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REVIEW ARTICLE

Lambert–Eaton myasthenic syndrome: Clinical review

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Abstract

Lambert–Eaton myasthenic syndrome (LEMS) is an autoimmune disease of the neuromuscular junction and approximately 60% of LEMS patients have a tumor, mostly small cell lung cancer, as a paraneoplastic neurological syndrome. LEMS patients develop a unique set of clinical characteristics, which include proximal muscle weakness, depressed tendon reflexes with post-tetanic potentiation and autonomic symptoms. Interestingly, slightly <10% of LEMS patients have cerebellar ataxia (LEMS with paraneoplastic cerebellar degeneration). Considering its pathomechanism, LEMS is a presynaptic disorder of neuromuscular transmission in which quantal release of acetylcholine is impaired by autoantibodies for P/Q-type voltage-gated calcium channels at active zones, although an animal model by immunizing purified P/Q-type voltage-gated calcium channels has not yet been successful.

Introduction

Lambert–Eaton myasthenic syndrome (LEMS) is a rare presynaptic disorder of neuromuscular transmission in which quantal release of acetylcholine is impaired by autoantibodies for voltage-gated calcium channels, as shown in Figure 1.[1–3] LEMS patients develop a unique set of clinical characteristics, which include proximal muscle weakness, depressed tendon reflexes with post-tetanic potentiation and autonomic changes.[4] Interestingly, slightly <10% of LEMS patients develop cerebellar ataxia, which was defined as LEMS with paraneoplastic cerebellar degeneration.[5–10] Approximately 60% of LEMS patients have an underlying malignancy, most commonly a small cell lung cancer (SCLC); it is therefore regarded as a paraneoplastic syndrome. In the present article, the authors reviewed the clinical picture, pathology and treatment of LEMS from a clinical point of view.

Epidemiology

The true incidence of LEMS in Japan is unknown. In epidemiological studies (1990–1999) in the Netherlands, LEMS was 46-fold less prevalent (2.32×10^{-6}) than myasthenia gravis (MG; 106.1×10^{-6}), whereas the annual incidence rate of LEMS was 14-fold lower (0.48×10^{-6}) than that of MG (6.48×10^{-6}).[11] In Table 1, three previous clinical studies of more than 50 patients with LEMS (O'Neill et al.,[12] Nakao et al.[13] and Titulaer et al.[10]) shared the following findings: (i) it is male-dominated; (ii) the average age of onset is 50–60 years; and (iii) it is complicated by SCLC in 42–61% of patients. In 110 Japanese patients with LEMS, the male-to-female ratio was 3:1, and the average age of onset was 62 years within the 17–80 years age range of patients. The incidence rate of SCLC (paraneoplastic LEMS) in Japan is 61%, and that of other cancers is 8%, and the remaining 31% have non-paraneoplastic LEMS. Compared with other reports, the epidemiological features of LEMS in Japan show a low frequency of autonomic symptoms, and the incidence rate of SCLC is high. Overall, LEMS is a disease with common characteristic features worldwide.

Symptoms, classification and prognosis

Nakao et al.[13] reported in 2002 that more than 90% of the initial neurological symptoms comprise a gait disturbance as a result of the weakness of proximal leg muscles, then awareness fatigability and a decrease in

