The Lambert-Eaton myasthenic syndrome

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Chapter 5

Differences in clinical features between the Lambert-Eaton myasthenic syndrome with and without cancer: an analysis of 227 published cases

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Abstract

To compare the clinical features of patients with the Lambert-Eaton myasthenic syndrome (LEMS) associated with carcinoma, with patients having LEMS but no cancer, reports on LEMS patients were analyzed systematically. Cancer was detected (CD group) in 62% of the 227 included cases. This CD group showed a male predominance (70%). No sex difference was found in patients in whom no cancer was detected (NCD group). Median age at onset of LEMS in the CD group was higher than in the NCD group (58 and 49.5 years, $p < 0.01$). Median interval between onset of symptoms and diagnosis of LEMS was longest in NCD cases ($p < 0.001$). CD patients had additional immunological disorders less frequently than NCD cases (6% and 27%, $p < 0.001$). Symptoms distinguishing the CD group from the NCD group were weight loss ($p < 0.001$) and need for prolonged artificial ventilation after anaesthesia ($p < 0.05$). This analysis shows significant differences between CD and NCD cases of LEMS. The male predominance and higher age at onset in patients with a tumour probably reflects the characteristics of patients with small cell lung cancer. The high frequency of additional immunological disorders in patients without malignancy, together with the younger age at onset suggests a similar etiology as other non-paraneoplastic autoimmune diseases.

Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is a rare antibody-mediated autoimmune disorder.[1,2] The target antigen, the presynaptic P/Q-type calcium channel, has been studied in great detail. However, the cause of the disease is still elusive. One clue is the association of this disease with small cell lung cancer (SCLC), which is found in over half of the patients.[3] This tumour expresses P/Q-type calcium channels, which suggests that the cause of the disease in these patients is an immunization by their tumour.[4] This explanation is not valid for the other half of the patients with LEMS, who do not have a detectable tumour. A study of 50 LEMS patients showed that patients in whom a cancer was detected (CD) had a higher ESR and smoked more frequently than patients without cancer.[3] No other tumour related factors nor any clinical features distinguishing tumour and non-tumour LEMS patients have been found. As LEMS is rare, this might be due to the small number of patients in most studies describing the clinical features of LEMS. We tried to find differences in clinical features by analyzing all published cases of patients with LEMS.

Methods

A literature search in the Medline® database (National Library of Medicine, Bethesda, Maryland), using the keywords "Lambert", "Eaton", and "myasthenic", was done to collect publications describing individual patients with LEMS. Publications written in English, French, German and Dutch published up to 1999 were taken into account. Papers from the reference list of these publications were screened for description of additional cases.

Case descriptions were included when clinical features were compatible with LEMS (proximal muscle weakness, lowered tendon reflexes and signs of autonomic dysfunction), diagnosis was confirmed by means of EMG (low amplitude of the compound muscle action potential and increment after high-frequency stimulation or maximal voluntary contraction), and when age, sex, and medical history were reported. When a patient was described in more than one publication, information from all case histories of the same patient were used. No assumptions were made about the presence of signs or symptoms. Pooled data of patients were not included in our analysis.

Median values were compared using the Mann Whitney test. Contingency tables were analyzed using a χ^2 test.

Results

Hundred-and-seventy-eight papers were found describing 270 single cases of LEMS, of which 227 cases in 155 publications fulfilled the criteria for inclusion. Of these cases, 139 patients were men, 88 patients were women (1.6:1). Median age at onset of LEMS was 57 years and ranged between seven and 80 years. A cancer was detected in 141 patients (62%), who had 24 different types of tumour (table 1). Time relationship of tumour diagnosis with the onset of symptoms of LEMS was given in 133 cases. Onset of LEMS preceded cancer diagnosis in 86% of these cases and was concurrent in seven patients (5%). Overall, the median time between onset of LEMS and cancer diagnosis was six months and ranged between six years before and five years after cancer diagnosis (figure 1).

Age and sex

In the CD cases 70% was male, whereas in cases in which no cancer was detected (NCD) 48% was male ($\chi^2 = 10.72$, $p < 0.01$). Median age of onset in CD patients (58 years) was significantly higher than in NCD patients (49.5 years) (Mann-Whitney test, $p<0.001$). Distribution of age showed an incidence peak between 50 and 70 years for both groups (figure 2). More than 80% of the CD patients had age at onset above 50 years, against only 50% in the NCD group ($\chi^2 = 26.51$, $p < 0.01$).

