CASE REPORT
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A Patient with Coexisting Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome

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Background The coexistence of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) is very rare and remains controversial.

Case Report A 48-year-old woman initially presented with noticeable right ptosis and intermittent diplopia. She then developed fluctuating proximal limb weakness and difficulty in swallowing. The serum titer of anti-acetylcholine-receptor antibody was elevated and the edrophonium (Tensilon) test was positive. However, repetitive nerve stimulation revealed abnormalities typical of LEMS. The patient exhibited a good response to treatment with anticholinesterase inhibitors and steroids, and long-term evaluation disclosed that she presented with the clinical, electrophysiological, and immunological characteristics of both diseases.

Conclusions The reported clinical and electrophysiological features suggest that this patient was a very rare case of combined MG and LEMS. **J Clin Neurol 2012;8:235-237**

Key Words myasthenia gravis, Lambert-Eaton myasthenic syndrome, overlap syndrome, repetitive nerve stimulation tests.

Introduction

Myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) are two distinct autoimmune disorders that affect neuromuscular transmission. MG is a postsynaptic disorder caused by the antibody-mediated destruction of acetylcholine receptors (AChRs) and blockage of the binding of acetylcholine to AChRs, whereas LEMS is a presynpatic disorder that is characterized by the presence of antibodies against voltage-gated P/Q-type calcium channels (VGCCs).[1] Coexistence of MG and LEMS in a patient is very rare, with only a few cases having been reported.[2-5] It is difficult to prove the coexistence of the two diseases, but it has been demonstrated by some authors by performing anti-AChR and anti-VGCC antibody tests or pathological and microphysiological explorations. We describe herein a patient with both diseases diagnosed on the basis of clinical features and electrophysiological and immunological findings. Furthermore, we analyzed serial assays for AChR antibodies and the findings of repetitive nerve stimulation (RNS) testing during a 10-year follow-up period.

Case Report

A 48-year-old woman presented with easy fatigability and ptosis. She initially noticed right eyelid drooping and experienced intermittent double vision. Two months after symptom onset she developed proximal limb weakness and had difficulty in climbing stairs and swallowing. She experienced marked diurnal fluctuation of symptoms, with them being worse in the afternoon and when she was fatigued. She did not report dry mouth, constipation, or blurred vision. Her past medical history was unremarkable. A neurological examination revealed right ptosis, which was worse after sustained upward gaze, and bulbar muscle weakness. She exhibited proximal muscle weakness at Medical Research Council grade 4/5. Deep-tendon reflexes were absent, but potentiated after brief voluntary contraction of the tested muscles.

Routine hematological, chemical, and serological tests re-

vealed no abnormalities except for seropositivity for antinuclear antibodies. The serum titer of antibodies against AChRs was elevated (5.9 nmol/L; normal level <0.1 nmol/L). The edrophonium (Tensilon) test disclosed clinical improvement of the right ptosis. Chest CT was negative for thymoma, and extensive exploration seeking a malignancy yielded negative results. RNS testing of the right ulnar nerve revealed low-amplitude compound muscle action potentials (CMAPs) at rest, which decreased by 25% on low-frequency (3 Hz) stimulation and increased by 500% on high-frequency (50 Hz) stimulation (Fig. 1). Her symptoms gradually improved after treatment with prednisolone (20 mg/day) and pyridostigmine (240 mg/day). Six months later azathioprine (50 mg/day) was added to the steroid medication due to reoccurrence of right ptosis.

During the 10-year follow-up the patient complained of intermittent ptosis, but there was no marked worsening of her myasthenic symptoms. The results of RNS tests were continuously consistent with the findings of LEMS. The electrophysiological findings were not aggravated compared with the initial investigation.

Four serial anti-AChR antibody titers measured over the 10-year follow-up period revealed constant elevation without clinical deterioration (range, 6.7-7.0 nmol/L) (Table 1). Follow-up chest CT revealed thymic hyperplasia, but there was no evidence of malignancy. She was maintained on pyridostigmine (240 mg/day), prednisolone (5 mg/QOD), and azathioprine (50 mg/day), with a stable course.

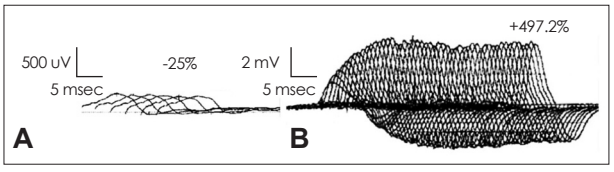

Fig. 1. "LEMS triad" on RNS. A: Low CMAP amplitude and decremental response on low-frequency (3 Hz) stimulation of the ulnar nerve. B: Marked incremental response on high-frequency (50 Hz) stimulation of the ulnar nerve. CMAP: compound muscle action potential, LEMS: Lambert-Eaton myasthenic syndrome, RNS: repetitive nerve stimulation.