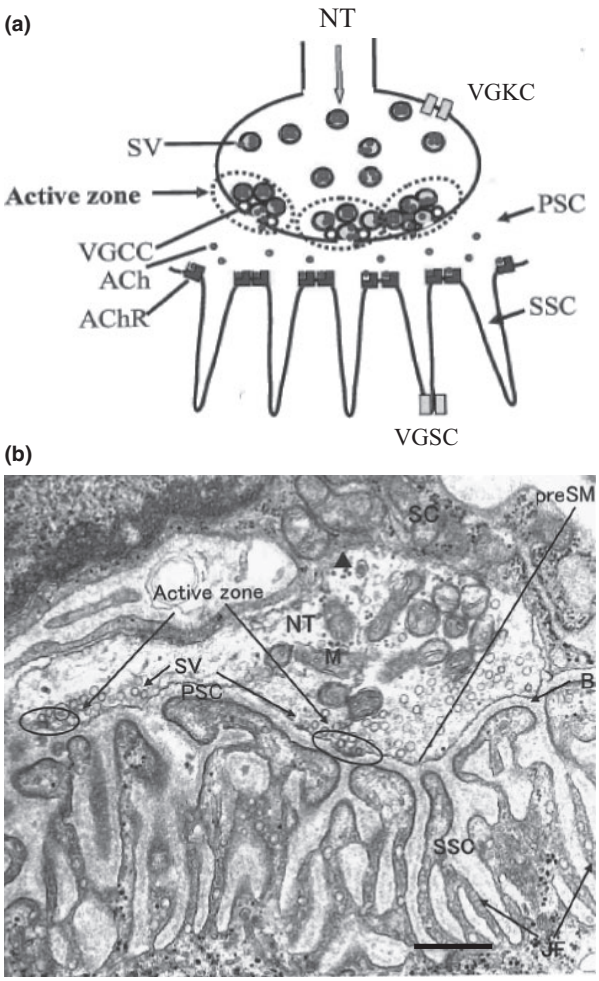

Figure 1 (a) In the schematic diagram of normal neuromuscular junctions (left), when the action potentials reach the nerve endings, Ca^{2+} flows from the outside of the cell to nerve endings inside. This influx is carried out through the P/Q-type voltage-gated calcium channels present at a high density in the active zone. When the Ca^{2+} concentration in the nerve endings is raised, synaptic vesicles and membrane fuse together. As a result, acetylcholine (ACh) is released from synaptic vesicles, and binds to the acetylcholine receptor on the muscle side. (b) In the electron microscope image shown, images of synaptic vesicles containing ACh being released from the nerve terminals can be observed. Agrin-MuSK-Lrp4 complexes are present in the dark high-electron density sites, which are the tip of the muscle side of the synapse folded together with Ach receptor (AChR). Lrp4, low-density lipoprotein-receptor related protein 4; M, mitochondria; MuSK, muscle-specific receptor tyrosine kinase; NT, nerve terminal; preSM, presynaptic membrane; PSC, primary presynaptic cleft; SSC, secondary presynaptic cleft; SV, synaptic vesicle. Bar, 500 nm. Reproduced from Mitsuhiro[61] with permission.

upper limb muscle strength. In severe cases, muscle weakness of the body appears,[14] including dysphagia, as a result, leading to respiratory failure requiring artificial respiration.[15,16] Other symptoms emerge as autonomic neurological disorders, such as dry mouth, mydriasis, blurred vision and bladder/rectal disorders, in approximately 30% of patients.

Table 1 Comparison of the clinical pictures of Lambert–Eaton myasthenic syndrome patients in the UK, Japan and the Netherlands

	O'Neill et al. *n* = 50	Nakao et al. *n* = 110	Titulaer et al. *n* = 97
Male:female	32:18	84:26	55:42
Median age at onset (years)	54	62	57
Neurological findings (%)			
Weakness of upper extremities	82	80	82
Weakness of lower extremities	90	97	100
Decreased deep tendon reflex	92	85	92
Ophthalmoplegia	NA	5	38
Blepharoptosis	54	28	46
Sensory disturbance	4	10	NA
Cerebellar ataxia	NA	9	9
Respiratory failure	6	5	NA
Autonomic symptoms (%)			
Dry mouth	74	31	78
Constipation	18	11	29
Impaired sweating	4	7	NA
Impotence	26	4	65
Incidence of SCLC (%)	42	61	54
Seropositivity of P/Q-VGCC Ab (%)	NA	85	93

NA, not available; SCLC, small cell lung cancer; VGCC Ab, voltage-gated calcium channel antibodies.

