The Lambert-Eaton myasthenic syndrome

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Chapter 6

The Lambert-Eaton myasthenic syndrome has a more progressive course in patients with lung cancer

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Abstract

We studied whether a difference exists in the development of symptoms of the Lambert-Eaton myasthenic syndrome (LEMS) between patients with or without small cell lung cancer (SCLC). We assessed symptoms in 38 LEMS patients, 13 with SCLC, by interviewing them using a structured checklist, backed up by a review of their clinical records, and compared the frequency and time scale of symptoms during the course of LEMS. Bulbar (87%) and autonomic (95%) symptoms for the whole group were more common than reported in the literature. Frequencies of symptoms did not differ significantly between patients with and without SCLC, but symptoms in patients with SCLC appeared within a shorter timeframe, indicating a more rapid clinical course. The presence of a particular symptom associated with LEMS did not predict the presence of SCLC, but in patients with a rapidly progressive LEMS the possibility of underlying lung cancer should be of particular concern.

Introduction

The Lambert-Eaton myasthenic syndrome (LEMS) is clinically characterized by muscle weakness and autonomic dysfunction. In half of the patients a small cell lung cancer (SCLC) is found, generally following the diagnosis of LEMS.[1,2] Specific symptoms of LEMS do not distinguish between patients with and without underlying SCLC,[1,3] but LEMS associated with SCLC may have a more progressive course, considering the shorter duration of disease until LEMS is diagnosed.[2] Previous studies describing the symptoms of LEMS have been retrospective and based on review of case records; consequently, the figures could be underestimations.[1,4,5] Furthermore, there has been no specific study of the rate of occurrence of symptoms. The present study aimed at defining as precisely as possible both the nature of symptoms and the rate of progression.

Methods

Data from patients known to have had a diagnosis of LEMS between 1998 and 2003 were collected as part of a national research project, as previously described.[2] The medical ethics committee of the Leiden University Medical Centre approved the study. After obtaining informed consent, patients were interviewed using a structured checklist to retrospectively record all symptoms related to LEMS, the date of their appearance, and factors influencing weakness. Symptoms present at onset of LEMS, but clearly related to another cause, were recorded, but were not considered as the initial symptom of LEMS. Clinical records were reviewed to record signs and symptoms during the disease course, the results of laboratory and electromyographic testing, and the presence of SCLC.[6] Inclusion criteria for LEMS were the presence of acquired variable muscle weakness, and either the presence of serum anti-P/Q-type voltage-gated calcium channel antibodies or an increment of more than 100% of the compound muscle action potential on high-frequency repetitive nerve stimulation or after maximum voluntary contraction. Patients with other disorders that might be confused with LEMS-related symptoms, patients with memory deficits, and patients who had been followed for less than 6 months from onset of symptoms were excluded.

Statistical comparisons between the two groups were made using Fisher's exact test or Kaplan-Meier plots and the log-rank test when appropriate. Statistical analysis was performed using SPSS 10 (SPSS Inc., Chicago, IL).

Results

We studied 38 patients (13 with SCLC) after exclusion of two patients with a memory deficit, one with coexisting myasthenia gravis, one with severe juvenile rheumatoid arthritis, and two in whom follow-up had been short. Patient characteristics are shown in Table 1. Median age was 57 years in both groups. Median follow-up was 15 months for patients with SCLC and 69 months for patients without a tumour.

