Yonsei Medical Journal
Vol. 40, No. 5, pp. 454−459, 1999

Clinical Analysis of 12 Korean Lambert-Eaton Myasthenic Syndrome (LEMS) Patients

Joon-Shik Moon[1], Il-Nam Sunwoo[2], Seung-Min Kim[2], Sang-Ahm Lee[3], Kwang-Ho Cho[4], Kee-Duk Park[5], Woo-Kyung Kim[2], Byung-Ok Choi[2], and Hwa-Young Chun[2]

Abstract

The Lambert-Eaton myasthenic syndrome (LEMS) heralds the occurrence of malignancy, especially small-cell lung cancer (SCLC), but it can also occur in the absence of cancer. Twelve patients were diagnosed as LEMS by clinical features and the classical electrophysiological triad, which includes a low amplitude of compound muscle action potentials (CMAP), decremental responses on low-rate stimulation, and incremental responses on high-rate stimulation on the repetitive nerve stimulation (RNS) test. There were 6 male and 6 female patients, ranging in age from 49 to 66 years. Malignancy(all were SCLC) was found in 7 patients. Males predominantly expressed the paraneoplastic form; whereas the primary autoimmune form was found only in women, who showed a good response to corticosteroid treatment. The neurological features were similar in both groups: proximal lower limb weakness, depressed muscle stretch reflexes, and dryness of mouth in nearly all patients. Bulbar dysfunction and limb paresthesia were a little more frequent in the paraneoplastic form. In RNS tests, the characteristic electrophysiological abnormalities were found in all patients and were more profound in the paraneoplastic form. We concluded that LEMS is commonly associated with malignancy, especially SCLC, but it should also be stressed that there are many female LEMS patients who do not harbor any malignancy at all, and that other treatment strategies such as immunotherapy should be considered for these patients.

Key Words: Lambert-Eaton myasthenic syndrome, malignancy, small cell lung cancer, electrophysiological study, paraneoplastic, autoimmune

INTRODUCTION

The Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disease that affects presynaptic neuromuscular transmission and is characterized by fatigable muscle weakness and autonomic symptoms. Lambert, Eaton, and colleagues initially described the disorder in patients who had highly-malignant small-cell carcinoma of the lung.[1-3] It is typically recognized as a paraneoplastic syndrome associated with small-cell lung cancer (SCLC), but subsequent experience has led to the recognition that patients with LEMS could have tumors originating in other organs and that some patients might not have a tumor. Estimates of the incidence of carcinoma in LEMS have ranged from 50−70%.[4-6]

In Korea, there have been only a few cases of paraneoplastic LEMS,[7,8] but no reports of primary autoimmune LEMS. In this study, we tried to analyze the clinical and electrophysiological features of LEMS and to investigate the clinical differences between its paraneoplastic and primary autoimmune forms.

MATERIALS AND METHODS

We observed 12 patients with LEMS at Severance Hospital and Wonju Christian Hospital from 1987 to 1997. Three cases of overlap myasthenic syndrome were not included.

The diagnosis of LEMS was based on the clinical features and the classical electrophysiological triad on the repetitive nerve stimulation (RNS) test. These clinical features include easy fatigability, proximal leg weakness, and diminished or absent muscle stretch

Received June 29, 1999
Accepted August 26, 1999
Departments of Neurology, [1]Yonsei University Wonju College of Medicine, Wonju, [2]Yonsei University College of Medicine, [3]Ulsan University Medical College, [4]Wonkwang University Medical College, [5]Ehwa Womans University Medical College, Seoul, Korea.
Address reprint request to Dr. I. N. Sunwoo, Department of Neurology, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea. Tel: 82-2-361-5463, Fax: 82-2-393-0705, E-mail: sunwooin@yumc.yonsei.ac.kr

reflexes. The classical triad of RNS test consists of a low amplitude of compound muscle action potential (CMAP) (less than 5 mV), decremental responses (more than 10%) at low-rate stimulation (LRS), and marked incremental responses (more than 100%) at high-rate stimulation (HRS) on one of the distal muscles.[9]

The RNS test was performed according to Oh's method[9] on the ADQ and FCU muscles with stimulation on the transsulcal segment of the ulnar nerve. The nerve was supramaximally stimulated with the skin temperature controlled above 32°C in the hand. The forearm and hand were tightly fixed on a heavy restraining board during the test in order to reduce the movement artifact.