Table 1. Cancers found in Lambert-Eaton myasthenic syndrome

Cancer types	N
Pulmonary malignancies	112
Small cell lung carcinoma	95
Lymphoma	7
Leukemia	6
Miscellaneous	16
Prostate carcinoma	3
Laryngeal carcinoma	3
Breast carcinoma	2
Gall bladder carcinoma	1
Rectal adenocarcinoma	1
Carcinoma of maxillar glandule	1
Malignant thymoma	1
Ameloblastoma	1
Lymph metastasis, unknown primary	3

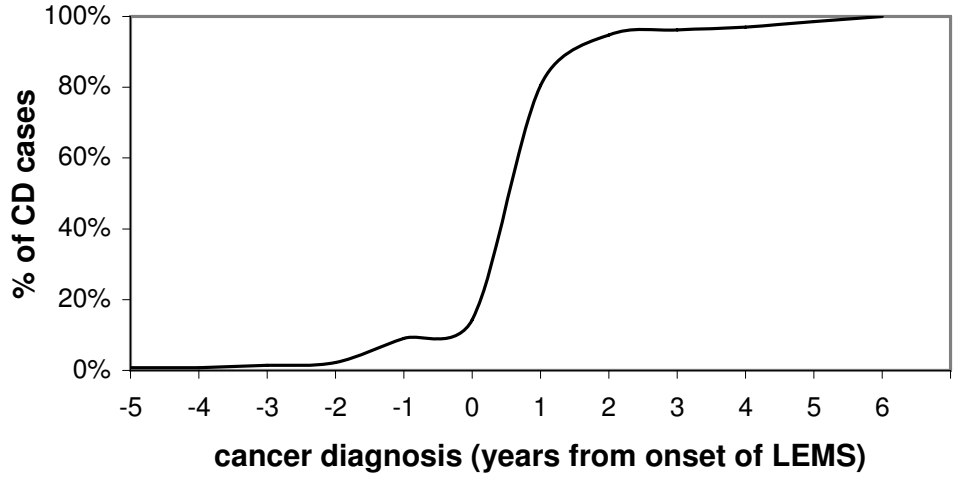

Figure 1. Time relationship of cancer diagnosis with the onset of symptoms of Lambert-Eaton myasthenic syndrome in 133 cancer detected (CD) cases.

Diagnosis of LEMS and additional immunological disorders

In 202 cases the interval between onset of symptoms and diagnosis of LEMS could be determined. The median interval was six months. The longest delay between onset and diagnosis was 36 years. Delay was longer in the NCD group (median 13,5 months) than in the CD group (5 months) (Mann-Whitney test, $p < 0.001$). Additional

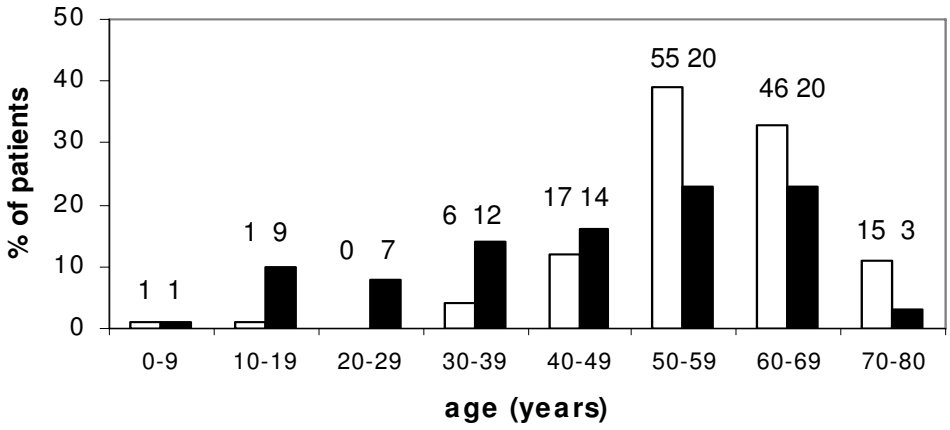

Figure 2. Age at onset of symptoms of Lambert-Eaton myasthenic syndrome in percentage of patients with cancer (open bars) and percentage of patients without cancer (solid bars). Absolute numbers of patients are given above the bars.

immunological disorders were mentioned in 32 patients (14%), of which seven patients had more than one. These disorders were found in nine CD patients (6%) and in 23 NCD patients (27%) (χ^2 = 18.29, p < 0.001). Associated immunological diseases were myasthenia gravis (in eight patients), pernicious anemia (5), hypothyroidism (5), systemic lupus erythematosus (3), hyperthyroidism (3), celiac disease (2), vitiligo (2), insulin-dependent diabetes (2), ulcerative colitis (1), Addison disease (1), discoid lupus (1), Sjögren disease (1) and rheumatoid arthritis (1).

