Lambert–Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies

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Lancet Neurol 2011; 10: 1098–107

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Lambert–Eaton myasthenic syndrome (LEMS) is a neuromuscular autoimmune disease that has served as a model for autoimmunity and tumour immunology. In LEMS, the characteristic muscle weakness is thought to be caused by pathogenic autoantibodies directed against voltage-gated calcium channels (VGCC) present on the presynaptic nerve terminal. Half of patients with LEMS have an associated tumour, small-cell lung carcinoma (SCLC), which also expresses functional VGCC. Knowledge of this association led to the discovery of a wide range of paraneoplastic and non-tumour-related neurological disorders of the peripheral and central nervous systems. Detailed clinical studies have improved our diagnostic skills and knowledge of the pathophysiological mechanisms and association of LEMS with SCLC, and have helped with the development of a protocol for early tumour detection.

Introduction

In 1953, Anderson and colleagues[1] described a 47-year-old man with progressive muscle weakness and diminished tendon reflexes. After a small-cell lung carcinoma (SCLC) was surgically removed, the patient's improvement was striking. A few years later, American neurologists Lambert, Eaton, and Rooke described six similar cases with a distinctive electrophysiological pattern seen with repetitive nerve stimulation.[2] This syndrome, with or without SCLC, has become known as Lambert–Eaton myasthenic syndrome (LEMS), and the diagnosis is still based on these electrophysiological criteria.

Over the past decade, our knowledge of epidemiological and clinical features of LEMS has expanded. Improved awareness and knowledge of the disease have shortened the diagnostic delay and led to fewer misdiagnoses. The discovery of pathogenic autoantibodies to voltage-gated calcium channels (VGCC) has facilitated diagnosis and improved our understanding of the pathophysiological mechanisms leading to LEMS; the finding of functional VGCC on the SCLC provided an aetiological basis for the disorder, at least in those with an underlying carcinoma. Clinical, genetic, and serological markers discriminated SCLC-related LEMS (SCLC-LEMS) from non-tumour LEMS (NT-LEMS). The validated Dutch-English LEMS Tumor Association Prediction (DELTA-P) score offers adequate prediction of the presence of SCLC in patients with LEMS early in the course of the disease.[3] Early diagnosis enables effective symptomatic or immunosuppressive treatment, or an early start to oncological treatment.

In this Review, we focus on the epidemiology, clinical discrimination of SCLC-LEMS from NT-LEMS, pathophysiology, and current treatment options, with the aim of improving diagnosis, accelerating screening times for SCLC, and optimising treatment.

Epidemiology

LEMS is a rare disorder with a reported estimated incidence of 0·48 per million.[4] However, in the 5 years after this estimate was reported,[4] incidence in the Netherlands rose to 0·75 per million, with a prevalence of 3·42 per million, probably because of improved recognition of the disorder (unpublished). The original description of LEMS as a disease in male patients older than 50 years[5,6] is only valid for the paraneoplastic form of the disease (SCLC-LEMS). Median age at onset in this group is 60 years, and 65% of patients are men.[3] NT-LEMS, however, is seen at all ages, with a peak age of onset of around 35 years and a second, larger peak at age 60 years.[3] In a study of NT-LEMS and SCLC-LEMS, women were slightly over-represented in the early-onset NT-LEMS group, but overall, 60 of 115 (52%) patients with NT-LEMS were female,[3] similar to historic data.[7] The age and sex distribution in NT-LEMS is similar to that reported for myasthenia gravis (MG),[8] as is the genetic association with HLA-B8-DR3. This haplotype is linked to autoimmunity, and is present in around 65% of patients with NT-LEMS;[9] however, the haplotype is more prevalent than in controls only in patients with young onset (unpublished), as in MG.[10] Common immunogenetic risk factors might have a role in the onset of LEMS or MG in the early-onset non-tumour group. There is an increase in susceptibility to autoimmune diseases in patients with NT-LEMS and their family members.[11,12]

Tumour association

50–60% of patients with LEMS have a tumour.[3] SCLC, a smoking-related lung carcinoma with neuroendocrine characteristics, is almost always the tumour type that occurs in patients with LEMS, although there have been a few reports of non-small-cell and mixed lung carcinomas.[5,13–17] Several papers describe associations of LEMS with non-lung-cancer tumours.[7] Statistically, it is likely that many of these would have arisen by chance, but for certain disorders (eg, prostate carcinoma, thymoma, and lymphoproliferative disorders), the cause might be paraneoplastic. Six LEMS patients with prostate carcinoma have been described.[18] In these patients, the tumours had neuroendocrine and small-cell characteristics, and symptoms of LEMS correlated with tumour activity. Prostate cancer is also the most common extrathoracic tumour in patients with anti-Hu syndrome, another paraneoplastic neurological syndrome that is mainly

Panel: **Criteria for diagnosis of LEMS**

Clinical features
- Proximal muscle weakness
- Autonomic symptoms
- Reduced tendon reflexes

VGCC antibodies

Repetitive nerve stimulation abnormalities
- Low compound muscle action potential
- And decrement >10% at low frequency (1–5 Hz)
- And increment >100% after maximum voluntary contraction or at high frequency (50 Hz)