RESULTS

There were 6 male and 6 female patients, ranging in age from 49 to 66 years. Cancer was detected in 7 patients, all of which were small-cell lung cancer (SCLC). In LEMS patients with cancer (SCLC/LEMS), males were predominant (6/7); in contrast, the 5 LEMS patients with no cancer detected (NCD/LEMS) were all female (5/5). All male SCLC/LEMS were heavy smokers. Weight loss was more frequent in SCLC/LEMS (4/7) than NCD/LEMS (1/5). Cough was more frequent in SCLC/LEMS (6/7) than NCD/LEMS (1/5) (Table 1-1 and 1-2).

The onset was gradual in all patients. Major symptoms of SCLC/LEMS were leg weakness (3/7) or generalized weakness (4/7). Those of NCD/LEMS were leg weakness (2/5) or generalized weakness (3/5), and one patient also complained of lower back pain. Overall, dry mouth (10/12), lower limb weakness (12/12), and generalized tiredness (12/12) were the most common symptoms in all LEMS patients.

SCLC/LEMS had a significantly shorter symptom

Table 1-1. Clinical Manifestations of 7 SCLC/LEMS Patients

Patient	①	②	③	④	⑤	⑥	⑦
Sex/Age(yr)	m/54	m/65	m/55	f/49	m/58	m/66	m/66
Date	87.3.18	87.3.29	88.7.19	93.9.17	93.11.9	95.7.10	97.7.25
Interval*	s.	13 months	s.	s.	s.	s.	s.
Chief complaints	leg w.	general w.	leg w.	general w.	general w.	general w.	leg w.
Symptom duration	2 months	5 months	12 months	15 months	4 months	1 month	6 months
Smoking	(+)	(+)	(+) 60 pack · yr	(−)	(+) 35 pack · yr	(+) 80 pack · yr	(+)
Weight loss	(+)	(+)	(+)	(−)	(+)	(−)	(−)
Cough	(+)	(+)	(+)	(+)	(+)	(+)	(−)
Accompanying symptoms		dry mouth dysarthria dysphagia facial w.	dry mouth dysarthria dysphagia leg paresthesia	dry mouth dysarthria ptosis	dry mouth dysarthria dysphagia diplopia paresthesia	dry mouth dysphagia paresthesia	dry mouth ptosis
Symptom fluctuation	(−)	(+)	(−)	(−)	(+)	(−)	(+)
Muscle weakness							
U/E proximal	(−)	(+)	(+)	(+)	(+)	(+)	(+)
distal	(−)	(−)	(+)	(+)	(+)	(−)	(−)
L/E proximal	(+)	(+)	(+)	(+)	(+)	(+)	(+)
distal	(+)	(−)	(+)	(+)	(+)	(−)	(−)
Reflexes	hyporeflexia	areflexia	areflexia	normal	areflexia	areflexia	areflexia
Treatment	ChTx Neostigmine	RTx	ChTx RTx	ChTx	ChTx Pyridostigmine Guanidine	ChTx	Surgery ChTx
Course	expired	expired	remitted	remitted	expired	expired	expired

SCLC/LEMS, Lambert-Eaton myasthenic syndrome with small cell lung cancer.
s., simultaneous; w., weakness; U/E, upper extremity; L/E, lower extremity; ChTx, chemotherapy; RTx, radiotherapy.
* the interval between the diagnosis of LEMS and that of the malignancy.