The post-tetanic potentiation of deep tendon reflexes is a specific neurological finding, in which reduced deep tendon reflexes recover for a few seconds after the maximal muscle contraction.

In addition, cerebellar ataxia occurs in <10% of patients. Usually, the symptoms are not confined only to the extraocular muscles, as in MG.[17,18] In LEMS patients, classification of severity, such as the QMG score in MG, has not been reported.

The prognosis of LEMS patients varies greatly depending on whether or not treatment is merged with that for the malignant tumor, in particular of SCLC.[19,20] If SCLC is present at LEMS onset, and the treatment for SCLC is responsive, the LEMS symptoms as well as the prognosis improve markedly.[21] In contrast, if the treatment of SCLC does not go well, life prognosis is limited to several years. In 2011, a joint study by the Netherlands and the UK reported the DELTA-P score to predict the occurrence of SCLC at LEMS onset.[22]

Pathogenesis and pathology

The voltage-gated calcium channels (VGCC), which are the target of the autoantibodies for LEMS, have been classified as shown in Table 2. The VGCC of

Table 2 Classification and characteristics of voltage-gated calcium channels

Electrophysiological	Molecular biological	Genetic	Pharmacological	Distribution
L	Cav1.1	1q31-32	Dihydropyridine	Skeletal muscle
	Cav1.2	12p13.3		Brain, cardiac muscle, smooth muscle
	Cav1.3	3q14.3		Brain, Pancreas, auditory hair cell
	Cav1.4	Xp11.23		Retina
P/Q	Cav2.1	19p13	M-agatoxinVIA(P) M-conotoxinMVIIC(Q)	Brain (cerebellum), nerve, neuromuscular junction
N	Cav2.2	9p34	M-conotoxin GVIA	Brain, nerve
R	Cav2.3	1q25-31	Ni^{2+}, SNX-482	Brain, nerve
T	Cav3.1	17q22	Ni^{2+}, mibefradil, kurtoxin	Brain, cardiac muscle
	Cav3.2	16p13.3		Brain
	Cav3.3	22q12.3-13.2		Brain

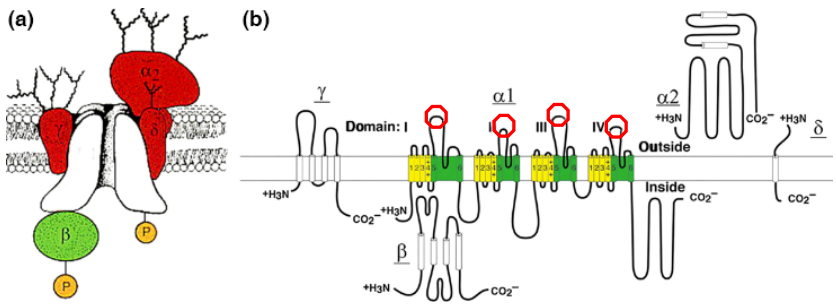

Figure 2 Schematic diagram of the P/Q-type voltage-gated calcium channel. Reproduced from Catterall[23] with permission.

nerve endings of the neuromuscular junction is considered a P/Q-type.[23,24] Pathogenesis of paraneoplastic LEMS is a three-step process.[2]

First, P/Q-type VGCC are suddenly expressed in the SCLC. Second, anti-P/Q-type VGCC autoantibodies are produced and the amount of P/Q-VGCC present in the nerve endings as a result of immunological cross-reactivity is reduced. Third, because of a decrease in P/Q-type VGCC at nerve endings, the influx of calcium ions is inhibited, resulting in reduced release of acetylcholine and consequently muscle strength is reduced. These results using neuronal cells containing P/Q-type VGCCs provide direct evidence that LEMS immunoglobulin G inhibits neurotransmitter release by acting on P/Q-type VGCC.[25,26] However, an animal LEMS model by immunizing purified P/Q-type VGCC has not been successful, therefore, the identification of which pathogenic autoantibodies are attacking P/Q type VGCC is not yet conclusive.