For diagnosis, clinical features should be present (proximal muscle weakness is required), combined with VGCC antibodies, or repetitive nerve stimulation abnormalities, or both. LEMS=Lambert–Eaton myasthenic syndrome. VGCC=voltage-gated calcium channels.

associated with SCLC.[19] In four patients with thymoma, two had clear remission of LEMS after surgery without chemotherapy.[20–23] The association of lymphoproliferative disorders with LEMS remains unclear; in 15 patients described, the timeframe of clinical symptoms of LEMS and lymphoproliferative disorders were not well connected.[3,24–27]

Diagnosis

Diagnosis of LEMS is based on clinical signs and symptoms, electrophysiological studies, and antibody testing (panel). The clinical triad typically consists of proximal muscle weakness, autonomic features, and areflexia.[5] Proximal leg muscle weakness is usually the first symptom noted by the patient (in 80%).[28] Weakness of the arms is present or develops quickly.[28,29] Weakness normally spreads proximally to distally, involving feet and hands, and caudally to cranially, finally reaching the oculobulbar region (figure 1). The speed of progression is much more pronounced in SCLC-LEMS than in NT-LEMS.[28] Occurrence of ocular symptoms ranges from 0–80%, and bulbar symptoms from 5–80%;[14,28,30–34] this wide range in prevalence is probably the result of inconsistency in the timing of assessment from presentation. When we increased a previously described cohort[28] from 97 to 234 patients, the frequency of ocular and bulbar symptoms rose from 30% and 32%, respectively, within 3 months of onset to 49% and 52%, respectively, within 12 months of onset, particularly in patients with SCLC-LEMS (figure 1, webappendix p 2).[3] Although isolated cases of purely ocular symptoms have been reported,[33,35,36] almost all patients with ocular symptoms or respiratory failure early in the disease course also had generalised weakness.[33,37] By contrast with MG, isolated weakness of the external eye muscles is rare.

Autonomic dysfunction

Autonomic dysfunction provides another clue to diagnosis of LEMS; the type of autonomic dysfunction can be very diverse, but is usually not very debilitating. Autonomic dysfunction is found in 80–96% of patients with LEMS,[3,5,28,31,32] although it was reported less frequently (37%) in a Japanese study.[14] In our cohort,[3,28] presence of autonomic symptoms rose from 66% within 3 months of onset to 91% for ever-occurrence. Dry mouth is the most common symptom, followed by erectile dysfunction in men and constipation. Orthostatic dysfunction, micturition difficulties, dry eyes, and altered perspiration are less common (webappendix p 3).

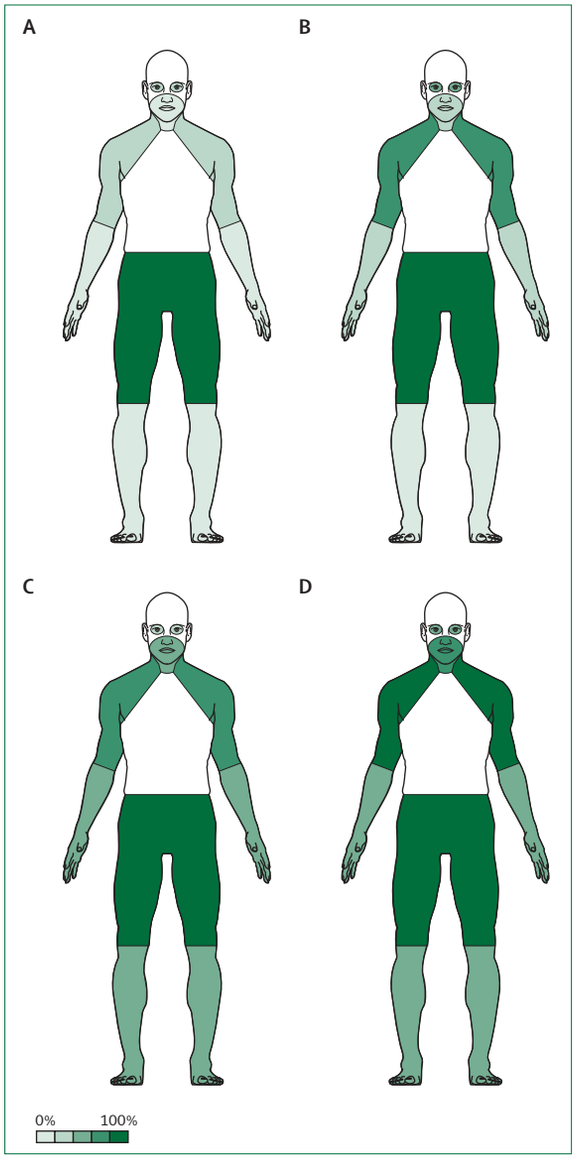


Figure 1: **Spreading of symptoms in patients with NT-LEMS and SCLC-LEMS**
Frequency of symptoms at 3 months (A) and 12 months (B) in patients with NT-LEMS, and frequency of symptoms at 3 months (C) and 12 months (D) in patients with SCLC-LEMS. The percentages describe the approximate proportion of patients who have that symptom within the given timeframe. NT=non-tumour. LEMS=Lambert–Eaton myasthenic syndrome. SCLC=small-cell lung cancer.