Table 1-2. Clinical Manifestations of 5 NCD/LEMS Patients

Patient	①	②	③	④	⑤
Sex/Age(yr)	f/53	f/50	f/63	f/53	f/58
Date	92.6.8	92.8.20	92.11.16	93.6.14	96.8.27
Follow-up period	7 years		7 years		
Smoking	(−)	(−)	(−)	(−)	(−)
Weight loss	(−)	(−)	(+)	(−)	(−)
Cough	(−)	(+)	(−)	(−)	(−)
Chief complaints	general w.	general w.	leg w.	general w.	LBP, leg w.
Symptom duration	2 years	2 months	4 months	3 years	3 months
Accompanying symptoms	dry mouth hypohidrosis	dry mouth ptosis	dry mouth	dysphagia diplopia neck muscle w.	dry mouth
Symptom fluctuation	(+)	(−)	(−)	(+)	(−)
Muscle weakness					
U/E proximal	(+)	(+)	(−)	(+)	(−)
distal	(−)	(+)	(−)	(+)	(−)
L/E proximal	(+)	(+)	(+)	(+)	(+)
distal	(−)	(+)	(−)	(+)	(−)
Reflexes	areflexia	areflexia	areflexia	areflexia	normal
Laboratory findings					
Anti-nuclear antibody	1 : 40 (+) (nucleolar)	(−)	1 : 40 (+) (nucleolar)	(−)	(−)
Anti-VGCC Ab	352.5 pM/L (May 1997)	n.d.	n.d.	n.d.	639.0 pM/L (Sep 1996)
Treatment	Pyridostigmine prednisone	None	Pyridostigmine prednisone	None	None
Course	improved	unknown	improved	unknown	unknown

NCD/LEMS, Lambert-Eaton myasthenic syndrome with no cancer detected.
w., weakness; LBP, lower back pain; U/E, upper extremity; L/E, lower extremity; Anti-VGCC Ab, anti-voltage-gated calcium channel antibody; n.d., not done.

duration than NCD/LEMS: 1 to 15 months in SCLC/LEMS versus 1 month to 3 years in NCD/LEMS. The cancer was found almost simultaneously at the time of diagnosis of LEMS in 5 SCLC/LEMS and the development of LEMS symptoms preceded the diagnosis of cancer by 13 months in 1 SCLC/LEMS.

Proximal leg weakness (12/12) and diminished muscle stretch reflexes (10/12) were the most common neurological signs. Motor weakness was more severe in the lower limbs than in the upper limbs, particularly affecting the proximal muscles. Fluctuation of muscle weakness was found in 5 patients. Continued testing produced fatigue with increasing weakness in 3 SCLC/LEMS and 1 NCD/LEMS. Ptosis was noticed in 2 SCLC/LEMS and 1 NCD/LEMS. Bulbar dysfunction was present in 4 SCLC/LEMS and 1 NCD/LEMS. Limb paresthesia was present in 3 SCLC/LEMS, but not in NCD/LEMS. Neck muscle weakness was present in 1 NCD/LEMS.

In the RNS test, SCLC/LEMS had a greater tendency to show more prominent post-exercise facilitation (PEF), decremental responses on LRS, incremental responses on HRS, and post-tetanic facilitation (PTF) than NCD/LEMS. Two patients (NCD/LEMS case 1 & 3) fulfilled only two of the criteria in the abductor digiti quinti (ADQ) muscle, low CMAP amplitude and decremental response at LRS, but showed the whole triad in the flexor carpi ulnaris (FCU) muscle. Another patient (SCLC/LEMS case 7) also fulfilled only two of the criteria initially, decremental response at LRS and incremental response at HRS, but during the follow-up study, the CMAP amplitude on the ADQ muscle became significantly lower (Table 2-1 and 2-2).

Anti-nuclear antibody (ANA) was 1 : 40 positive in 2 NCD/LEMS, but other laboratory findings for

Table 2-1. The Initial RNS Findings of 7 SCLC/LEMS Patients

Patient		①	②	③	④	⑤	⑥	⑦
Sex/Age(yr)		m/54	m/65	m/55	f/49	m/58	m/66	m/66
Date		87.3.18	87.3.29	88.7.19	93.9.17	93.11.9	95.7.10	97.7.25
Recording site		ADQ	ADQ	ADQ	ADQ	ADQ	ADQ	ADQ
CMAP	Rest (mV)	2.2	1.6	1.9	3.8	0.2	0.8	7.2
	After exercise (%)	263	425	380	483	483	416	79
LRS	2Hz (%)	−50	−52	−50	−27	−58	−23	−36
	3Hz (%)	−60	−55	−66	−33	−57	−25	−44
	5Hz (%)	−53	−39	−62	−31	−56	−30	−42
HRS (%)		500	222	300	143	341	300	139
PTF (%)		−47	−18	−66	−21	−32	−23	−39
PTE (%)		−53	−41	−55	−41	−45	−32	−38

RNS, repetitive nerve stimulation.
CMAP, compound muscle action potentials; ADQ, abductor digiti quinti muscle; LRS, low-rate stimulation; HRS, high-rate stimulation; PTF, post-tetanic facilitation; PTE, post-tetanic exhaustion.