P/Q-type VGCC is a channel protein, consisting of α1, β, α2-δ and γ subunits, as shown in Figure 2. The α1 subunit has a potential sensor function, having a IV one domain from I, and each domain might have a transmembrane portion from S1 to S6. Regarding the main immunogenic region that autoantibodies bind to causing reduction of the amount of P/Q-type VGCC, the loop structure (red circle, Fig. 2) connecting the S5 and S6 in IV from domain I of the α1 subunit 7 is extracellular, and these regions are speculated to be the main immunogenic region.[27–29]

In LEMS patients, observing neuromuscular junctions using an electron microscope shows there is no complement-mediated membrane disruption at the nerve endings,[30–32] such as seen in acetylcholine receptor antibody-positive MG as shown in Figure 3.[33] In addition, <10% of LEMS patients develop cerebellar ataxia. P/Q-type VGCC autoantibodies cross the blood–brain barrier, reducing the amount of P/Q-type VGCC in the cerebellar molecular layer, which might cause paraneoplastic cerebellar degeneration, as shown in Figure 4. In the cerebellums of paraneoplastic cerebellar degeneration LEMS patients, compared with control cerebellums, the amount of P/Q-type VGCC in the cerebellar molecular layer decreased markedly, but the amount of N-type VGCC and voltage-gated potassium channels in the vicinity was normal.[9] Pathogenic mechanisms that show such conditions are not only considered to

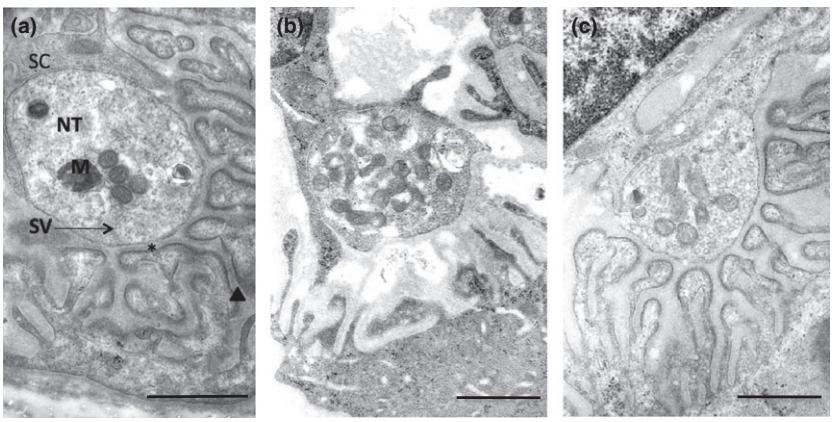

Figure 3 Electron micrograph of the neuromuscular junction of the biceps. In the (a) normal and (c) Lambert–Eaton myasthenic syndrome patients, the postsynaptic structure is intact. (b) In myasthenia gravis patients, the expansion of the primary synaptic cleft and secondary synaptic cleft, and degradation products of synaptic folds are observed. M, mitochondria; NT, nerve endings; SC, Schwann cell; SV, synaptic vesicles. *The primary synaptic cleft. ▲, The secondary synaptic cleft. Bar, 1 μm. Reproduced from Yoshimura et al.[33] with permission.