See Online for webappendix

Tendon reflexes

Patients with LEMS might show decreased or absent tendon reflexes. A characteristic, although not very sensitive, phenomenon is post-exercise facilitation, a short-term return of tendon reflexes and muscle strength to normal range after muscle contraction. It is present in 40% of patients[38,39] and can mask the lowered tendon reflexes. Therefore, if a diagnosis of LEMS is suspected, tendon reflexes should be tested after a period of rest.

Misdiagnosis and differential diagnosis

LEMS often starts with mild upper leg weakness, by contrast with MG, where ptosis and diplopia usually dominate the clinical presentation. The clinical pattern in LEMS is less specific than that in MG and can be difficult to recognise. Therefore, diagnostic delay can be long, particularly in patients with NT-LEMS. In two studies of patients with LEMS, median time to diagnosis was 4 months (range 0·6–40) in SCLC-LEMS and 12 months (1–265) and 19 months (2–300) in NT-LEMS.[3,32] Reasons for the delay in diagnosis include the non-specific onset in most patients, with symmetric, often mild, proximal weakness and slow progression of symptoms in many patients. In our combined Dutch and British cohorts, 58% of patients were initially misdiagnosed (webappendix pp 1–2).[3,28] MG is most often confused with LEMS, especially if oculobulbar muscles are involved.[33] However, 90% of patients with MG show oculobulbar symptoms first, as opposed to only 5% with LEMS.[34] Generally, muscle weakness in MG develops in a craniocaudal direction (in LEMS it is the reverse),[34] and most patients with MG do not have autonomic dysfunction and reduced tendon reflexes.

Proximal, symmetric muscle weakness suggests myopathy, especially inclusion body myositis in older patients. Pain and raised creatine kinase are rare in LEMS, but common in most types of myositis. Again, in this differential diagnosis autonomic symptoms suggest LEMS. Patients with lumbar canal stenosis can present with fatigability of leg muscles, but the patient's history will differentiate it from LEMS. Many patients with LEMS complain about difficulties getting out of a chair. These starting problems can resemble early-phase Parkinson's disease or lower body parkinsonism. Since the patient's verbal history of symptoms often suggests greater severity than indicated by the actual signs at examination, depression or even a psychosomatic disorder is sometimes considered.

In some patients, symptoms develop in a subacute manner. Combined with abnormalities detected in a suboptimum electrophysiological examination, these symptoms can resemble those of neuropathy, Guillain-Barré syndrome (GBS), or amyotrophic lateral sclerosis (ALS). However, patients with LEMS do not have sensory symptoms or pronounced pain, and by contrast with GBS, the CSF does not typically show increased protein concentrations.[40] ALS has a more marked atrophic pattern than LEMS, can be asymmetric, and more often starts in the upper extremities.[41]

Electromyography

Repetitive nerve stimulation (RNS) is the electrophysiological study of choice to diagnose LEMS (panel). The first compound muscle action potential (CMAP) amplitude is already low in these patients, and becomes even lower at low stimulating frequencies (2–5 Hz).[42] In patients with LEMS, decrement can be present at frequencies as low as 0·1 Hz. A decrease of CMAP amplitude (decrement) of at least 10% is considered abnormal,[42] and 94–98% of patients with LEMS show a substantial decrement;[39,43] however, since patients with MG also show a large decrement, this is not a specific feature. To discriminate between LEMS and MG, high-frequency stimulation (50 Hz) or, preferably, post-exercise stimulation is done. An increase in CMAP amplitude (increment) higher than 100% is considered abnormal. The increase in CMAP amplitude is very short-lived, and is highest if the stimulus follows as soon as possible after cessation of muscle exercise. Post-exercise stimulation has a sensitivity of 84–96%[39,43,44] and is 100% specific for LEMS. High-frequency stimulation has comparable sensitivity, but is very painful and should be avoided if possible. A cut-off of 60% to consider the CMAP increment significant has been proposed, since it raises sensitivity to 97%, while specificity (to exclude MG) is still 99%.[39]

Single-fiber electromyography might be slightly more sensitive than RNS, but it does not distinguish between MG and LEMS and requires technical experience.[42] RNS, if done properly, is technically simpler and is sensitive and specific. The sensitivity of RNS is increased by withdrawal of symptomatic medication 12 h before examination and if the temperature of the examined muscles is maintained at above 32°C.[42]

VGCC antibodies

Antibodies to P/Q-type VGCC are responsible for the clinical symptoms of LEMS. These antibodies have been detected in 85–90% of patients with LEMS, and some studies report a percentage close to 100% in LEMS patients with SCLC.[45–48] To create a diagnostic assay, P/Q-type and N-type VGCC are extracted from mammalian brain and specifically labelled using ω-conotoxin MVIIC or GVIA derived from the *Conus* genus of piscivorous snails. Immunoprecipitation of these labelled channels by antibodies in the sera of patients with LEMS generates a sensitive diagnostic assay. Antibodies to N-type and L-type VGCC have also been reported in LEMS (in 30–40% and 25% of patients, respectively), but all of these patients also had the P/Q-type VGCC.[46,49] One exception is a report of two patients with squamous-cell carcinoma and only N-type VGCC antibodies.[50] An alternative diagnostic assay system was