Table 2-2. The Initial RNS Findings of 5 NCD/LEMS Patients

Patient		①	②	③	④	⑤
Sex/Age(yr)		f/53	f/50	f/63	f/53	f/58
Date		92.6.8	92.8.20	92.11.16	93.6.14	96.8.27
Recording site		ADQ	ADQ	ADQ	ADQ	TA
CMAP	Rest (mV)	1.5	0.3	3.5	0.6	3.3
	After exercise (%)	73	1514	11	129	29
LRS	2Hz (%)	−31	−21	−43	−35	−38
	3Hz (%)	−38	−3	−52	−35	−48
	5Hz (%)	−38	−23	−47	−32	−43
HRS (%)		81	1060	58	384	745
PTF (%)		−2	−13	−6	−31	−22
PTE (%)		−2	−13	−55	−28	−47

CMAP, compound muscle action potentials; ADQ, abductor digiti quinti muscle; TA, tibialis anterior muscle; LRS, low-rate stimulation; HRS, high-rate stimulation; PTF, post-tetanic facilitation; PTE, post-tetanic exhaustion.

autoimmune disorders were all negative. Anti-VGCCs (voltage-gated calcium channels) antibody titers were measured in 2 NCD/LEMS at 352.5 pmol/L and 639.0 pmol/L, respectively (less than 20.0 pmol/L in normal control).

Muscle biopsy was performed in 1 NCD/LEMS, who showed type II fiber atrophy.

Of 7 SCLC/LEMS, 2 patients showed complete remission by aggressive radiotherapy and chemotherapy. Of 5 NCD/LEMS, 3 patients showed a dramatic improvement after a few months of corticosteroid treatment.

DISCUSSION

LEMS results from an immune-mediated reduction in the number of presynaptic active zones and active zone particles which is the representative of voltage-gated calcium channels (VGCCs), following cross-linking by divalent anti-VGCCs IgG antibodies and resulting in a decreased number of acetylcholine quanta released from the nerve terminal in response to nerve impulses. VGCCs are also present in the cell membrane of SCLC and, in susceptible individuals, may be the trigger for the formation of anti-VGCCs antibodies.[10]

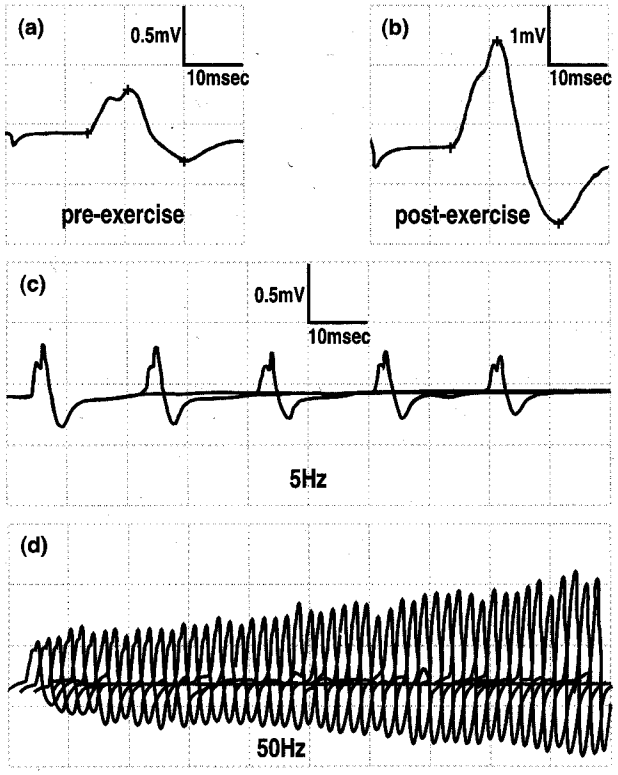

Fig. 1. Repetitive nerve stimulation test on the abductor digiti quinti muscle of SCLC/LEMS case 6. (a) before exercise, (b) after 30 seconds' exercise, (c) 5 Hz stimulation, (d) 50 Hz stimulation.