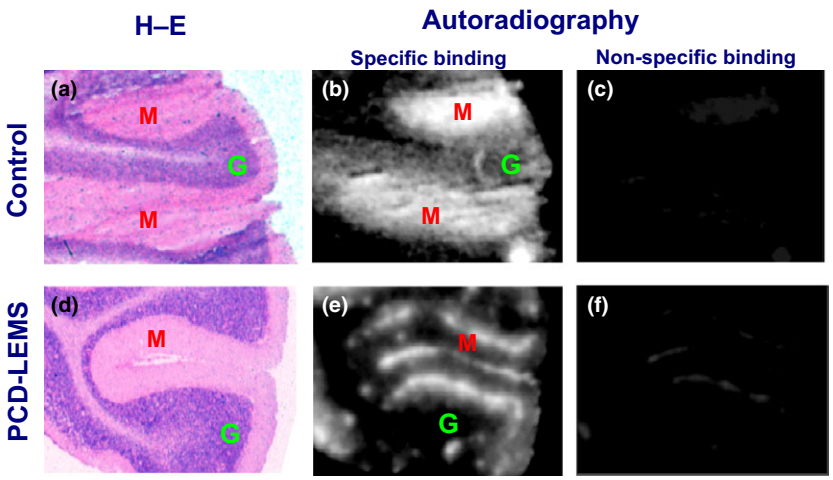

Figure 4 In the autopsied cerebellum of a Lambert–Eaton myasthenic syndrome (LEMS) with paraneoplastic cerebellar degeneration (PCD-LEMS) patient, the amount of P/Q-type voltage-gated calcium channel of molecular layer is reduced. Autoradiographic localization of ^{125}I-omega-conotoxin MVIIC-binding sites in adjacent sections of autopsied cerebellar tissue. Hematoxylin–eosin staining in (a) a control patient and (d) a PCD-LEMS patient (magnification: ×64). Sections were exposed to 200 pM ^{125}I-omega-conotoxin MVIIC either (b,e) without or (c,f) with 0.5 μmol/L unlabeled omega-conotoxin MVIIC. Compared with (b) the control patient, the toxin-binding sites of P/Q-type voltage-gated calcium channels of (e) the PCD-LEMS patient were markedly reduced in the molecular layer. G, granular layer of the cerebellum; M, molecular layer of the cerebellum. Reproduced from Fukuda et al.[9] with permission.

be caused by autoantibodies. Thus, the authors speculate that the same mechanism for down-regulation of P/Q-type VGCC in the cerebellar molecular layer is also acting in the active zone of the nerve endings of the neuromuscular junction.

Supplementary examinations

Repetitive stimulation test

Compound muscle action potential is remarkably decreased in LEMS. This finding is specific to LEMS and is not seen in MG. Repetitive stimulation frequency is 2–50 Hz.[34,35] Amplitude decrement is recorded with 2–5 Hz low-frequency stimulation. Amplitude is markedly increased at 50 Hz high-frequency stimulation, which is termed the waxing phenomenon.

P/Q-type VGCC antibody test

Specificity: P/Q-type VGCC autoantibodies are negative in almost all SCLC cases without LEMS.[36]