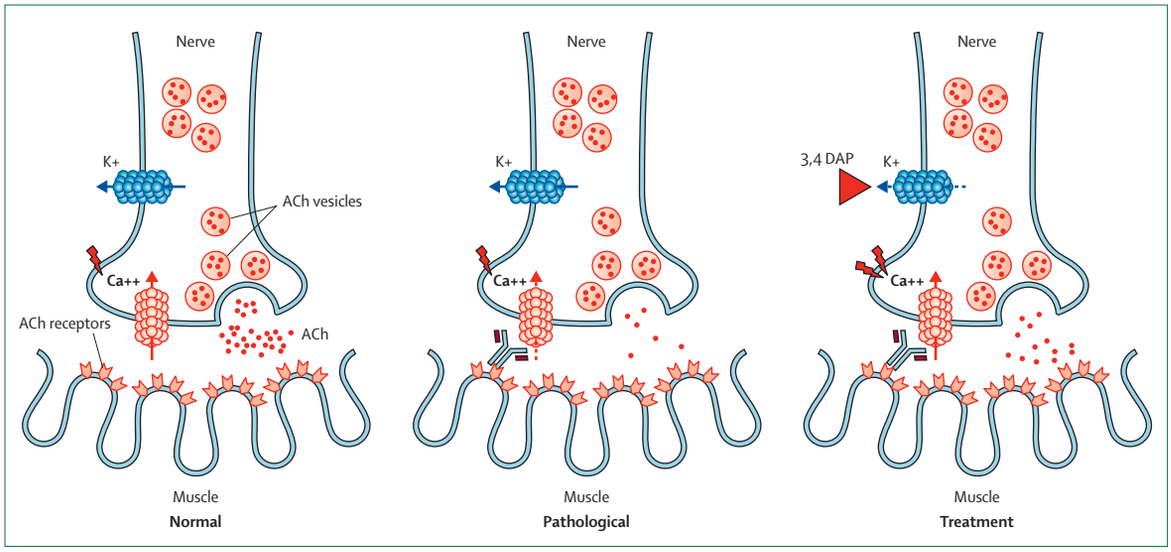


Figure 2: **Pathophysiology of LEMS and effects of symptomatic treatment**
(A) Normal depolarisation of the presynaptic nerve terminal by ion channels leads to influx of calcium ions and subsequent release of ACh-containing vesicles; ACh binds to the ACh receptor, leading to depolarisation of the postsynaptic synapse and ultimately to muscle contraction. (B) In LEMS, VGCC antibodies block calcium influx, leading to reduced ACh vesicle release from the presynaptic membrane; therefore, reduced ACh is available to bind to postsynaptic ACh receptors. (C) Treatment with 3,4-diaminopyridine (red triangle) blocks the efflux of potassium ions, prolonging the duration of depolarisation. Longer depolarisation keeps the pathologically affected calcium channels open longer, increasing calcium ion influx and intracellular calcium concentration and thereby improving the ability of the ACh vesicles to fuse and release neurotransmitter. LEMS=Lambert–Eaton myasthenic syndrome. ACh=acetylcholine. VGCC=voltage-gated calcium channels. DAP=diaminopyridine.

developed using the spider venom ω-phonetoxin IIA,[51] which labels P/Q-type and N-type VGCC, to label rat cerebellar extracts. However, a reduced sensitivity of 84% for patients with clinically defined LEMS makes this assay less viable.

Antibodies to P/Q-type VGCC are highly specific to LEMS, but have been detected in 1–4% of patients with SCLC without neurological dysfunction.[48] Similarly, these antibodies are also found in the serum and CSF of a small number of patients with subacute cerebellar ataxia, both with and without clinical symptoms of LEMS, nearly all of whom had an associated SCLC.[52]

The VGCC is a complex protein consisting of multiple subunits. The pore-forming α_1 subunit is responsible for the biochemical and electrophysiological characteristics of VGCC, so the search for immunodominant antigenic sites has focused on this subunit. Using ELISA-based and western blotting techniques, antibodies to linear peptide epitopes derived from specific extracellular regions, particularly the S5–6 region of linker domains II and IV of the α_1 subunit, have been detected in 50% of patients with LEMS and 5% of controls.[53,54] Additionally, antibodies that recognised domain IV were more common in patients with NT-LEMS (37·5%) than in those with SCLC-LEMS (4·6%).[55] Around 40% of patients with LEMS had antibodies that recognised a recombinant form of the β subunit, but since this subunit is entirely intracellular, these antibodies should be considered secondary to the disease process.[56]

Pathophysiology

A pathogenic role for P/Q-type VGCC antibodies is likely because the antigen is present in SCLC and at the neuromuscular junction. The autoantibodies target VGCC on the presynaptic nerve terminal of the neuromuscular junction and on the surface of SCLCs. Autoimmunity is implicated, because passive transfer of the disease has been described from an affected mother to baby, resulting in transient neonatal weakness.[57,58] Passive transfer of human autoantibodies to mice also induces disease. Active immunisation with peptides results in a mild LEMS-like disease in rats.[59] Mice with mutations in the P/Q-type VGCC *Cacna1a* gene show some of the electrophysiological characteristics of LEMS.[60] Clinically, LEMS is compatible with an autoimmune disease since patients show a good response to immunomodulating therapy,[61,62] and patients with NT-LEMS have the autoimmune-prone HLA B8-DR3-type.[9]