It has generally been stated that 50−90% of newly diagnosed cases of LEMS will prove to have an underlying malignancy,[5] although there seems to be a trend during the past decade for the tumor frequency to decrease.[6] SCLC is the most common tumor in association with LEMS, although other malignancies such as renal cell carcinoma, mixed parotid tumor, systemic mastocytosis, breast carcinoma, pancreatic or lung adenocarcinoma, hematologic malignancies like lymphoma or lymphosarcoma (reticulum cell sarcoma) have also been reported.[11] Malignancy was found in about 60% in our series and all of them were SCLC.

The prevalence of LEMS is known to be about 3−5% among patients with SCLC.[12,13] In our series, however, only 7 patients (1%) were found to have LEMS among 675 patients with SCLC from 1987 to 1997. We believe that the lower incidence of LEMS in Korea might be due to poor suspicion of LEMS by physicians because all the LEMS patients were diagnosed by neurologists, not by internists or surgeons, although the possibility of ethnic differences cannot be excluded.

In most patients, SCLC is found within 2 years after the diagnosis of LEMS, but the diagnosis can be delayed by as much as 5 years.[14] In most of our patients, SCLC was diagnosed at nearly the same time as the diagnosis of LEMS except in a patient (SCLC/LEMS case 2) in whom the diagnosis of SCLC was delayed 13 months after the diagnosis of LEMS. The longest interval between the onset of LEMS and the radiological evidence of a tumor was 13 months in our series, compared to 2.3 years reported by Lambert et al.[1] and 3.8 years reported by O'Neill et al.[5]

O'Neill[5] observed a marked male preponderance in LEMS whereas Gutmann[6] found the reverse. In our series, we observed a slight male preponderance as a whole, but most female LEMS had no malignancy, in contrast to the male preponderance of SCLC. Nearly all SCLC/LEMS were smokers and all NCD/LEMS were non-smokers, as expected. Cough was more frequent in SCLC/LEMS, suggesting its relevance to lung cancer. Weight loss was present in 4 SCLC/LEMS while it was present in only 1 NCD/LEMS.

There have been only a few reports about muscle pathology in LEMS showing type II fiber atrophy,[15,16] but O'Neill[5] insisted that this change might be a consequence of disuse.

The primary and paraneoplastic forms of LEMS are similar in clinical manifestations, but bulbar dysfunction and limb paresthesia seem to be more frequently present in the paraneoplastic form. Limb paresthesia might reflect subclinical paraneoplastic polyneuropathy, though the nerve conduction study may be normal. In contrast to O'Neill's study, ptosis or jaw weakness were rare in our series. The paraneoplastic form had a tendency toward more profound electrophysiological abnormalities, but not enough to distinguish SCLC/LEMS from NCD/LEMS based only on clinical and electrophysiological findings.

The primary and paraneoplastic forms of LEMS appear to have identical pathophysiology. Calcium channel antibodies are present in both forms. In the paraneoplastic form, the antigenic stimulus for antibody production is undoubtedly the VGCCs present in the membranes of small-cell carcinoma cells, and the antibodies directed against this tumor protein cross-react with neuronal calcium channels.[17,18] Therefore, neurologic improvement can be expected in SCLC/LEMS with the treatment of malignancy and

this was confirmed in our series.

The antigenic stimulus in NCD/LEMS still remains unknown, but patients without cancer demonstrate a genetic tendency of organ-specific autoantibody formation and autoimmune diseases.[4,5] O'Neill et al found 34% of LEMS patients to have either a personal or family history of autoimmune thyroid disease, pernicious anemia, vitiligo, celiac disease, or type I diabetes mellitus. By contrast, no definite autoimmune disease or auto-antibodies were found in our series except weakly positive ANA in 2 NCD/LEMS. Even though their positivity was weak, it is possible that a certain autoimmune mechanism intervened and we speculate that this discrepancy might have resulted from the small population in our series. Nonetheless, the complete recovery from LEMS both clinically and electrophysiologically after treatment with corticosteroid could justify the suggestion that immunotherapy with corticosteroid or intravenous immunoglobulin should be performed in NCD/LEMS, i.e., the primary autoimmune type.[19]

In conclusion, although LEMS is commonly associated with malignancy, especially SCLC, it should be stressed that there are also many female LEMS patients who do not harbor any malignancy, and for those patients who show no evidence of malignancy, other treatment strategies such as immunotherapy should be considered. LEMS is a reversible disease, at least in part, therefore, aggressive treatment should be administered in order to achieve the maximal clinical and electrophysiological improvement irrespective of whether patients have malignancy or not.

