The Lambert-Eaton myasthenic syndrome

Wirtz, P.W.

Chapter 2

The epidemiology of myasthenia gravis, Lambert-Eaton myasthenic syndrome and their associated tumours in the northern part of the province of South Holland

P.W. Wirtz,[1] M.G. Nijnuis,[1] M. Sotodeh,[1] L.N.A. Willems,[2] J.J. Brahim,[2] H. Putter,[3] A.R. Wintzen,[1] J.J. Verschuuren,[1] for the Dutch Myasthenia Study Group

[1]Departments of Neurology, [2]Pulmonology and [3]Medical Statistics, Leiden University Medical Centre, Leiden, The Netherlands

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Abstract

We studied the epidemiology of myasthenia gravis (MG) and the Lambert-Eaton myasthenic syndrome (LEMS), and their association with small cell lung carcinoma (SCLC) and thymoma, in a well defined region of the Netherlands. Available data on all the patients with MG, LEMS, thymoma or SCLC living between January 1, 1990 and December 31, 1999 in the northern region of South Holland, with a population of 1.7 million inhabitants, were evaluated. A total of 202 patients with MG (20 with thymoma) and ten patients with LEMS (seven with SCLC) were identified. LEMS was 46 times less prevalent (2.32×10^{-6}) than MG (106.1×10^{-6}), whereas the annual incidence rate of LEMS was 14 times lower (0.48×10^{-6}) than of MG (6.48×10^{-6}), reflecting the poor survival of LEMS patients with SCLC. SCLC was diagnosed in 1593 patients, seven (0.44%) of whom developed LEMS. Mean age at diagnosis of SCLC was significantly lower in SCLC patients with LEMS ($p=0.006$). A thymoma was diagnosed in 32 patients, of whom the ten patients with MG (31%) had a younger age at diagnosis of thymoma than the patients without MG ($p=0.27$). This study confirms the increasing prevalence of MG over the last few decades as reported by others, and underscores the relative rarity of LEMS. The frequency of LEMS in our patients with SCLC was lower than reported in previous studies. In patients with a SCLC or thymoma, the tumour was diagnosed at younger age in those, who had the associated myasthenic syndrome.

Introduction

Myasthenia gravis (MG) and the Lambert-Eaton myasthenic syndrome (LEMS) are both autoimmune diseases of the neuromuscular junction, characterised by variable weakness of oculobulbar and limb muscles. Oculobulbar involvement is more prominent in MG, while proximal leg weakness, lowered or absent tendon reflexes and autonomic dysfunction are characteristic findings in LEMS.[1,2] Pathogenic antibodies in MG are usually directed against the postsynaptic acetylcholine receptor, in LEMS against presynaptic voltage-gated calcium channels (VGCC). LEMS is presumably much rarer than MG, but so far the epidemiology of both disorders has not systematically been compared in one region. In about half of the patients with LEMS a small cell lung carcinoma (SCLC) is found.[1] Based on studies of seven groups of in total 778 SCLC patients, it was estimated that about 3% of the patients with a SCLC have LEMS.[3] However, the frequency of LEMS in SCLC patients has not been studied in one region over a prolonged period, which could result in a higher detection rate than in cross-sectional studies. In the present study, we compared the frequency of MG and LEMS, and determined the rate of occurrence in their related tumours over a 10-year period in a region of the Netherlands, with a population of 1.7 million inhabitants.

Patients and methods

Study area

The study period was from January 1, 1990, to December 31, 1999. The area under investigation was the northern region of the province of South Holland, the Netherlands, comprising 1,725,317 inhabitants at the end of the study period. The eleven hospitals in the area, among which one is a university hospital, all have neurological departments, and are located in The Hague (4 hospitals), Leiden (2), Zoetermeer (1), Voorburg(1), Gouda (1), Delft (1) and Leiderdorp (1).