Symptoms and signs

In 131 case histories the presenting symptom of LEMS was described. Most common presenting symptom was leg weakness (60%), followed by generalized weakness (18%), muscle pain or stiffness (5%), dry mouth (5%), arm weakness (4%), diplopia (4%) and dysartria (2%). Ptosis, difficulty swallowing, blurred vision and impotence were each described as the presenting symptom in only one case history. No differences between CD and NCD patients were found. Symptoms as experienced by patients during the course of the disease are listed in table 2. Weight loss was more common in the CD group (28%) than in the NCD group (8%) (χ^2 = 13.31, p < 0.001), as was prolonged artificial ventilation after anesthesia (9% and 1%; χ^2 = 5.34, p < 0.05). Signs found during the course of LEMS are listed in table 3. No features

Table 2. Symptoms as reported by patients with Lambert-Eaton myasthenic syndrome

Symptom	N (%)	Symptom	n (%)
Muscle weakness	219 (96)	Autonomic symptoms	111 (49)
Leg weakness	198 (87)	Dry mouth	88 (39)
Arm weakness	126 (55)	Impotence	16 (12)*
Neck weakness	15 (7)	Obstipation	14 (6)
Easy fatigability	75 (33)	Miction problems	13 (6)
Oculobulbar symptoms	116 (51)	Dry eyes	9 (4)
Ptosis	48 (21)	Blurred vision	8 (4)
Diplopia	48 (21)	Impaired sweating	6 (3)
Dysartria	44 (19)	Dizziness	5 (2)
Difficulty swallowing	54 (24)	Unspecified	1 (0)
Difficulty chewing	12 (5)	Respiratory symptoms	36 (16)
Sensory symptoms	35 (15)	Difficulty breathing	29 (13)
Numbness/paraesthesia	12 (5)	Artificial ventilation	26 (11)
Muscle aching/stiffness	27 (12)	Spontaneously required	13 (6)
Weight loss	47 (21)	Due to anesthesia	13 (6)

*% of male population

Table 3. Signs in patients with Lambert-Eaton myasthenic syndrome during the course of the disease

Signs	N (%)	Signs	n (%)
Cranial nerve signs	99 (44)	Muscle weakness	
Ptosis	69 (30)	Leg weakness	200 (88)
Diplopia	27 (12)	Proximal	186 (82)
Dysartria	35 (15)	Distal	60 (26)
Facial weakness	29 (13)	Arm weakness	165 (73)
Tendon reflexes		Proximal	149 (66)
Depressed or absent	202 (89)	Distal	47 (21)
Normal	10 (4)	Neck weakness	27 (12)
Facilitation	59 (26)	Respiratory weakness	13 (6)
Muscle wasting	33 (14)	No muscle weakness	15 (7)
Ataxia	23 (10)	Sensory impairment	19 (8)

distinguished between the CD and NCD cases. No patient had distal leg paresis with normal proximal strength. Of the 47 patients with weakness of the distal upper limbs, only four had normal proximal arm strength. Of 27 patients with diplopia on examination, 20 patients exhibited ptosis as well. In 23 patients (10%) cerebellar ataxia was found; in 19 of them a malignancy was detected.

Discussion

This study of 227 patients with LEMS showed significant differences between patients with a tumor and those without one, which so far had not been recognized in smaller groups of patients. Patients with a tumor were more often male, had higher age at onset of LEMS and had a shorter delay between onset of symptoms and diagnosis of LEMS. The frequency of additional immunological disorders was lower in this group. The patients more often had weight loss or need for prolonged artificial ventilation after anesthesia.

The higher frequency of male patients in the CD group is most likely related to the lower incidence of SCLC in females.[5] Previous studies found a higher frequency of male patients in this group as well (table 4).[6,7] In the NCD group the proportion of women was significantly higher then in the CD group, as was found in two previous studies.[6,7] Patients in the CD group had a significantly higher age at onset of symptoms than patients in the NCD group. The relatively high age at onset of SCLC could well account for this difference.[5] In LEMS patients without related tumor, we found that half of them developed LEMS before the age of 50 years. O'Neill et al. found a similar age distribution in the study of 50 LEMS patients.[3] Furthermore, it

Table 4. Sex distribution and percentage of cancer related cases in Lambert-Eaton myasthenic syndrome

