. Spiral computed tomography chest scan.*

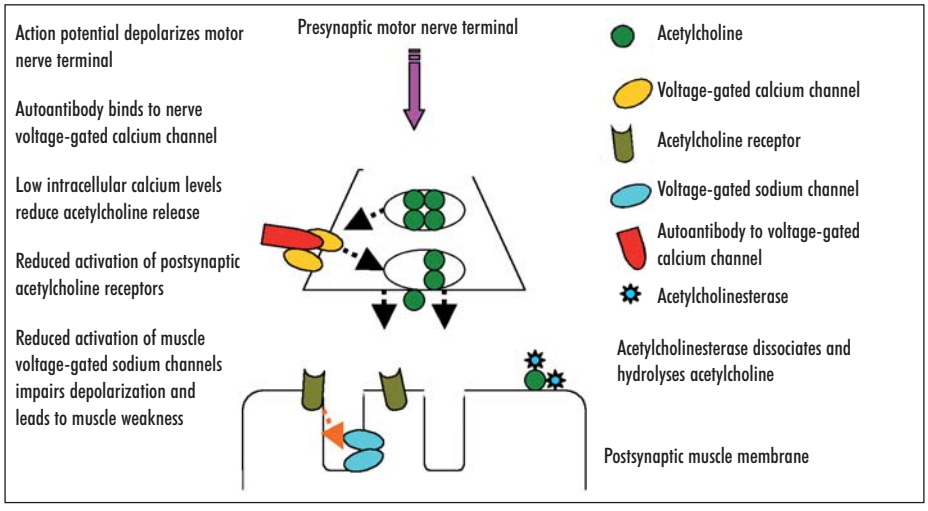


*Figure 3. Neuromuscular transmission in Lambert–Eaton myasthenic syndrome.*

Lambert–Eaton myasthenic syndrome associated with small cell lung cancer, differentiating it from sporadic Lambert–Eaton myasthenic syndrome (Sabater et al, 2008).

Repetitive nerve stimulation at low frequency (2–5 Hz) produces a reduction in the amplitude of successive compound muscle action potentials (decrement) in both Lambert–Eaton myasthenic syndrome and myasthenia gravis. However, only in Lambert–Eaton myasthenic syndrome does repetitive nerve stimulation at high frequency (20–50 Hz), or maximum voluntary contraction, increase the amplitude of successive compound muscle action potentials (post-activation facilitation). This is caused by accumulation of calcium in the nerve terminal, which enhances release of acetylcholine (Meriggioli and Sanders, 2005).

It is mandatory to look for an underlying tumour, especially small cell lung carcinoma, in later-onset patients and those with risk factors for malignancy – especially smoking (Palace and Hilton-Jones, 2004). A spiral computed tomography of the chest is performed at presentation and, if negative, a whole body positron emission tomography scan is recommended. If no tumour is found, scanning should be repeated at regular intervals guided by clinical course.

The definitive management for paraneoplastic Lambert–Eaton myasthenic syndrome is treatment of the underlying malignancy (Skeie et al, 2006). The first-line treatment for all forms of Lambert–Eaton myasthenic syndrome is 3,4-diaminopyridine, a drug that enhances nerve action potentials by blocking neuronal voltage-gated potassium channel repolarization. If symptomatic treatment with 3,4-diaminopyridine is insufficient, immunotherapy with prednisolone – alone or combined with azathioprine or ciclosporin – can help achieve long-term control. In severe cases, plasma exchange or intravenous immunoglobulin improve muscle strength within days – although the benefits are temporary, lasting 6–8 weeks (Skeie et al, 2006). BJHM

**Table 1. Main differential diagnoses of acquired proximal muscle weakness**

| | |
|---|---|
| Inflammatory myopathies | Dermatomyositis |
| | Polymyositis |
| Metabolic and endocrine disorders | Hypothyroidism |
| | Cushing's disease |
| Drugs and toxins | Alcohol |
| | Drugs (e.g. steroids, statins) |
| Neuromuscular transmission disorders | Myasthenia gravis |
| | Lambert–Eaton myasthenic syndrome |

**Table 2. Key differences between Lambert–Eaton myasthenic syndrome and myasthenia gravis**

| | Lambert–Eaton myasthenic syndrome | Myasthenia gravis |
|---|---|---|
| Pathophysiology | Autoantibodies to presynaptic neurone voltage-gated calcium channels | Autoantibodies to postsynaptic muscle acetylcholine receptors |
| Clinical | Usually presents with proximal lower limb muscle weakness that ascends over time | Usually presents with ocular muscle weakness that descends (craniocaudal; ocular → bulbar → limb muscles) over time |
| | Autonomic and sensory features common | Autonomic and sensory features absent |
| | Reduced or absent reflexes at rest | Normal reflexes |
| | Initial muscle strength augmentation and reflex potentiation | Fatigable weakness |
| Neurophysiology | Compound muscle action potential increment on high frequency (20–50 Hz) repetitive nerve stimulation | Compound muscle action potential decrement on low frequency (2–5 Hz) repetitive nerve stimulation |

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