Classic diseases revisited

Lambert-Eaton myasthenic syndrome

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Summary

The Lambert-Eaton myasthenic syndrome is a neuromuscular disorder characterised by defective neurotransmitter release at autonomic neurones and presynaptic terminals of the neuromuscular junction. It is caused by an IgG autoantibody formed against especially the P/Q type of voltage-gated calcium channels (VGCC) which is an essential component of the mechanism of neurotransmitter release. Many patients have an associated small cell carcinoma of the lung which appears to provide the antigenic stimulus for antibody production, although there is another group with no underlying malignancy. Both groups show an association with immunological disorders. Assay of VGCC antibody titres and electrophysiological tests help to differentiate Lambert-Eaton myasthenic syndrome from other disorders of the neuromuscular junction. Several drugs and therapeutic interventions capable of producing significant clinical improvement are currently available. Patients should also be investigated for underlying tumours, the specific treatment of which can result in remission or amelioration of symptoms.

Keywords: Lambert-Eaton myasthenic syndrome; voltage-gated calcium channels

The Lambert-Eaton myasthenic syndrome (LEMS) is an antibody-mediated autoimmune disorder of neuromuscular transmission characterised by muscle weakness, hyporeflexia or areflexia and autonomic dysfunction.

History

In 1953 Anderson and colleagues reported the case of a 47-year-old man with a bronchial neoplasm, progressive proximal muscle weakness and hyporeflexia who developed prolonged apnoea following administration of succinylcholine. They concluded that there was “strong clinical evidence for believing that the severe muscle weakness was of the myasthenic type”.¹ This patient showed the features of what we know today as LEMS.

At a meeting of the American Physiological Society in 1956, Lambert, Eaton and Rooke presented a report on six patients with defective neuromuscular transmission associated with malignant neoplasms. They identified that some of the clinical and electrophysiological features were different from what was expected in myasthenia gravis.² Subsequently in 1957, Eaton and Lambert summarised the clinical and electrophysiological characteristics of the myasthenic syndrome.³

Aetiology and epidemiology

LEMS can be broadly divided into two groups depending on whether it is associated with carcinoma or not. However, the electrodiagnostic and clinical characteristics do not differ in those two groups.

Approximately 60% of LEMS patients have associated small cell carcinoma of the lung (SCLC).⁴ The incidence of LEMS in patients with SCLC is 3%.⁵ Its association with other malignancies has been reported less commonly (box 1).^{3–10} O'Neill and colleagues found that in a patient presenting with LEMS the possibility of having an underlying SCLC falls sharply after two years and becomes negligible after 4 to 5 years.⁴

Both groups of LEMS patients have an autoimmune basis suggested by the presence of organ-specific and non-organ-specific antibodies.⁴ Various autoimmune diseases and other immunological disorders have been reported in association with LEMS,^{4 11–14} which provides further evidence for autoimmunity (box 2).

In LEMS, about 25% of patients have autoimmune diseases and 35–45% are positive for organ-specific antibodies.^{4 15} The prevalence of autoantibodies is higher in the group with no underlying carcinoma.^{4 15} When both groups are considered together, more than 80% of patients present over the age of 40.⁴ Generally, carcinoma-associated LEMS patients tend to present at an older age than LEMS without carcinoma (mean ages 57.9 and 48 years, respectively).⁸ If the diagnosis of LEMS is made before the age of 30 it is unlikely to be associated with an underlying tumour.^{4 8}

The sex differences in the two groups are less clear. O'Neill *et al*, in their series, found a statistically significant male predominance in the group without associated carcinoma and when both groups were considered together.⁴ Male predominance was also seen in the series published by Lennon *et al* in 1982.¹⁵ However, Gutmann and colleagues in 1992 did not find such a sex difference in their study (table 1).⁸ This discrepancy in the carcinoma-associated group could be due to changing patterns in smoking, which is a strong risk factor for the development of SCLC.

