

# Seropositive Myasthenia Gravis Associated with Small-Cell Lung Carcinoma

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**Received** June 8, 2010  
**Revised** September 1, 2010  
**Accepted** September 1, 2010

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**Background** Lambert-Eaton myasthenic syndrome is well known to be a classical paraneoplastic syndrome of small cell lung carcinoma (SCLC). Three cases of seronegative myasthenia gravis (MG) and SCLC were previously reported.

**Case Report** A 65-year-old man developed a severe progressive respiratory failure with clinical features of MG. Tests showed a decremental response in the repetitive nerve stimulation test, abnormal single-fiber electromyography, and positive acetylcholine receptor antibody. SCLC was confirmed by the lung biopsy.

**Conclusions** This case represents the first case of seropositive MG and SCLC.

**J Clin Neurol 2011;7:43-46**

**Key Words** acetylcholine receptor antibody, myasthenia gravis, small cell lung cancer.

## Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is well known to be a classical paraneoplastic syndrome of small cell lung carcinoma (SCLC). Association of myasthenia gravis (MG) and SCLC is rarely known. We report a case of acetylcholine receptor antibody (AChR-ab) positive MG and SCLC.

## Case Report

In June 1987, a 65-year-old African-American man noticed a weakness in leg muscles a week before admission to a local hospital. Weakness got worse and spread to upper arms. Shortness of breath developed, requiring endotracheal intubation and ventilatory support. Initially, Guillain-Barré syndrome was suspected. However, spinal fluid evaluation was normal with protein at 30 mg/dL. CK and muscle biopsy were also normal.

The patient was transferred to the University of Alabama University Hospital. Neurologic examination showed bilateral ptosis, marked weakness (1-2 Medical Research Council grade) in proximal muscles, moderate (3 Medical Research Council grade) weakness in distal muscles, normal reflexes except diminished ankle reflex and normal sensory function. Edrophonium test was

equivocal and another spinal fluid evaluation was also normal with protein at 21 mg/dL. Because of marked decremental response in the repetitive nerve stimulation (RNS) test, the diagnosis of MG crisis was made. Plasmapheresis was initiated together with prednisone (60 mg a day) and pyridostigmine (540 mg a day). Third spinal fluid evaluation on the third admission date was also normal with protein at 36 mg/dL. Another edrophonium test on the 12<sup>th</sup> admission date showed a definite positive response. With continued treatment for MG crisis, MG Foundation of America status was improved from V to IIIa in three weeks period of time.

Chest X-ray showed a nodule (2×3.5 cm) in the right upper lobe and hilar adenopathy. CT scan showed a lobulated parenchymal mass with a soft tissue density in the right hilar area, and many scattered small nodules in the right posterior pleural space. Thymoma was not found. Transthoracic needle biopsy confirmed the diagnosis of SCLC. The patient was treated with three days of chemotherapy (CIS-Platinum and VP-16) for SCLC. One month after the chemotherapy, the patient developed septicemia and respiratory failure leading to adult respiratory distress syndrome and died two months after onset of weakness.

Nerve conduction study (NCS) on the first admission day: Motor NCS showed mild prolongation of terminal latency and

low compound muscle action potential (CMAP) amplitude in the median (4.8 ms/4 mV), ulnar (3.6 ms/3.0 mV), peroneal (7.0 ms/1 mV), and posterior tibial (9.1 ms/0.4 mV) nerves and mildly slow motor NCV (38.1 and 37.5 m/s) in two posterior tibial nerves. F-wave latency was mildly prolonged in all motor nerve. Sensory NCS showed low CNAP amplitude and mildly slow NCV in the median (40 m/s; 8 μV), ulnar (34.3 m/s; 7 μV), and sural (33.3 m/s; 2 μV) nerves. These findings were interpreted as mild axonal motor-sensory neuropathy. NCS was not repeated.

The RNS test on the first admission day showed a low CMAP

amplitude and a marked decrement at low rate stimulation (LRS; 2-5 Hz) and high rate stimulation (HRS; 50 Hz) in the abductor digiti quinti muscle, and a low CMAP amplitude and a marked decrement at LRS in the orbicularis oculi muscle (Table 1).<sup>1</sup> There was an improvement in decrement with edrophonium though clinical improvement was equivocal. These were interpreted to be indicative of severe MG.<sup>1</sup> Further deterioration was noted in the RNS test on the 11<sup>th</sup> day. On the 12<sup>th</sup> day, there was minimal improvement in the RNS response. There was a definite electrophysiological and clinical improvement with edrophonium injection. On the 24<sup>th</sup> day, the RNS test showed