Table 1. Patient characteristics and symptoms

	SCLC (n=13)	no SCLC (n=25)	All (n=38)
Patient characteristics			
Male: female (% man)	12:1	12:13	24:14
Median age at onset, years (range)	56 (35-73)	53 (18-65)	54 (18-73)
P/Q-type Ca channel antibodies	13 (100%)	24 (96%)	37 (97%)
Ptosis	7 (54)	14 (56)	21 (55)
Double vision	7 (54)	12 (48)	19 (50)
Slurred speech	11 (85)	18 (72)	29 (76)
Difficulty swallowing	7 (54)	14 (56)	21 (55)
Difficulty chewing	7 (54)	8 (32)	15 (39)
Neck weakness	4 (31)	9 (36)	13 (34)
Proximal weakness legs	13 (100)	25 (100)	38 (100)
Distal weakness legs	6 (46)	8 (32)	14 (37)
Proximal arm weakness	12 (92)	22 (88)	34 (89)
Hand weakness	9 (69)	13 (52)	22 (58)
Wheelchair dependence	6 (46)	7 (28)	13 (34)
Autonomic symptoms	13 (100)	22 (92)	36 (95)
Blurred vision	6 (46)	7 (28)	13 (34)
Dry eyes	3 (23)	5 (20)	8 (21)
Dry mouth	13 (100)	21 (84)	34 (89)
Male sexual impotence	10 (83)	9 (75)	19 (79)
Micturition difficulty	3 (23)	6 (24)	9 (24)
Constipation	8 (62)	11 (44)	19 (50)
Orthostasis	5 (39)	5 (20)	10 (26)
Impaired ability to perspire	4 (31)	4 (16)	8 (21)
Cerebellar ataxia	1 (8)	1 (4)	2 (5)

Numbers in parentheses are percentages, unless otherwise indicated.

The most frequent presenting symptom was leg weakness (23 patients, 61%), or dry mouth (9 patients, 24%). Other presenting symptoms were sexual impotence in two patients and arm weakness, double vision, blurred vision and constipation in one patient each. The frequency of specific presenting symptoms did not differ between patients with and without SCLC. Three patients, all with SCLC (p=0.03), reported an acute onset of weakness; the others described the onset as gradual.

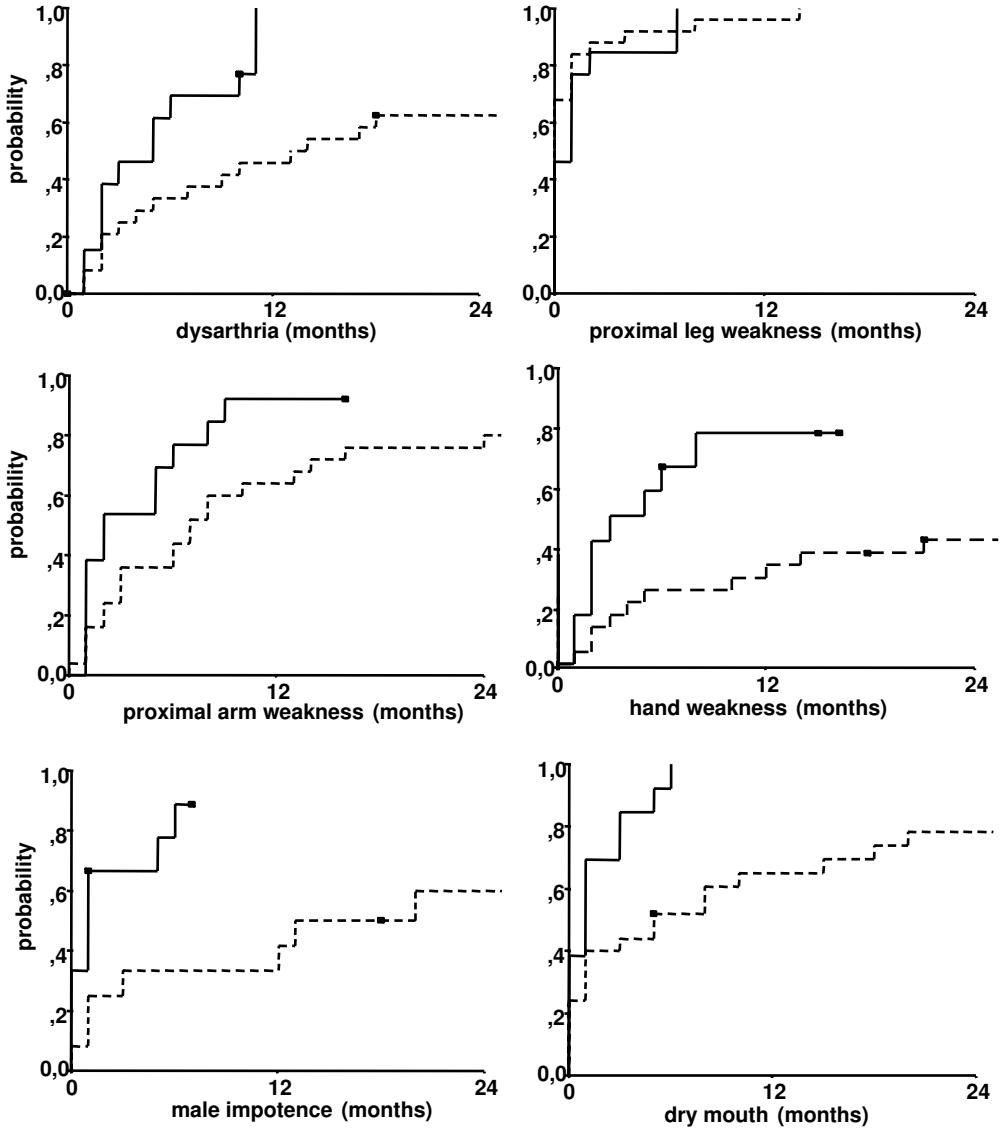
The frequency of different symptoms is shown in Table 1. No significant differences were found between the two groups. Figure 1 shows the probability of the eight most common symptoms that occurred since onset of LEMS in the two groups. In both, leg weakness was the most frequent presenting symptom. Subsequent symptoms occurred earlier during the disease course in patients with underlying SCLC, which reached significance for dysarthria (p=0.02), difficulty in chewing (p=0.046), hand weakness (p=0.008), dry mouth (p=0.003), and sexual impotence in men (p=0.009). In patients with SCLC, there were eight symptoms (proximal leg weakness, dry mouth, impotence, proximal arm weakness, double vision, hand weakness, slurred speech, constipation) with a median onset of less than six months after the onset of LEMS, compared to only two symptoms (proximal leg weakness, dry mouth) in patients without a tumour.