Discussion

The clinical features and electrophysiological findings indicate the coexistence of MG and LEMS in our patient. The predominant oculobulbar symptoms, thymic hyperplasia, elevated anti-AChR antibody titers, and the positive edrophonium test favor a diagnosis of MG. However, the areflexia with facilitation after voluntary contraction is a typical finding in LEMS, and the results of the RNS test support concomitant LEMS. Based on these findings, we consider that this patient had "MG and LEMS overlap syndrome". It is difficult to distinguish MG from LEMS with only clinical manifestations, but some features may be helpful. Patients with LEMS tend to exhibit proximal leg weakness, autonomic dysfunction, and absent or decreased deep-tendon reflexes, but with posttetanic potentiation upon clinical testing, whereas patients with MG present with more oculobulbar symptoms and fewer autonomic changes than LEMS patients.

An elevated anti-AChR antibody titer is generally specific to MG patients, but a previous report argued that seropositivity of this antibody may represent a nonpathogenic epiphenomenon or a false-positive response.[6,7] However, the anti-AChR antibody titers in seropositive LEMS patients were reportedly low (0.88-3.03 nM),[7] and the only significant increases were in those with lung carcinomas. There have been several cases of establishing the immunological basis of combined MG and LEMS with positive anti-AChR and anti-VGCC antibody tests; none of these cases also had either thymoma or small-cell lung cancer.[2] Over a follow-up period of almost 10 years, our patient exhibited continuously high anti-AChR antibody titers but did not have lung cancer. These features also suggest that she had autoimmune-based MG and LEMS with molecular mimicry of AChRs and VGCCs, and not paraneoplastic syndrome of LEMS with MG.

Electrophysiologically, the classical pattern of LEMS includes a low CMAP amplitude at rest, decremental response on low-frequency stimulation, and an incremental response (>100%) on high-frequency stimulation or after brief intense exercise.[8] The strict criteria of LEMS on the RNS test were

Table 1. Serial anti-AChR antibody and RNS test results

Year	AChR-ab (nmol/L)	RNS (AMD)			RNS (FCU)		
		CMAP (mV)	LRS (%)	HRS (%)	CMAP (mV)	LRS (%)	HRS (%)
1999	5.9	3.40	-7.8	194.5	0.56	-25.0	497.2
2002	6.7						
2003		13.60	-4.5	41.7	3.16	-16.0	38.7
2004	7.0						
2007		4.9	-17.0	165	1.0	-13.0	279
2008	6.9						

AChR-ab: anti-AChR antibody, AMD: abductor digiti minimi, CMAP: compound muscle action potentials, FCU: flexor carpi ulnaris, LRS: low-rate stimulation, RNS: repetitive nerve stimulation, HRS: high-rate stimulation.

fully satisfied by our case. In MG, the CMAP amplitude is rarely reduced and decrements are evident upon stimulation at both low and high frequencies.[9,10] One patient was reported to show the classical MG pattern on the first RNS test, but the LEMS pattern on subsequent tests during 13 years of follow-up.[2] On the contrary, long-term evaluation of our patient disclosed that she presented with the clinical, electrophysiological, and immunological characteristics of both diseases, without any change in the initial findings.

Another case, reported to have combined MG and LEMS with pathologic evidence of both pre- and postsynaptic neuromuscular junctions, presented with typical clinical and electrophysiological findings of LEMS and seropositivity for anti-AChR antibodies, as in our case.[11] The decreased frequency and amplitude of the miniature end-plate potentials and electron-microscopy evidence of acetylcholine quantal content is not a prerequisite for a diagnosis of LEMS. To improve the diagnosis of an "MG and LEMS overlap syndrome", we believe that an additional VGCC antibody titer test should be performed.

In conclusion, the reported patient had coexisting MG and LEMS based on clinical features, electrophysiological criteria, high anti-AChR antibody titers, and response to treatment. The exact mechanism underlying the coexistence of these two rare autoimmune diseases remains unclear. Anticoantigens of AChR and VGCC sensitization may be initiated by molecular mimicry between a single viral or bacterial epitope and a small sequence region on AChRs and VGCCs, or by superantigen activation of CD4+ T cells expressing a particular Vβ gene family of T-cell receptor and recognizing a limited set of autoantigen epitopes. Activation of CD4+ T cells against even one epitope may be followed by spreading of the CD4+ response to the entire AChR or VGCC antigen.

Conflicts of Interest

The authors have no financial conflicts of interest.

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