Functional studies

The autoimmune cause of LEMS was established by a series of passive transfer experiments in which mice injected with serum or IgG from patients with LEMS showed the same electrophysiological and morphological changes seen in the patients. The injected mice showed a reduction in the quantal content, which represents the number of acetylcholine packages released per nerve impulse over a range of extracellular calcium ion concentrations, indicating a functional effect on the

presynaptic VGCC.[63] Similarly, there was a reduction in the density and distribution of active zone particles, thought to be the morphological representation of the VGCC.[64] Together, these results suggest that the LEMS IgG induces a functional loss in VGCC, resulting in reduced Ca^{2+} entry during depolarisation and a subsequent decrease in neurotransmitter release (figure 2). LEMS IgG was equally effective in C5-deficient mice, suggesting that late complement components are not required,[65] which is in line with the lack of complement disposition seen in biopsied material from patients with LEMS.

The P/Q-type VGCC present at the neuromuscular junction are also functionally expressed in SCLC[66] and in the cerebellum. Using patch-clamp recordings, rat cerebellar and granule-cell neurons cultured overnight in LEMS IgG showed a substantial reduction in current through the P-type VGCC, mirrored by an apparent concomitant rise in the levels of R-type VGCC. There was little effect on currents through the N-type or L-type VGCC.[67] A similar effect on the VGCC channel profile was observed in the passive transfer model of LEMS. Under normal conditions, nearly 95% of neurotransmitter released at the adult mouse neuromuscular junction can be blocked by the specific P-type VGCC blocker ω-agatoxin IVA, but in mice injected for 9 days with LEMS IgG, the ω-agatoxin IVA-sensitive component was substantially reduced, with a concomitant increase in N-type and L-type channels.[68] This plasticity in VGCC expression after pathological insult might partly explain why VGCC antibodies do not have a more devastating effect and why there might be phenotypic differences between tissues affected and between individual patients.

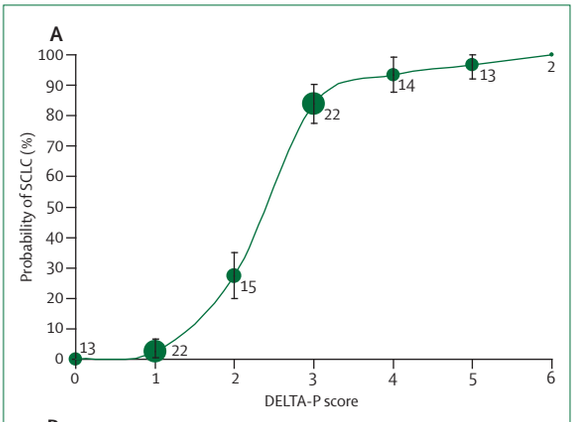
Komai and colleagues[59] showed that six of ten rats actively immunised with short peptides derived from the extracellular region (S5–6 linker domain 3) of the α1 subunit of the VGCC showed some features of LEMS, including reduced quantal content, facilitation at high frequency nerve stimulation, and a moderate degree of weakness.

VGCC have been shown to link to laminin β, maintaining active zones on the presynaptic membrane. Mice with mutations that hinder this link show a loss in aggregation of active zones, as seen in LEMS. However, no electrophysiological or clinical features were seen in these mice.[69,70]

Mutations in the *CACNA1A* gene, which codes for the alpha subunit of P/Q-type VGCC, cause hemiplegic migraine or episodic ataxia type 2. In both conditions, ataxia is part of the clinical spectrum. This is not surprising since P/Q-type VGCC are also expressed in Purkinje cells in the cerebellum. Cerebellar degeneration is also found in a small proportion of patients with LEMS, particularly those with SCLC-LEMS.[28] Mice with a *Cacna1a* mutation showed ataxia, mild clinical weakness, and electrophysiological disturbances of the neuromuscular synapse.[60] A post-mortem study showed a marked reduction in P/Q-type VGCC in the cerebellum of a LEMS patient with paraneoplastic cerebellar degeneration compared with controls, and compared with a LEMS patient without central involvement.[71] It is unclear why the immune response extends to the CNS in only a small proportion of patients with LEMS.

Seronegative LEMS and other antibodies

10–15% of patients with LEMS have no detectable P/Q-type VGCC antibodies. Nakao and colleagues[14] studied a cohort (n=17) of these seronegative patients with clinically definite LEMS. The clinical phenotype in this cohort was very similar to that in seropositive patients; however, the incidence of SCLC was only 12%, compared with 60–70% in seropositive patients.[14] Electrophysiological features were similar but less prominent.[72] Passive transfer of seronegative LEMS sera to mice seemed to reproduce the typical electrophysiological changes seen in mice passively transferred with seropositive sera. Seronegative LEMS might therefore be caused by the same antibodies but at a lower, subthreshold concentration, or by antibodies to a



B

	Categories	<3 months of onset	Score
D	**D**ysarthria, dysphagia, chewing, neck weakness: bulbar weakness	Absent Present	0 1
E	**E**rectile dysfunction	Female Male: absent Male: present	0 0 1
L	**L**oss of weight	Absent or <5% ≥5 %	0 1
T	**T**obacco use at onset	Absent Present	0 1
A	**A**ge of onset	<50 years ≥50 years	0 1
P	Karnofsky performance score	70–100 0–60	0 1
	DELTA-P score		0–6

Figure 3: **Predicted percentage of SCLC in patients with LEMS, based on the Dutch-English LEMS Tumor Association Prediction (DELTA-P) score**
The DELTA-P score is calculated as a sum score according to the different categories listed. The DELTA-P score can range from 0 to 6. Point sizes are proportional to the number of patients with a specific score, which is also represented by the percentage beside the circle. Vertical bars show SEM. SCLC=small-cell lung cancer. LEMS=Lambert-Eaton myasthenic syndrome. Reproduced from Titulaer and colleagues,[3] by permission of the American Society of Clinical Oncology.