REFERENCES

1. Lambert EH, Eaton LM, Rooke ED. Defect of neuromuscular conduction associated with malignant neoplasm. Am J Physiol 1956;187:612-3.
2. Eaton LM, Lambert EH. Electromyography and electrical stimulation of nerves in diseases of the motor unit: observations on a myasthenic syndrome associated with malignant tumors. JAMA 1957;163:1117-24.
3. Rooke ED, Eaton LM, Lambert EH, Hodgson CH. Myasthenia and malignant intrathoracic tumor. Med Clin North Am 1960;44:977-88.
4. Lennon VA, Lambert EH, Whittingham S, Fairbanks V. Autoimmunity in the Lambert-Eaton myasthenic syndrome. Muscle Nerve 1982;5(9 Suppl):S21-S25.
5. O'Neill JH, Murray NMF, Newsom-Davis J. The Lambert-Eaton myasthenic syndrome. A review of 50 cases. Brain 1988;111:577-96.
6. Gutmann L, Phillips LH, Gutmann L. Trends in the association of Lambert-Eaton myasthenic syndrome with carcinoma. Neurology 1992;42:848-50.
7. Lee SA, Sunwoo IN, Ro JK, Park KD. A case of remitted Lambert-Eaton myasthenic syndrome with small cell lung carcinoma following chemotherapy and radiotherapy. J Korean Neurol Assoc 1992;10:401-6.
8. Kim BM, Lee KW, Roh JK, Lee SB, Myung HJ, Bang YJ. Combined paraneoplastic phenomena of Lambert-Eaton syndrome and subacute sensory neuronopathy. J Korean Neurol Assoc 1993;11:444-50.
9. Oh SJ. Techniques of the repetitive nerve stimulation test. In: Oh SJ, editor. Electromyography: Neuromuscular transmission studies. Baltimore: Williams & Wilkins; 1988. p.31-86.
10. Elrington G, Newsom-Davis J. Clinical presentation and current immunology of the Lambert-Eaton myasthenic syndrome. In: Lisak RP, editor. Handbook of myasthenia gravis and myasthenic syndrome. New York: Marcel Dekker, Inc.; 1994. p.81-102.
11. McEvoy KM. Diagnosis and treatment of Lambert-Eaton myasthenic syndrome. Neurol Clin 1994;12:387-99.
12. Hawley RJ, Cohen MH, Saini N, Armbrustmacher VW. The carcinomatous neuromyopathy of oat cell lung cancer. Ann Neurol 1980;7:65-72.
13. Erlington GM, Murray NMF, Spiro SG, Newsom-Davis J. Neurological paraneoplastic syndromes in patients with small cell lung cancer. A prospective survey of 150 patients. J Neurol Neurosurg Psychiatry 1991;54:764-7.
14. Levin KH. Paraneoplastic neuromuscular syndromes. Neurol Clin 1997;15:597-614.
15. Oh SJ. The Eaton-Lambert syndrome: Report of a case. Arch Neurol 1972;27:91-4.
16. Henriksson KG, Nillson O, Rosen I, Schillen HH. Clinical, neurophysiological and morphological findings in Eaton-Lambert syndrome. Acta Neurol Scand 1977;56: 117-40.
17. Lennon VA, Lambert EH. Autoantibodies bind solubilized calcium channel-omega-conotoxin complexes from small cell lung carcinoma: A diagnostic aid for Lambert-Eaton myasthenic syndrome. Mayo Clin Proc 1989;64:1498-504.
18. Morris CS, Esiri MM, Marx A. Immunocytochemical characteristics of small cell lung carcinoma associated with the Lambert-Eaton myasthenic syndrome. Am J Pathol 1992; 140:839-45.
19. Bird SJ. Clinical and electrophysiological improvement in Lambert-Eaton myasthenic syndrome with intravenous immunoglobulin therapy. Neurology 1992;42:1422-3.