Series	No. of patients	CD/NCD (% CD)	Males/Females (% males)		
			All patients	CD	NCD
O'Neill et al.[3]	50	25:25 (50)	32:18 (64)	14:11 (56)	18:7 (72)
Lennon et al.[6]	64	18:46 (28)	29:35 (45)	11:7 (61)	18:28 (39)
Tim et al. [7]	73	31:42 (42)	35:38 (48)	17:14 (55)	18:24 (43)
Motomura [11]	110	76:34 (69)	ratio 3:1	n.a.	n.a.
This study*	227	141:86 (61)	139:88 (63)	98:43 (70)	41:45 (48)

CD = cancer detected; NCD = non-cancer detected; n.a. = not available

*This study contained no patients from the studies by Lennon et al.,[6] Tim et al.,[7] and Motumura.[11] From the study by O'Neill et al.,[3] ten patients, who were described in separate case histories, were included.

parallels the age distribution of myasthenia gravis.[8] Considering the similarities in pathogenesis between LEMS and myasthenia gravis, the existence of a group of relatively young patients in LEMS is not surprising. As LEMS is typically thought to occur in old, smoking males, this group of younger LEMS patients might so far have been underestimated.

In our group, 27% of NCD cases had a concurrent immunological disorder, in contrast to only 6% in the CD group. The frequency in the NCD group is exceedingly high, given a prevalence of autoimmune disorders of 2% in an outpatient population.[9] This finding, together with the high proportion of women and the relatively young age at onset in the NCD group, suggests that the etiology of LEMS in this group is similar to the one of other non-cancer related autoimmune diseases.

Median interval between onset of symptoms and diagnosis of LEMS was significantly longer in NCD cases than in CD group. This could be due to the fact that detecting a tumor, especially a SCLC, can contribute in the diagnosis of LEMS. It could also suggest a more progressive course of LEMS in patients with underlying malignancy, but there are no data supporting this hypothesis. The higher occurrence of weight loss in CD cases compared to NCD patients is not surprising, as patients with a malignancy often suffer from cachexia, although this was not found in the study by O'Neill.[3] Almost all patients who required prolonged artificial ventilation after anesthesia had a malignancy, which possibly reflects a combination of respiratory muscle weakness, more pronounced by neuromuscular blocking agents, and an impaired ventilatory function in CD cases by virtue of the tumor, especially a SCLC. Paraneoplastic cerebellar degeneration is described in patients with LEMS without other antineuronal antibodies, but the pathophysiology and especially the role of anti-VGCC-antibodies is not known in detail.[10] We found description of ataxia in 10% of

published cases, which corroborates a study in 110 Japanese LEMS patients, of whom 9% had cerebellar involvement.[11]

One might wonder if the group in this study is representative for LEMS patients in general, while publications of larger groups of LEMS patients up to now so far show variation in sex distribution and percentage of malignancy related cases (table 4).[3,6,7,11] The relatively large group of CD cases in this study, compared to other studies, could be due to the fact that initially only cases associated with a pulmonary malignancy were reported. Next, a large number of case histories were published because of its occurrence with malignancies not formerly associated with LEMS, thereby further increasing the CD group. On the other hand, some patients in our NCD group, especially those in which duration of follow-up from onset of LEMS was short, could have had an occult malignancy not yet detected. Furthermore, in a recent study of 110 Japanese patients a malignancy was detected in 69% of them, which is even higher than in this study.[11]

Interpretation of the frequency of clinical features in this study must of course be prudent. Although only reports with adequate clinical data were included, the completeness of the case reports varied. For example, the low prevalence of autonomic symptoms in this study compared to other reports probably reflects the incompleteness of several case histories.[3,12] However, other important characteristics of the group described in this study, like the age at onset, presenting symptoms, and the prevalence of non-autonomic signs and symptoms, are more or less similar to those described in these previous studies.[3,6,7]

In conclusion, this analysis of clinical data reported in patients with LEMS shows significant differences between CD and NCD cases of LEMS, which have not been reported before. When a patient with LEMS is a relatively old male, who has weight loss, he is probable to have an underlying malignancy. When a patient, male or female, presents with LEMS at relatively young age and has an additional autoimmune disorders, presence of a tumor is unlikely.

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Appendix

Included publications *(journal name/ year - volume number - first page number)*. If more than one case history of a publication was included, the number of cases is given between parentheses.