VGCC epitope not recognised in the current diagnostic assays. Alternatively, seronegative patients with LEMS might be caused by antibodies to a different molecule altogether that can generate a comparable phenotype.

Autoantibodies to other proteins have occasionally been described in patients with LEMS. Several studies reported antibodies to synaptotagmin, a synaptic vesicle protein partly exposed at the surface during exocytosis, in anti-VGCC-positive and anti-VGCC-negative patients with LEMS.[47,73,74] Takamori and colleagues[74] noted that some rats actively immunised with short peptides derived from synaptotagmin showed electrophysiological features similar to LEMS.

Muscarinic acetylcholine receptors m1 (AChRm1) have been detected at the neuromuscular junction where they are thought to modulate cholinergic neurotransmission. Using western blot techniques, antibodies to AChRm1 were detected in 14 of 20 VGCC-positive patients with LEMS, five of five VGCC-negative patients with LEMS, and seven of 25 patients with MG.[75]

Antibodies against SOX1 are found in 65% of patients with SCLC-LEMS and 22–32% of patient with SCLC (with or without anti-Hu syndrome),[48,76–79] but in only 5% of patients with NT-LEMS.[48,76] The SOX1 protein, part of the Sry-like high mobility group superfamily of developmental transcription factors, is thought to prevent differentiation of neural progenitor cells. Normally it becomes dormant shortly after birth, but it is found in some types of tumour cells. It is unknown why more patients with SCLC-LEMS than patients with anti-Hu syndrome or SCLC alone have SOX1 antibodies, but it might indicate a common (genetic) predisposition. HuD antibodies are linked to the anti-Hu syndrome and SCLC.[19] They are present in 30% of patients with SCLC-LEMS, but have no additional screening value over SOX1.[48]

There is no satisfactory evidence for pathogenicity of any of these antibodies, although some might be relevant for detection of an underlying tumour. The relevance of autoantibodies detected by use of ELISA or western blotting is uncertain. Both techniques can be used to detect antibodies to linear sequences, which are unlikely to be in a conformationally native state and are of questionable relevance.

Prediction and screening for SCLC

Screening for an SCLC is very important, since it affects treatment and prognosis of patients with LEMS. Patients with SCLC-LEMS are more likely to have limited disease than patients with SCLC without LEMS (65% *vs* 39%), probably because of early detection.[16] Clinical symptoms of LEMS are nearly always present before SCLC is detected, although the symptoms are sometimes mild and aspecific. Diagnosis of SCLC preceded recognition of LEMS in only 6% of patients.[16]

In most patients, diagnosis of LEMS leads the physician to search for SCLC, since only some patients presenting with neurological symptoms have lung complaints, and these are mostly mild.[16] Screening detected 91% of SCLC within 3 months and 96% within 1 year of diagnosis of LEMS.[16] All patients in whom SCLC was detected more than 2 years after diagnosis of LEMS had undergone inferior screening (chest radiograph, low-quality CT, or only one screening).[5,16,80,81] Many factors affect risk of SCLC. Among patients with LEMS, older age, male gender, weight loss, and being a (former) smoker are associated with underlying SCLC.[3,5–7,9,16] Swift development and spreading of clinical symptoms after onset (figure 1) is also seen mostly in SCLC-LEMS,[3,28,29] as is a Karnofsky performance status of less than 70 (ie, patients need at least some assistance with their activities in daily living).[3] Serologically, raised erythrocyte sedimentation rate,[3,5] abnormal leucocyte cell count,[3] and presence of SOX1 antibodies[48,76] are markers for SCLC-LEMS, whereas HLA-B8 and HLA-DR3 are markers for NT-LEMS.[3,9] Although the presence of SOX1 antibodies has a specificity of 95% for SCLC-LEMS, sensitivity is only 65%.[48] A proposed prediction algorithm for SCLC-LEMS, using smoking and HLA-B8, had good sensitivity and specificity (83% and 86%, respectively);[9] however, none of these was sufficient to guide screening. Therefore, a multivariate analysis, using a Dutch cohort of more than 100 patients, was performed and the outcomes were validated in a similar group of British patients with LEMS.[3] The DELTA-P score, developed in this study, was shown to be simple, sensitive, specific, and reproducible. The probability for SCLC can be calculated at diagnosis of LEMS, and varies from 0–2·6% with a DELTA-P score of 0–1, up to 83·9–100% with a score of 3–6 (figure 3).