Immunogenetics

There is a significant association with HLA-B8 in both groups of LEMS, which appears to be stronger in the group with no associated carcinoma. The frequency

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Malignancies other than SCLC known to be associated with LEMS

- lymphoproliferative disorders
- carcinoma of the breast, colon, stomach, gall bladder, kidney, and bladder
- adenocarcinoma of the lung, pancreas, and prostate
- intrathoracic carcinoid

Box 1

Immunological disorders associated with LEMS

- thyroiditis
- Addison's disease
- vitiligo
- pernicious anaemia
- SLE/DLE
- rheumatoid arthritis
- Sjögren's syndrome
- juvenile-onset diabetes mellitus
- scleroderma
- coeliac disease
- psoriasis

Box 2

Clinical features of LEMS

Limbs and trunk

- lower/upper limb weakness: proximal > distal
- exacerbation of weakness by prolonged exercise, hot bath or hot weather
- muscle pain and stiffness
- respiratory muscle weakness: spontaneous or induced by anaesthesia
- depressed or absent reflexes
- post-tetanic potentiation of reflexes

Cranial nerves

- symptoms: diplopia, drooping of eye lids, slurred speech, dysphagia, difficulty in chewing, weaker voice, head lolling
- signs: ptosis, neck weakness, jaw weakness, facial weakness, palatal weakness

Autonomic features

- dry mouth
- impotence
- constipation
- poor bladder and bowel control
- impaired sweating
- tonic pupils
- orthostatic hypotension/lightheadedness
- impaired oesophageal and intestinal motility

Box 3

Table 1 Sex differences in LEMS with and without cancer

Reference	No of patients	All			With cancer			Without cancer		
		Male	Female	Male %	Male	Female	Male %	Male	Female	Male %
4	50	32	18	64	14	11	56	18	7	72
8	28	12	16	43	6	8	43	6	8	43
15	64	35	29	55	7	11	39	28	18	61

of the immunoglobulin G (IgG) heavy chain marker G1m(2) is also found to be increased in both groups.¹⁶

Pathophysiology

The release of neurotransmitters at presynaptic motor nerve terminals of the neuromuscular junction and autonomic neurones depends on the influx of calcium through the voltage-gated calcium channels (VGCC).^{17–20} IgG from patients with LEMS has been shown to block the VGCCs.²¹ These antibodies result in symptoms by decreasing the release of neurotransmitters. They occur in both groups of LEMS patients.

The VGCCs are classified as L, N, P/Q, R, and T depending on their electrophysiological and pharmacological properties.^{22–24} They are found in various tissues, including neuronal cells, neuroendocrine cells and the cardiovascular system. In the nervous system they are present at the neuromuscular junction, autonomic neurones,^{19–20} and the central nervous system, particularly the cerebellum.²⁵ Different types of VGCCs may co-exist at one synapse.^{23–26}

Acetylcholine release from mammalian motor nerve terminals depends on P/Q type VGCCs.^{17–18} In LEMS, antibodies directed against these VGCCs decrease the release of acetylcholine,^{27–28} resulting in muscle weakness. N, P and Q type VGCCs play a key role in the neurotransmitter release at autonomic neurones.^{19–20} IgG autoantibodies from patients with LEMS have been shown to interfere with neurotransmitter release from postganglionic sympathetic and parasympathetic neurones by down-regulating mainly the P/Q type of VGCCs,²⁹ which probably explains the mechanism of autonomic dysfunction.

The SCLC tumour cells have been shown to express VGCCs of L, N and P/Q sub-types.^{30–32} In SCLC-associated LEMS they appear to provide the antigenic stimulation for antibody production which cross-reacts with the VGCCs in the nervous system. The resulting down-regulation in VGCCs would account for the clinical features.

Clinical features

Lambert and colleagues in their original series gave a classical description of the clinical features,^{2–3} and these were supplemented in subsequent reports (box 3).^{4–33–35} The cardinal clinical characteristics described by Eaton and Lambert were weakness and fatigability of muscles, temporary increase in strength after voluntary exercise, depressed or absent tendon reflexes, marked sensitivity to curare (as in myasthenia gravis) and relatively poor response to neostigmine.³ Tendon reflexes show marked potentiation after sustained contraction of the appropriate muscle for 10–15 seconds.⁴

The onset of symptoms is usually gradual and insidious. Occasionally it could be subacute. The commonest presenting symptom is leg weakness. Mild and transient cranial nerve symptoms such as diplopia, drooping of eye lids and dysphagia are reported by around 70% of patients. However, cranial nerve signs are very rare except for ptosis (54%) and weakness of neck flexion (34%).⁴ Although patients complain of diplopia, ophthalmoplegia on examination is extremely unusual in LEMS.