Discussion

In general, frequency of bulbar and autonomic symptoms was higher in our study than in previous ones, which did not use a structured interview or report the length of follow-up.[1,4,7] Moreover, after the initial symptom, subsequent symptoms occurred earlier in patients with underlying SCLC, suggesting a more progressive course of LEMS in accordance with our previous clinical impression. This could partly explain the shorter delay in SCLC-related LEMS diagnosis that we found in a recent epidemiological survey in the Netherlands.[2] Apparently, SCLC initiates a more aggressive immune reaction than the HLA-B8DR3 associated response in LEMS without a tumour,[8] yet calcium-channel antibody titres do not differ significantly between LEMS patients with and without SCLC.[9] Although the earlier occurrence of symptoms does not necessarily imply a more progressive severity of symptoms, the latter is practically impossible to study prospectively, as LEMS responds well to (immuno)therapy. Some of the patients with SCLC stated that the onset of weakness was acute, an observation also made by O'Neill et al.[1]

Our study could be subject to selection bias, as we could not interview all patients encountered in our epidemiological survey.[2] A review of their clinical records, however, did not suggest this, except for two patients with SCLC and a rapidly fatal

Figure 1. Probability of appearance of most common symptoms (in months) from onset of LEMS during the first two years. The solid line represents LEMS patients with SCLC and the broken line LEMS patients without SCLC. Censored cases of patients (end of follow-up) are indicated by squares.



course. A second bias could be a recall bias, as follow-up was often long, especially in patients without SCLC. Our data were, however, obtained by both a structured interview and from the patient's clinical records. We did not find important discrepancies between the two sources, except for autonomic symptoms, which had frequently not been documented in the clinical records. Finally, results could have been biased because the interviewer was not blinded to the SCLC status of the patients. We tried to reduce this bias by structuring the interviews.

In conclusion, the presence of a particular symptom associated with LEMS does not predict the presence of SCLC; however, in patients with rapidly progressive LEMS, the possibility of underlying lung carcinoma merits special concern.

Acknowledgements

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