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<td>ランベルト・エアトン筋肉疾患の臨床評価</td>
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<td>著者</td>
<td>本村隆之；中田鈴香；平石寛</td>
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<tr>
<td>引用</td>
<td>Clinical and Experimental Neuroimmunology, 7(3), pp.238-245; 2016</td>
</tr>
<tr>
<td>発行日</td>
<td>2016-08</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/10069/37240">http://hdl.handle.net/10069/37240</a></td>
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<tr>
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Lambert–Eaton myasthenic syndrome: Clinical review

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Keywords
Lambert–Eaton myasthenic syndrome; P/Q-type voltage-gated calcium channel; paraneoplastic neurological syndrome; small cell lung cancer

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 that of myasthenia gravis (MG) (6.48 × 10−4).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...
upper limb muscle strength. In severe cases, muscle weakness of the body appears, including dysphagia, as a result, leading to respiratory failure requiring artificial respiration. Other symptoms emerge as autonomic neurological disorders, such as dry mouth, mydriasis, blurred vision and bladder/rectal disorders, in approximately 30% of patients.

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 <5% of patients. Usually, the symptoms are not confined only to the extraocular muscles, as in MG. 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. If SCLC is present at LEMS onset, and the treatment for SCLC is responsive, the LEMS symptoms as well as the prognosis improve markedly. 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.

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

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

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

<table>
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<tr>
<th>Electrophysiological</th>
<th>Molecular biological</th>
<th>Genetic</th>
<th>Pharmacological</th>
<th>Distribution</th>
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<tr>
<td>L</td>
<td>Cav1.1</td>
<td>1q31-32</td>
<td>Dihydropyridine</td>
<td>Skeletal muscle</td>
</tr>
<tr>
<td></td>
<td>Cav1.2</td>
<td>12p13.3</td>
<td></td>
<td>Brain, cardiac muscle, smooth muscle</td>
</tr>
<tr>
<td></td>
<td>Cav1.3</td>
<td>3q14.3</td>
<td></td>
<td>Brain, Pancreas, auditory hair cell</td>
</tr>
<tr>
<td></td>
<td>Cav1.4</td>
<td>Xp11.23</td>
<td></td>
<td>Retina</td>
</tr>
<tr>
<td>P/Q</td>
<td>Cav2.1</td>
<td>19p13</td>
<td>M-agatoxin(VIA(P)</td>
<td>Brain (cerebellum), nerve,</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>M-conotoxinMVIIC(Q)</td>
<td>neuromuscular junction</td>
</tr>
<tr>
<td>N</td>
<td>Cav2.2</td>
<td>9p34</td>
<td>M-conotoxin GVia</td>
<td>Brain, nerve</td>
</tr>
<tr>
<td>R</td>
<td>Cav2.3</td>
<td>1q25-31</td>
<td>Ni2+, SNX-4B2</td>
<td>Brain, nerve</td>
</tr>
<tr>
<td>T</td>
<td>Cav3.1</td>
<td>17q22</td>
<td>Ni2+, mibebradil, kurtoxin</td>
<td>Brain, cardiac muscle</td>
</tr>
<tr>
<td></td>
<td>Cav3.2</td>
<td>16p13.3</td>
<td></td>
<td>Brain</td>
</tr>
<tr>
<td></td>
<td>Cav3.3</td>
<td>22q12.3-13.2</td>
<td></td>
<td>Brain</td>
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Figure 2 Schematic diagram of the P/Q-type voltage-gated calcium channel. Reproduced from Catterall23 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.\(^{36}\)
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 or polymyopathy require differential diagnosis.44 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-Davis46 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-diaminopyridine48–52 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 \(^5^3–^5^5\) and/or high-dose intravenous immunoglobulin \(^5^6–^5^8\) 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. \(^5^9,^6^0\) 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.

**Acknowledgments**

We thank Professor Atsushi Kawakami, Professor Akira Tsujino and many colleagues (Nagasaki University Hospital), and Emeritus Professor Mitsuhiko Tsujihata (Nagasaki Kita Hospital).

This work was supported in part by the Japan Society for the Promotion of Science Grand-in-Aid (26461302), and the Health and Labor Sciences Research Grant on Intractable Diseases (Neuroimmunological Diseases) from the Ministry of Health, Labor and Welfare of Japan.

**Conflict of interest**

None declared.

**References**


50. Oh SJ, Claussen GG, Hatanaka Y, Morgan MB. 3,4-Diaminopyridine is more effective than placebo in a randomized, double-blind, cross-over drug study in LEMS. Muscle Nerve. 2009; 40: 795–800.


