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Disclosures: Grant/Research Support: AbbVie, Amgen, AstraZeneca, Genentech, Zai Lab; Advisory Board: Amgen, AstraZeneca, Daiichi Sankyo, Fosun International, Genentech, Janssen, Zai Lab.



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3 Things You Should Know About Recognizing LEMS in Patients With SCLC

RELEASE DATE: March 1, 2025

EXPIRATION DATE: March 1, 2026

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Identify clinical presentations of Lambert-Eaton myasthenic syndrome (LEMS) in SCLC patients.
- Apply diagnostic protocols for accurate and timely detection of LEMS in SCLC.

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ACKNOWLEDGMENT OF COMMERCIAL SUPPORT

This activity is supported by an educational grant from Catalyst Pharmaceuticals, Inc.

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Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune neuromuscular disorder that results in muscle weakness.¹ In this first of 2 articles on LEMS, the biology, key symptoms, and antibody testing related to LEMS will be discussed. The second article will further address diagnostic tests and treatment. Here are 3 things you should know about recognizing LEMS in patients with small cell lung cancer (SCLC).

1 Although LEMS is a rare disorder, it is often associated with SCLC.

LEMS Pathophysiology

In the normal neuromuscular junction, depolarization of the nerve results in the ingress of calcium ions through voltage-gated calcium channels (VGCCs).¹ This results in vesicles containing the neurotransmitter acetylcholine (ACh) to migrate to the presynaptic membrane of the nerve and release ACh, which leads to muscle contraction (**Figure 1A**).¹ In LEMS, autoantibodies to VGCCs inhibit the influx of calcium ions, ultimately leading to reduced release of ACh and symptoms such as muscle weakness (**Figure 1B**).¹

Prevalence of LEMS

The point prevalence of LEMS (ie, the proportion of a

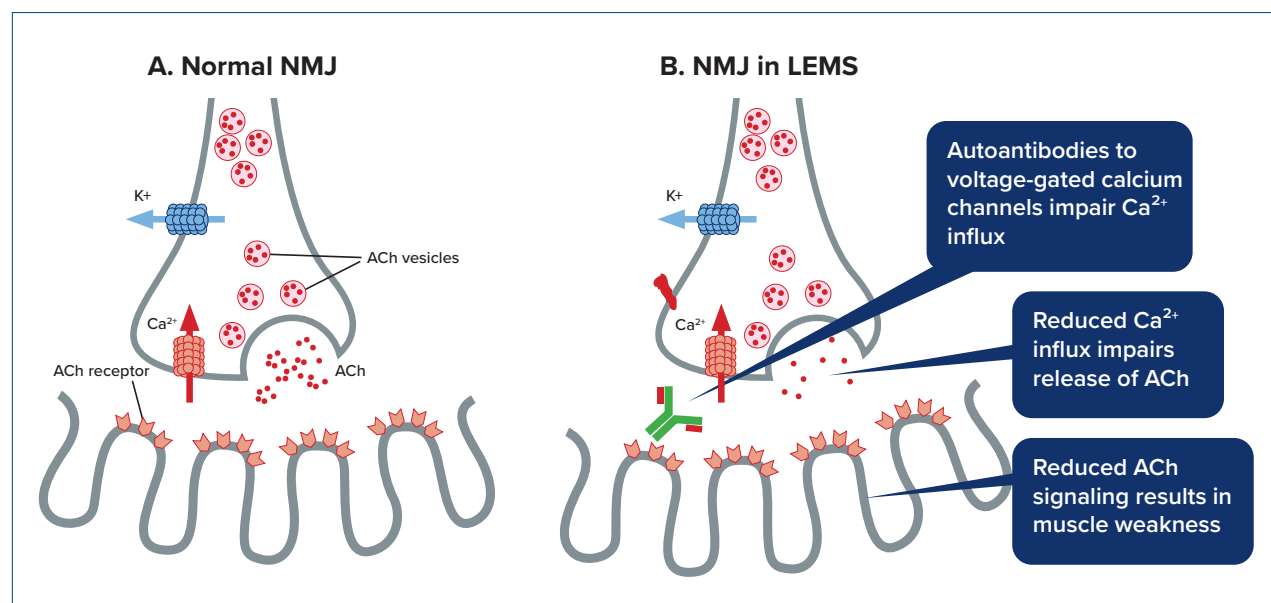
population with LEMS at a specific point in time) was estimated to be 2.6 per 1 million for confirmed cases and 3.3 per 1 million for confirmed and probable cases.² This was based on an analysis of 12.5 million records from the US Veterans Affairs population from October 1, 1999, through September 30, 2013, with the latter date used to calculate the point prevalence.²

LEMS and SCLC

LEMS can be classified into 2 main subtypes: paraneoplastic LEMS that is associated with cancer and nonparaneoplastic (autoimmune) LEMS.³ The typical age of onset for paraneoplastic LEMS is 60 years; for nonparaneoplastic LEMS, the first peak occurs at 35 years of age, and a second peak is noted at 60 years of age.

Approximately half of LEMS cases occur in association with SCLC.⁴ Patients with SCLC-LEMS may have improved survival. In a retrospective analysis involving 81 patients, those with SCLC-LEMS had an overall survival of 17 months, which was significantly longer than the 7.0 months seen in patients with non-LEMS SCLC ($P < .0001$).⁵ However, the quality of life score related to physical health was significantly worse in patients with LEMS than in the general population (55.9 vs 76.3 points, respectively; $P < .0001$).⁵

FIGURE 1. Pathophysiology of LEMS¹



ACh, acetylcholine; Ca^{2+} , calcium ion; LEMS, Lambert-Eaton myasthenic syndrome; NMJ, neuromuscular junction.