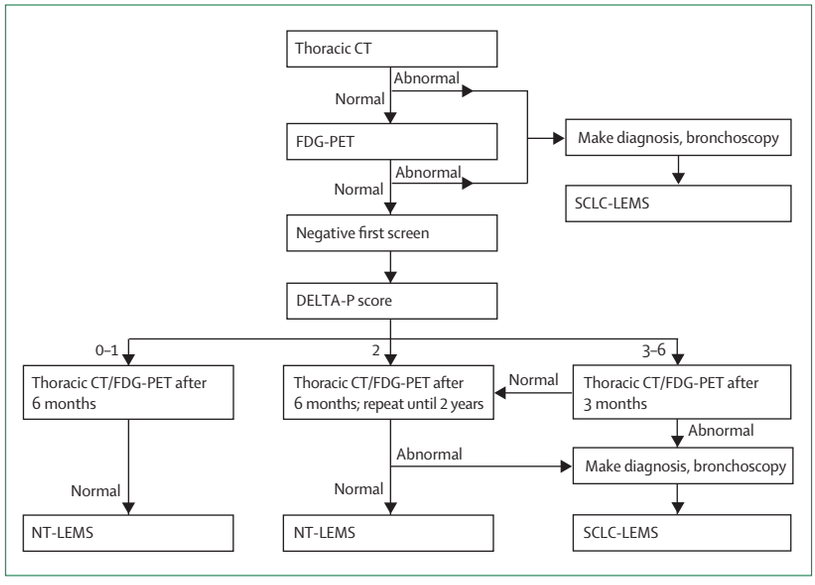


Figure 4: **Flowchart of recommended screening for SCLC in patients with LEMS**[3,16,70]
SCLC=small-cell lung cancer. LEMS=Lambert–Eaton myasthenic syndrome. FDG-PET= ^{18}F-fluorodeoxyglucose PET. NT=non-tumour.

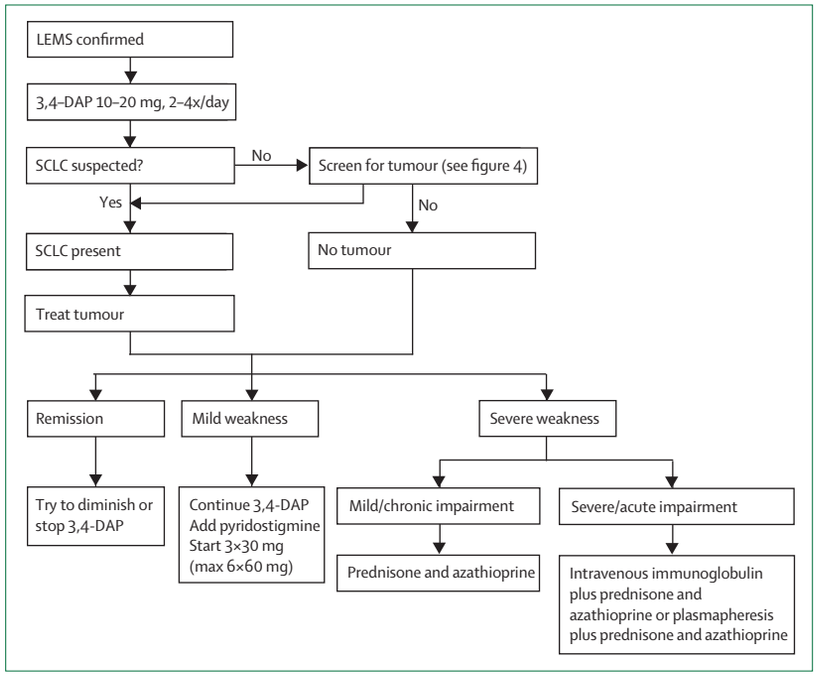


Figure 5: **Treatment scheme for LEMS**
LEMS=Lambert–Eaton myasthenic syndrome. DAP=diaminopyridine. SCLC=small-cell lung cancer.

All patients with LEMS, even those with a low chance of SCLC as calculated by use of the DELTA-P score, should be screened with thoracic CT and ^{18}F-fluorodeoxyglucose (FDG)-PET or an integrated FDG-PET/CT.[16,82] A chest radiograph should not be used for screening since it has insufficient sensitivity. If negative, a second screening with thoracic CT or FDG-PET should be done after 3–6 months, depending on the DELTA-P score (figure 4).[3,16,82]

Treatment

The first choice for symptomatic treatment of patients with LEMS is 3,4-diaminopyridine. An algorithm for treatment of LEMS is proposed in figure 5, in line with published guidelines.[83,84] A recent Cochrane review[85] described the results of four randomised controlled trials in a total of 54 patients with LEMS.[86–89] All trials reported a significant improvement in muscle strength score, myometric limb measurement, or CMAP amplitude after treatment. In general, 3,4-diaminopyridine is well tolerated; the most common side-effects are perioral tingling and digital paresthesias, and some patients report gastrointestinal symptoms.[85] The most frequent serious adverse events are seizures; this risk seems to be dose-dependent and is described at doses of around 100 mg per day.[88,90] Supraventricular tachycardia has been reported after iatrogenic intoxication with 360 mg 3,4-diaminopyridine,[91] and one patient died from a myocardial infarction a few weeks after starting the drug, but a causal relationship was unclear.[92] Prolongation of the QT interval is often mentioned as a possible side-effect, but was not seen in any of 27 patients.[86–88] 3,4-diaminopyridine was previously thought to act by blocking voltage-gated potassium channels, prolonging the action potential at the motor nerve terminals and lengthening the opening time of the VGCC (figure 2).[93] However, recent findings suggest that aminopyridines might also potentiate neuromuscular transmission by targeting the VGCC β subunit directly.[94] Guanidine, pyridostigmine, or both are also used in treatment of LEMS, when 3,4-diaminopyridine is not readily available. These compounds have been studied in (small) open-label case series,[15,95] but not in clinical trials. Some patients with LEMS reported benefits from adding pyridostigmine to 3,4-diaminopyridine.[15,86] A small crossover trial using intravenous administration of pyridostigmine showed no additional benefit of this drug.[89]