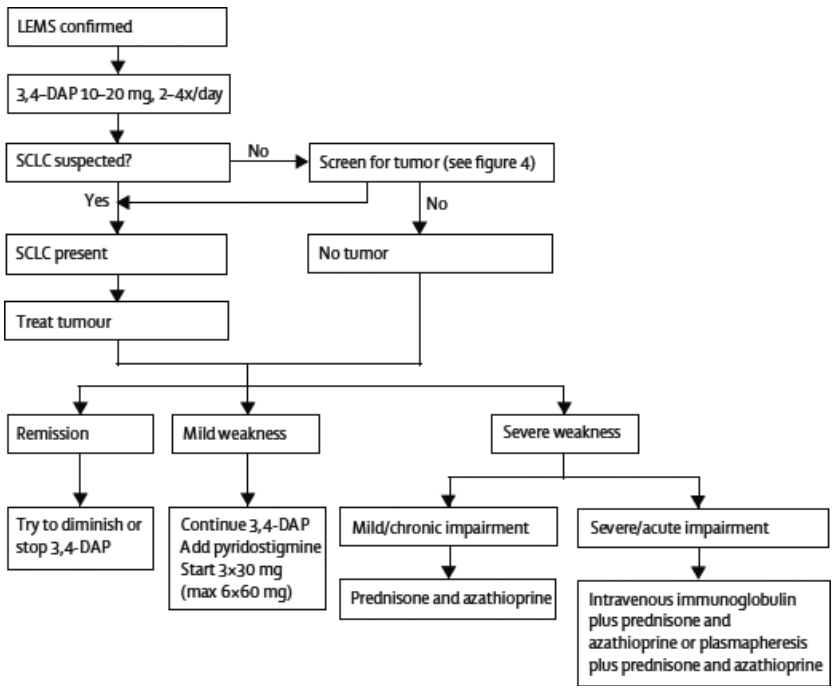

Figure 5 Treatment scheme for Lambert–Eaton myasthenic syndrome. Reproduced from Titulaer et al.[3] with permission. SCLC, small cell lung cancer.

Seropositivity: they are positive in almost all LEMS cases with SCLC, and in 85–90% of non-SCLC LEMS patients.[37–41]

Saxon test

This test is useful to evaluate autonomic function in LEMS patients. Sterilized gauze is chewed for 2 min, and weighed. Normally, over 4 g of saliva is secreted, but it is significantly decreased in LEMS patients. Oral administration of 3,4-diaminopyridine might increase saliva secretion.[42]

Diagnosis and differential diagnosis

Clinical symptoms and electrophysiological studies are essential for diagnosis of LEMS. Of LEMS patients, 10–15% are P/Q-type VGCC antibody-negative.[13,43] Patients with proximal muscle weaknesses, peripheral neuropathy and symptoms resembling MG[44] or polymyopathy require differential diagnosis.[45] More than 60% of LEMS patients have coexisting SCLC.

Treatment

General principles of LEMS treatment focus on detecting SCLC and its treatment. Treating SCLC with chemotherapy, radiotherapy and/or surgery could markedly improve LEMS symptoms.[19] A LEMS treatment manual was proposed by Professor Newsom-Davis[46] of Oxford University and thereafter, revised by Titulaer et al.[3] (Fig. 4) and Evoli et al.[47]

Newsom-Davis' research group has reported that SCLC with LEMS have a better prognosis than those without LEMS.[20,21] This observation suggests that immunological mechanisms of LEMS might delay the progression of SCLC. More than 60% of LEMS patients have concurrent malignancy (mostly SCLC), and more than 80% present LEMS symptoms before tumor detection. Thus, after the diagnosis of LEMS, detection of malignancy must be carried out immediately. Immunotherapy including steroid and immunosuppressant therapies could facilitate tumor progression in LEMS patients with SCLC. Palliative treatment is recommended to treat LEMS with SCLC with 3,4-diaminopyridine[48–52] and/or cholinesterase inhibitors to improve clinical symptoms, and focus on treating the SCLC. It is recommended to proceed with tumor detection before LEMS treatment; that is, within 2 years of LEMS diagnosis.[12]

LEMS without malignancy is defined as those cases without SCLC 2 years after LEMS diagnosis. Approximately 30% of LEMS patients are non-malignancy-related in Japan. In these cases, initial treatment includes 3,4-diaminopyridine and cholinesterase inhibitors. If these treatments are ineffective, steroid

therapy and immunosuppressants can be used. If the immunotherapy does not sufficiently improve muscle weaknesses and residual severe motor impairment occurs, or in cases in which immunotherapy is contraindicated, plasma exchange[53–55] and/or high-dose intravenous immunoglobulin[56–58] treatments are recommended. These treatments are selected with regard to treatments used for MG. Rituximab is being considered for refractory LEMS patients and its utility has been reported.[59,60] Unfortunately, none of these treatments above are covered by Japanese national health insurance.

Conclusions

An important issue that remains in LEMS clinical research is that animal models using active immunization have not yet succeeded. Therefore, the identities of pathogenic autoantibodies that attack P/Q-type VGCC have not been conclusively shown. In the clinical aspects, there is a limit to the clinical application of calcium channel of antibody measurement kits for insurance purposes, and the treatment with 3,4-diaminopyridine requires further study.

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Conflict of interest

None declared.

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