Acta Haematol 1979-62-214
Acta Med Scand 1982-212-429
Acta Neurol Belg 1970-70-495
Acta Neurol Scand 1977-56-117 (2)
Am J Med 1972-55-354
Anesthesiology 1992-76-142
Ann Dermatol Venereol 1982-109-737
Ann Dermatol Venereol 1983-110-537
Ann Hematol 1988-76-45
Ann Med Interne (Paris) 1969-120-313 (2)
Ann Med Interne (Paris) 1971-122-959
Ann Med Interne (Paris) 1975-126-205
Ann Med Interne (Paris) 1991-142-439
Ann Med Interne (Paris) 1995-146-55
Ann Med Interne (Paris) 1996-147-222
Ann Otolaryngol Chir Cervicofac 1973-90-314
Ann Neurol 1981-10-448 (3)
Ann Neurol 1982-11-570 (4)
Ann Oncol 1995-6-291
Arch Intern Med 1968-122-33
Arch Neurol 1972-27-69 (3)
Arch Neurol 1972-27-91
Arch Neurol 1974-31-183
Arch Neurol 1975-32-815
Arch Neurol 1979-36-572
Arch Neurol 1980-37-315
Arch Neurol 1986-43-1186
Arch Neurol 1998-56-172 (2)
Arch Otolaryngol 1984-110-123
Arch Phys Med Rehabil 1977-58-457
Arch Phys Med Rehabil 1990-71-995
Arch Phys Med Rehabil 1992-73-98
Arq Neuropsiquiatr 1998-56-457 (2)
Brain1988-111-577 (10)
BMJ 1966-2-1573
BMJ 1977-1-946
Cancer 1980-46-1123
Cancer 1991-68-421
Chest 1988-3-604
Clin Neurol Neurosurg 1979-81-4
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Electromyogr Clin Neurophysiol 1994-34-87
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Internist 1991-32-292
Ital J Neurol Sci 1997-18-157
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J Kans Med Soc 1982-83-617
J Neuroophtalmolol 1997-17-202
J Neurol 1977-217-95 (2)
J Neurol 1990-237-324
J Neurol 1995-242-210
J Neurol Sci 1988-87-61 (2)
J Rheumatol 1996-23-1292
J Surg Oncol 1983-24-23
J Surg Oncol 1987-34-239
J Neurol Neurosurg Psychiatry 1962-25-3 (3)
J Neurol Neurosurg Psychiatry 1974-37-1214 (6)
J Neurol Neurosurg Psychiatry 1977-40-1109
J Neurol Neurosurg Psychiatry 1979-42-247
J Neurol Neurosurg Psychiatry 1980-43-978
J Neurol Neurosurg Psychiatry 1984-47-806 (2)
J Neurol Neurosurg Psychiatry 1988-51-436 (2)
J Neurol Neurosurg Psychiatry 1988-51-880
J Neurol Neurosurg Psychiatry 1991-54-452 (2)
J Neurol Neurosurg Psychiatry 1992-55-409
J Neurol Neurosurg Psychiatry 1998-64-819
J Neurol Neurosurg Psychiatry 1998-65-609
Lancet 1953-02-1291
Mayo Clin Proc 1968-43-689
Med Klin (Munich) 1993-88-393
Med Welt 1983-34-19
Muscle Nerve 1984-7-250
Muscle Nerve 1984-7-680 (2)
Muscle Nerve 1984-7-754
Muscle Nerve 1986-09-519
Muscle Nerve 1989-15-12
Muscle Nerve 1989-12-844 (2)
Muscle Nerve 1990-13-360
Muscle Nerve 1991-14-625 (2)
Muscle Nerve 1991-14-863
Muscle Nerve 1991-14-914
Muscle Nerve 1991-14-1227 (3)
Muscle Nerve 1993-16-712
Muscle Nerve 1993-16-716
Muscle Nerve 1993-16-986
Muscle Nerve 1994-17-689
Muscle Nerve 1994-17-1073
Muscle Nerve 1995-18-715 (3)
Muscle Nerve 1995-18-867 (2)
Muscle Nerve 1996-19-1328 (2)
Muscle Nerve 1997-20-674
Muscle Nerve 1997-20-735
N Engl J Med 1994-331-528
N Y State J Med 1991-91-29
N Z Med J 1990-103-240 (2)
Ned Tijdschr Geneeskd 1969-113-2194
Ned Tijdschr Geneeskd 1978-2-369 (2)
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Nervenarzt 1984-55-436
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Neurol India1977-25-184
Neurology 1967-17-286
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Neurology 1968-18-757 (2)
Neurology 1973-23-1084 (2)
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Neurology 1976-26-944
Neurology 1979-29-720
Neurology 1980-30-634
Neurology 1981-31-265 (4)
Neurology 1983-33-1157 (5)
Neurology 1984-34-1324 (3)
Neurology 1987-37-1411
Neurology 1989-39-249
Neurology 1991-41-1682
Neurology 1992-42-1422
Neurology 1992-42-1944 (6)
Neurology 1993-43-236
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Neurology 1996-46-1143
Neurology 1998-50-470 (2)
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