**Table 1.** Repetitive nerve stimulation data

Day	1 <sup>st</sup> day		11 <sup>th</sup> day	12 <sup>th</sup> day		24 <sup>th</sup> day <sup>‡</sup>		Normal				
Muscle	ADQ	Orbicularis oculi	ADQ	ADQ	ADQ	ADQ	FCU	ADQ	FCU	Orbicularis oculi		
CMAP (mV)	3.0	0.3	2.0	3.2	3.0 <sup>†</sup>	6.0	4.0	4.8	3.0	1.1		
PEF (%)			+50	+6		+17	0	+37				
LRS (%)	2 Hz	-29	-15*	-50	-35	-25	-3	0	0	-7	-8	-8
	3 Hz	-17			-46	-38	-6	-6	-10	-7	-9	-8
	5 Hz	-24			-26	-24	-11	+3	0	-5	-11	-8
HRS (%)	50 Hz	-36			-54	-56	-38			-18	-19	
PTE (%)	5 Hz	-29				-17		+5		-8	-11	
MGFA		V		V		V		IIIa				

\*2 minutes after injection, <sup>†</sup>3 minutes after injection, <sup>‡</sup>2 hour after pyridostigmine by mouth.

-: decrement, +: increment, ADQ: abductor digiti quinti muscle, CMAP: compound muscle action potential, FCU: flexor carpi ulnaris muscle, HRS: high rate stimulation, LRS: low rate stimulation, MGFA: MG Foundation of America, PEF: post-exercise facilitation.

**Table 2.** Clinical, electrophysiological and immunological features in four cases of MG with SCLC

Case	Age/ Sex	Clinical feature	Repetitive nerve stimulation test <sup>†</sup>				Edrophonium test	AChR-antibody	Treatment	Outcome
			CMAP (mV)	PEF (%)	LRS (%)	HRS (%)				
Hazard 1986	55/M	Diplopia and weakness in neck flexor and proximal muscles	10		-28 (2 Hz)	-22 (20 Hz)	Positive	Negative*	Chemotherapy and radiation for SCLC Pyridostigmine for MG	MG remission in 17 months
Fujita 1994	49/M	Ptosis, dyspnea, proximal muscle weakness, difficulty in walking, chewing, and swallowing.	1.5 or 3.0		-25 (3 Hz)	-70? (20 Hz)	Positive	Negative		
Miyoshi 1995	56/M <sup>‡</sup>	Ptosis, proximal muscle weakness			-27 (3 Hz)	-39 (15 Hz)	Positive	Negative	Chemotherapy for SCLC Pyridostigmine for MG	MG remission in 3 years
Our case	55/M	Respiratory failure, Ptosis, limb weakness proximally worse	2 to 3.2	+6 to +50	-17 to -46 (3 Hz)	-36 to -56 (50 Hz)	Equivocal to positive	Positive	Chemotherapy for SCLC Pyridostigmine, prednisone, & plasma exchange for MG	MG improved but death in 2 months

\*Initially not tested but negative at MG remission, <sup>‡</sup>SCLC found 20 months after MG diagnosis, An artifact? <sup>†</sup>RNS test on ADQ muscle except APB muscle in Miyoshi's case.

-: decrement, +: increment, AChR: acetylcholine receptor, ADQ: abductor digiti quinti muscle, CMAP: compound muscle action potential, HRS: high rate stimulation, LRS: low rate stimulation, MG: myasthenia gravis, PEF: post-exercise facilitation, RNS: repetitive nerve stimulation, SCLC: small cell lung carcinoma.

normal findings except a decrement at the LRS in the flexor carpi ulnaris muscle. At that time, the patient was in MG Foundation of America status IIIa. Single-fiber electromyography in the extensor digitorum communis muscle on the 24<sup>th</sup> day showed markedly increased mean value of mean-consecutive-difference (174  $\mu$ s) and frequent blocking in 7 SFPPs (Fig. 1).

AChR-ab tests were positive by two laboratories: 3.4 (normal <0.7 nmol/L) and 30.55 (normal <0.03 nmol/L). Voltage gated calcium channel antibody was not tested in this patient because this test was not available in 1987.