Autonomic symptoms are experienced by 80% of patients.⁴ Severe autonomic dysfunction may be found on testing even when symptoms are minimal.³⁶ Both the sympathetic and parasympathetic systems are affected in LEMS.^{29–33}

Investigations

ANTIBODIES TO VGCCS

Over 90% of patients belonging to both groups of LEMS have antibodies against P/Q type VGCCs.^{30–37} This finding appears to be particularly strong in carcinoma-associated LEMS where almost all patients are positive for antibodies against the P/Q type of VGCCs. Antibodies against N type VGCCs are found

Table 2 Occurrence of anti-VGCC antibodies in LEMS patients (all figures are expressed as percentages)

<i>Antibody type</i>	<i>With lung cancer</i>	<i>With other cancers</i>	<i>Without cancer</i>	<i>All patients</i>	<i>Normal subjects</i>
<i>Lennon et al³⁰</i>					
P/Q	100	100	91	95	2
N	73	17	36	49	0
<i>Antibody type</i>	<i>With SCLC</i>	<i>Without cancer</i>	<i>Status uncertain</i>	<i>All patients</i>	<i>Normal subjects</i>
<i>Motomura et al³⁷</i>					
P/Q	96	88	93	92	0
N	40	22	47	33	0

in less than 50% of patients when both groups of LEMS are considered together.^{30 37} However, when considered separately, these antibodies are found more commonly in LEMS associated with primary lung cancer.³⁰ Therefore, the detection of N-type antibodies may increase the possibility of finding an underlying primary lung cancer (table 2).³⁰

ELECTRODIAGNOSIS

Electrophysiological tests are useful for diagnosis as well as for monitoring the course of the illness. Compound muscle action potential (CMAP) after a supramaximal stimulus, postactivation potentiation (increase in the CMAP amplitude immediately after maximal voluntary contraction), repetitive nerve stimulation, and single fibre electromyography often help to differentiate LEMS from myasthenia gravis (table 3).^{3 35 38-42} Postactivation exhaustion (decrease in the CMAP amplitude 2–4 minutes after maximal voluntary muscle contraction) is seen in both the LEMS and myasthenia gravis. The results should be interpreted taking the entire picture, including the clinical presentation, into consideration.

The analysis of end-plate potentials and miniature end-plate potentials obtained from *in vitro* microelectrode studies can also help to differentiate LEMS from myasthenia gravis.^{38 43}

EDROPHONIUM TEST

The edrophonium test may be positive in LEMS but the response is usually weaker than that in myasthenia gravis.⁴

Treatment options

3,4-DIAMINOPYRIDINE

3,4-Diaminopyridine improves muscle strength and autonomic disturbances in LEMS without serious side-effects.^{7 44} It is used for symptomatic relief and is effective in both groups of LEMS. It blocks voltage-gated potassium channels which leads to prolongation of the action potential at motor nerve terminals and the open time of the VGCCs.⁴⁵ This process results in increased influx of calcium enhancing quantal neurotransmitter release.

The optimal dose of 3,4-diaminopyridine can vary from 5 mg tid to 25 mg qid. Its beneficial effects are felt about 20 minutes after an oral dose and last for about 4 hours. The maximum response occurs in 3 to 4 days due to cumulative effect. The commonest side-effect is peri-oral paraesthesia. Seizures have been reported in overdosage and rarely at therapeutic dosage.⁴⁶

GUANIDINE

Guanidine is an effective drug for symptomatic relief but its use is restricted by serious side-effects, including bone marrow toxicity, nephrotoxicity, hepatotoxicity, dermatitis and atrial fibrillation.^{47 48}

ANTICHOLINESTERASE DRUGS

Lambert, in his first report, noted the poor response of his patients to neostigmine.² Anticholinesterases alone produce mild or no improvement in LEMS. However, they seem to potentiate the effects of 3,4-diaminopyridine.⁷ Anticholinesterases can be used in combination with 3,4-diaminopyridine,⁷ or low-dose guanidine,⁴⁹ to produce symptomatic relief.