If 3,4-diaminopyridine satisfactorily controls the symptoms of LEMS, no further treatment is needed. If symptoms remain, long-term treatment with prednisone and azathioprine should be considered. Prednisone, given most often in combination with azathioprine, was needed in 80 of 114 (70%) patients with NT-LEMS, expanding a previously described cohort of 47 patients,[96] and in 46 of 104 (44%) with SCLC-LEMS (unpublished). The effectiveness of the combined prednisone–azathioprine therapy has only been shown in a retrospective study,[62] but is supported by the positive results of the combined treatment in MG.[97] Patients with SCLC are given chemotherapy, such as cisplatinum and etoposide.[98] If remission of symptoms is incomplete, prednisone might induce improvement. There are no suggestions that immunosuppressive treatment is contraindicated in patients with SCLC-LEMS.[99]

One crossover trial reported significant improvement in limb strength after treatment with intravenous immunoglobulin.[61] Rituximab was effective in three LEMS patients with severe myasthenic weakness.[100,101] In our experience, most patients can be treated sufficiently with symptomatic treatment combined with prednisone and azathioprine, in addition to chemotherapy. Acute treatment with intravenous immunoglobulin, plasmapheresis,[15] or additional immunosuppressive agents is rarely needed.

Future directions

Optimisation of screening for LEMS is important, as is optimum symptomatic treatment with limited side-effects. Most side-effects of 3,4-diaminopyridine, such as seizures, are dose-dependent, and the peak dose limits the therapeutic window of this drug. Possible improvement in terms of side-effects and LEMS symptoms might be obtained by slow-release tablets, or a combination of 3,4-diaminopyridine with pyridostigmine. Studies with 3,4-diaminopyridine or pyridostigmine have been small. A study of nine patients did not show a superimposed effect with the combination of these drugs.[89] If only a proportion of patients with LEMS are likely to benefit from combination therapy, a larger trial will be needed.

Search strategy and selection criteria

We searched PubMed, the Cochrane library, the authors' own databases, and reference lists of selected studies for reports in English, German, French, and Spanish, published since 1954. We used the search terms "Lambert–Eaton myasthenic syndrome", "LEMS", or "myasthenic syndrome". We mainly selected articles from the past decade, but did not exclude highly regarded previous publications.

Although clinical recognition of LEMS has improved, the diagnostic process could be further enhanced if a non-radioactive assay were available. The radioimmunoassay for VGCC antibodies, with good sensitivity of 85–90% and excellent specificity of higher than 99%, requires the use of radioactive epitopes, and the reliability of the assay is highly dependent on the experience of the investigator.

There are many other questions that need to be answered in relation to this rare but fascinating autoimmune channelopathy. The types of autoantibodies in the 10–15% of patients with LEMS who are seronegative, most of whom respond well to immunotherapy, need to be clarified. The role for VGCC antibodies, and possibly T cells, in patients with VGCC-antibody paraneoplastic cerebellar degeneration remains unclear.

Patients with SCLC-LEMS have better survival than SCLC patients without neurological dysfunction, even if these patients with SCLC have VGCC antibodies. The clinical significance of VGCC antibodies in the 3–4% of SCLC patients without neurological dysfunction is unknown. It is unlikely that the improved survival is merely due to lead-time bias, but a more fundamental biochemical cause has not been proven either. More insight into the underlying mechanisms might elucidate pathways to immune therapy aimed at SCLC.

As with many autoimmune disorders, it is unknown which factors contribute to the start of LEMS. In patients with an associated tumour, it might be that an immune reaction against antigenic determinants on the tumour's surface triggers autoantibody production, and these antibodies crossreact with VGCC on the nerve terminals and cause neurological disease. In LEMS patients without tumours, the original trigger that starts the autoimmune reaction is unknown. Strict diagnostic criteria and detailed insight into the pathophysiology make LEMS an excellent candidate to study mechanisms of both general autoimmunity and tumour immunology.

Contributors

MJT and JJGMV had the idea for the Review. All authors collected data, contributed to the literature search, and wrote separate sections. All authors commented on consecutive versions of the manuscript.

Conflicts of interest

The neurology department of the Leiden University Medical Center received fees from BioMarin Ltd in 2009–10 for consultancies by JJGMV. JJGMV did not receive any personal payments from BioMarin Ltd. BL and her department receive royalties and payments for antibody assays. MJT declares that he has no conflicts of interest.

Acknowledgments

MJT is supported by a fellowship of the Dutch Cancer Society. This study was partly supported by a grant from the Prinses Beatrix Fonds.

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