2 LEMS may be confused with other diseases, and it is likely underdiagnosed.

Key Symptoms of LEMS

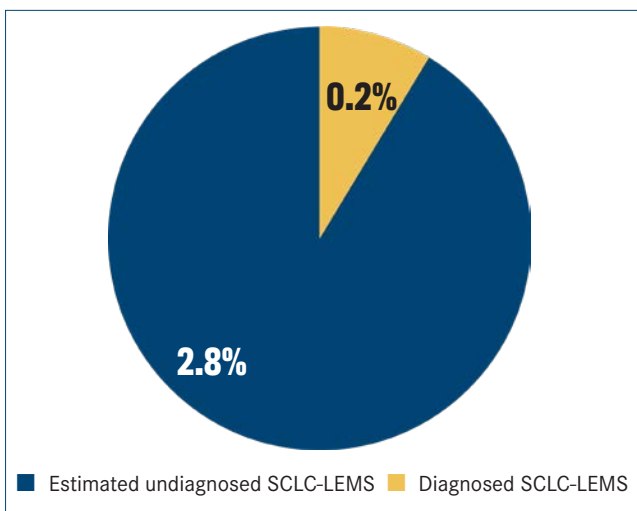
The key symptoms in patients with LEMS are (1) weakness in the proximal muscles, particularly in the legs; (2) weak or no reflexes; and (3) autonomic dysfunction.³ There does not appear to be a major difference in symptoms between paraneoplastic and nonparaneoplastic LEMS.³

Confusion With Other Neurologic Disorders and Underreporting of LEMS

The symptoms present in patients with LEMS may be mistaken for those of other disorders. Indeed, in a combined Dutch and British cohort of 241 patients, 58% of patients with LEMS received a different diagnosis first; these incorrect diagnoses included myasthenia gravis (MG), Guillain-Barré syndrome, and amyotrophic lateral sclerosis.¹

The second article in this series will go more into detail regarding differential symptoms, but 1 key difference is that patients with LEMS have reduced or absent reflexes, but patients with MG have normal reflexes.⁶ Because of incorrect diagnoses, the actual incidence and prevalence of LEMS may be underestimated, with 90% or more cases of LEMS being undiagnosed in patients with SCLC (Figure 2).⁷

FIGURE 2. Potential Underdiagnosis of SCLC-LEMS in Real-World Data⁷



LEMS, Lambert-Eaton myasthenic syndrome; SCLC, small cell lung cancer.

FIGURE 3. DELTA-P Scoring System to Evaluate Patients With LEMS for SCLC¹⁰

ABBREVIATION	CATEGORY	SCORE
D	Dysarthria, dysphagia, chewing, neck weakness: bulbar weakness	0
	Absent	1
E	Erectile dysfunction	0
	Female	0
	Male	1
L	Loss of weight	0
	Absent or <5%	1
T	≥5%	1
	Tobacco use at onset	0
A	Absent	0
	Present	1
P	Age of onset, years	0
	< 50	1
	≥ 50	1
P	Karnofsky performance score	0
	70-100	1
	0-60	1
DELTA-P score		0-6

DELTA-P, Dutch-English LEMS Tumor Association Prediction; LEMS, Lambert-Eaton myasthenic syndrome; SCLC, small cell lung cancer.

3 No-cost testing is available for patients with symptoms related to LEMS.

Testing of Patients With LEMS Symptoms

To ensure timely detection and diagnosis of LEMS, the NCCN guidelines for SCLC recommend a neurologic consult and/or a comprehensive paraneoplastic antibody panel if a paraneoplastic neurologic syndrome is suspected.⁸ No-cost anti-VGCC antibody testing is available for patients who have symptoms suggestive of LEMS as a result of a collaboration between a national diagnostic test provider and Catalyst Pharmaceuticals.⁹ It should be noted that 10% to 15% of patients with LEMS may not demonstrate the presence of anti-VGCC antibodies, so a negative antibody test should be followed up with electrodiagnostic testing.¹

Cancer Screening for Patients With LEMS

LEMS can precede cancer and can be discovered after cancer diagnosis.⁷ Therefore, cancer screening should be considered for patients with LEMS-related symptoms and/or positive results on an anti-VGCC antibody test. The Dutch-English LEMS Tumor Association Prediction (DELTA-P) scoring system was developed to predict which patients with LEMS are at risk for also having SCLC (**Figure 3**).¹⁰ Various factors such as age at onset, smoking history, and bulbar involvement contribute to the score; patients with a score of 0 or 1 have an extremely low risk (0% or 3%, respectively) of having SCLC, whereas those with a score of 3 or higher have a high risk ($\geq 84\%$). ■

KEY REFERENCES

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1 How do reflexes in patients with LEMS typically compare with those in patients with MG?

- A. Stronger
- B. Similar
- C. Weaker

2 Which of the following is TRUE regarding diagnostic testing for LEMS?

- A. A negative anti-VGCC antibody test is sufficient to rule out LEMS.
- B. Cancer screening is not necessary for patients with a positive anti-VGCC antibody test.
- C. No-cost anti-VGCC antibody testing is available for patients with LEMS-related symptoms.
- D. All of the above

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