STEROIDS AND IMMUNOSUPPRESSIVES

The beneficial effect of long-term therapy with prednisolone has been shown in individual case reports.^{37 50} A retrospective study has shown that prednisolone combined with azathioprine is more effective than prednisolone alone in LEMS

Treatment of LEMS

- 1 For muscle weakness and autonomic symptoms: DAP *or* DAP + pyridostigmine
If DAP is not available: low dose guanidine + pyridostigmine
- 2 Screen for an underlying malignancy: specific treatment of the malignancy if present
- 3 No response to steps 1 and 2: steroids *or* steroids and immunosuppressives
- 4 Any patient with severe weakness: plasma exchange *or* IVIG

Box 4

Table 3 Electrodiagnostic differences between LEMS and myasthenia gravis

	LEMS	Myasthenia gravis
1 Amplitude of CMAP to a single supramaximal stimulus	Decreased	Normal or near normal
2 Postactivation potentiation	Marked increase in CMAP by more than 100%	May be seen, and when present less marked than in LEMS
3 Repetitive nerve stimulation: At slow rates (2–5Hz)	Decremental pattern	Decremental pattern (>10% decrement in generally considered to be abnormal)
At fast rates (30–50Hz)	Incremental pattern (over 2–20 times)	May show incremental pattern, but usually less marked than in LEMS
4 SFEMG	Increased jitter and intermittent impulse blocking, which improve with higher firing rates	Increased jitter and impulse blocking which get worse with higher firing rates
5 Microelectrode studies: MEPP amplitudes	Normal	Small or undetectable
EPP quantal content	Low	Normal
Distribution of EPP amplitudes	Poisson's distribution	Normal distribution

CMAP : compound muscle action potential; SFEMG : single fibre electromyography; (M)EPP : (miniature) end-plate potential

with no associated carcinoma.⁵¹ Although there are no prospective randomised controlled trials, it is reasonable to consider this option for long-term therapy in patients unresponsive to 3,4-diaminopyridine.

PLASMA EXCHANGE

Repeated plasma exchanges have been shown to produce significant symptomatic improvement in LEMS patients,^{51–52} reaching a peak at two weeks and subsiding by 6 weeks.⁵¹ It is effective in both groups of LEMS. Plasma exchange is particularly helpful in patients with severe weakness.^{51–52}

One of the disadvantages of plasma exchange is lack of selectivity. Protein A immunoabsorption is a technique used to remove IgG from plasma selectively. The success of this method has been reported in a patient resistant to plasma exchange and intravenous immunoglobulin.⁵³

INTRAVENOUS IMMUNOGLOBULIN

The benefits of intravenous immunoglobulin (IVIG) were first shown in individual case reports.^{54–55} In a double-blind, placebo-controlled, cross-over trial involving LEMS patients with no carcinoma, IVIG (1 g/kg body weight/day for 2 days) produced a significant increase in muscle strength peaking at 2 to 4 weeks and effects lasting up to 8 weeks. The clinical response was associated with a significant fall in antibodies to VGCCs.⁵⁶ IVIG can be used as an alternative to plasma exchange in patients with severe weakness.

There are no data available on IVIG therapy in LEMS associated with carcinoma; it may well also be effective in this group as the underlying disease mechanism is antibody mediated.

The treatment strategy in individual patients mainly depends on the severity of symptoms, the degree of response to symptomatic treatment, and the presence or absence of an associated malignancy (box 4).

Management of LEMS associated with SCLC

These patients can be treated with 3,4-diaminopyridine for symptomatic relief. The specific treatment of the underlying tumour usually results in improvement or remission of symptoms.^{57–58} In such patients the only further treatment required may be continuation of 3,4-diaminopyridine. When the specific tumour therapy fails to resolve symptoms, further treatment with prednisolone should be considered.⁵⁹ Those who present with severe weakness will benefit from plasma exchange or IVIG.⁵⁹

Management of LEMS with no associated cancer

3,4-Diaminopyridine therapy is beneficial in this group and, if successful, no additional treatment is required. Those who have not responded should be treated with prednisolone and/or azathioprine as long-term therapy.⁵⁹ Once

remission is achieved, prednisolone could be tapered to the minimum maintenance dose. If the weakness is severe, plasma exchange or IVIG should be considered.

Investigating for an underlying malignancy is an important step in the management of LEMS. In the majority of patients, symptoms of LEMS precede the diagnosis of underlying malignancy, the risk of which becomes low after 4 to 5 years.⁴ However, in high-risk patients such as smokers, it is worth undertaking regular screening for SCLC even after this length of time.⁵⁹

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