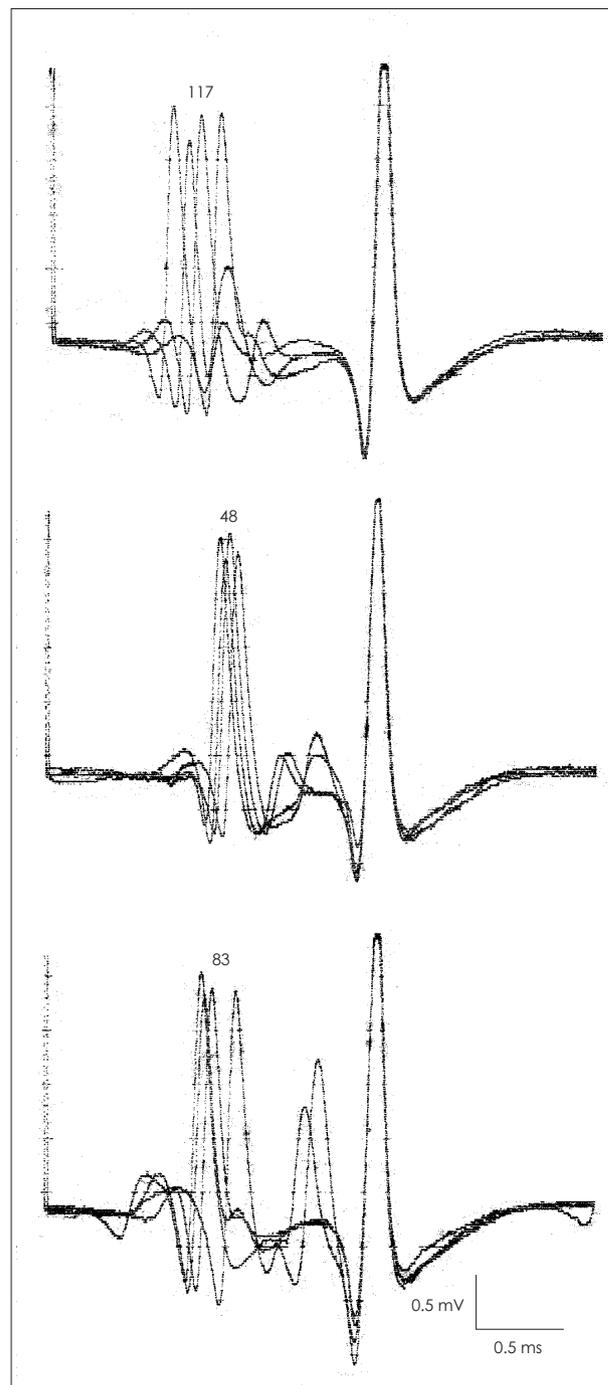
## Discussion

Our patient had seropositive MG, SCLC and mild axonal motor-sensory neuropathy. Guillain-Barré syndrome was initially suspected but less likely in view of the repeated normal spinal fluid findings and mild axonal neuropathy in the NCS. Axonal neuropathy is most likely a paraneoplastic syndrome of SCLC.

The RNS tests during MG crisis in our case showed a rather typical RNS test of myasthenic crisis: low CMAP amplitude and decrement at LRS and HRS. In myasthenic crisis, this pattern was observed in 25% of cases.<sup>2</sup> Lower CMAP, though within normal limit, and decrement at LRS and HRS are a rather characteristic pattern in severe MG.<sup>1</sup> With clinical improvement, the CMAP amplitude became normal and decrement at LRS was the only abnormality in this case. This is the most common RNS pattern in MG.<sup>1</sup> Single-fiber electromyography showed findings typical of neuromuscular transmission defect. LEMS was ruled out by a lack of an incremental response after brief exercise [post-exercise facilitation (PEF)] or at HRS.<sup>3</sup> 50% increment in PEF in the abductor digiti quinti muscle at the 11<sup>th</sup> day is slightly higher than normal 37% limit but definitely lower than 60% increment, the required criteria for the diagnosis of LEMS.<sup>3</sup> Transient increment in PEF or HRS was previously reported in a few severe MG cases.<sup>3</sup>

Fifty percentage of LEMS patients were known to have carcinoma, mostly SCLC.<sup>4</sup> Only three cases showing combined MG and SCLC features have been reported (Table 2).<sup>5-7</sup> They were male and aged 49 to 56. All three cases were seronegative. In two cases, SCLC was found at the time when the diagnosis of MG was made. In Myoshi's case, SCLC was found 18 months after the diagnosis of MG. All three cases had classical oculo-proximal muscle weakness of MG.<sup>7</sup> One case had bulbar weakness. Ours is the only one with MG crisis. Diagnosis of MG was confirmed by edrophonium test and decrement at LRS (25-28%) and HRS (22-70%). The diagnosis of MG in Fujita's case is questionable in view of "decrement" in 20 Hz stimulation due to artifacts and discrepancy in the first CMAP amplitude at 3 Hz (1.5 mV) and 20 Hz stimulation (3.0 mV).<sup>5</sup>

This may represent an 100% PEF typical of LEMS. With pyridostigmine therapy for MG and chemotherapy for SCLC, MG was in remission in two cases in 17-36 months. Our patient died 2 months after the diagnosis of MG. No follow-up information was available in one case. One may argue that our case represents a case of LEMS with positive AChR-ab.



**Fig. 1.** Three single fiber potential pairs showing a marked jitter. Number above single fiber potentials represent MCD value in  $\mu$ s. Neuromuscular blocking is noted in the second slave potential in the bottom single fiber potential pairs. MCD: mean-consecutive-difference.

Lennon<sup>8</sup> found a positive AChR-ab in 13% of LEMS patients. However, electrophysiological findings do not support the diagnosis of LEMS. Thus, we believe that our patient is the first one with seropositive MG and SCLC.

#### Conflicts of Interest

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The authors have no financial conflicts of interest.

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