Patients

All 51 neurologists and clinical neurophysiologists within the defined region participated. Each of them was asked to list his patients with MG and LEMS who had lived in the defined region in the study period. Furthermore, we checked the standard hospital databases using ICD-9 codes 358.0 and 358.1, the neurological databases using the Dutch coding system according to Kortbeek (codes 8.900, 8.910, 8,911, 8.912, 8.920, 8.940, 8.950), and the neuromuscular database in the university hospital. The patient records were studied using a structured checklist, on which demographic and clinical features of each patient were recorded. Clinical features included time of onset of symptoms, time of diagnosis, neurological signs and symptoms during the

disease course, and results of diagnostic tests. Incidence and demographic features of SCLC and thymomas were provided by the Comprehensive Cancer Centre West, a government funded institution, which systematically collects data on all neoplasms occurring in the population living within the study region. Population figures for the study area were published by the Statistics Netherlands.[4]

Inclusion criteria

Patients with a diagnosis of MG were included if they had antibodies against the acetylcholinereceptor, an abnormal EMG, or an unequivocal response to an acetylcholinesterase inhibitor, in addition to variable ocular, bulbar or generalised muscle weakness. An EMG was considered compatible with MG when a decrement of compound muscle action potential amplitude of more than 10% was seen during repetitive low frequency nerve stimulation (3-5 Hz). Patients with a diagnosis of LEMS were included if they had an abnormal EMG or anti-VGCC antibodies, in addition to variable muscle weakness. An EMG was considered compatible with LEMS when it showed an increment of more than 100% after maximal voluntary muscle contraction or repetitive high frequency stimulation (>20 Hz).

Diagnosis of SCLC was made by cytology or histology. Diagnosis of thymoma was made histologically.

Statistics

Incidences and prevalences were calculated with 95% confidence intervals (CI) based on the Poisson distribution. Differences in continuous variables were tested with the independent-samples t-test.

Results

A total of 202 patients with MG and ten patients with LEMS were identified (Table 1). In the group of 202 MG patients, 17 patients had died before January 2000 and two patients were lost to follow-up. Accordingly, the number of surviving patients by

Table 1. Characteristics of the patients

Disease	MG n=202	thymoma n=32	LEMS n=10	SCLC n=1593
male: female	78:124	13:19	6:4	1116:477
mean ± SD age at onset (years)	48 ± 22	60 ± 13	58 ± 14	67 ± 10
associated tumour (n, %)*	20 (10%)	-	7 (70%)	-
associated syndrome (n, %)*	-	10 (31%)	-	7 (0.44%)

MG: myasthenia gravis; LEMS: Lambert-Eaton myasthenic syndrome; SCLC: small cell lung carcinoma
*thymoma associated with MG, SCLC associated with LEMS.

January 1, 2000, was at least 183 and the point prevalence 106.1 x 10^{-6} (95% CI 90.7-124.3). Prevalence corrected for age was higher in females than in males up to the age of 60 years, was equal for both sexes aged 60-80 years, but higher in male inhabitants over 80 years (Figure 1). The annual incidence of MG was 6.48 x 10^{-6} (95% CI 5.35-7.84). In both sexes, the age and sex specific incidence was highest in inhabitants over 60 years (Figure 2). The mean age of onset was 48 years (range 4-90), and higher in male (54 years) than in female patients (45 years; t=2.89, p=0.004). In 41 patients (20%) MG remained restricted to ocular muscles during the disease course. Sixty-nine patients (34%) were thymectomised, of whom 20 patients (29% of thymectomised patients) had a thymoma. The most frequently used diagnostic test was the acetylcholine receptor antibody assay (Table 2), which was positive in 154 of 195 patients (79%). In 25 seronegative patients diagnosis was supported by an abnormal acetylcholine receptor antibody assay (Table 2), which was positive in 154 of 195 patients (79%). In 25 seronegative patients diagnosis was supported by an abnormal electromyographic test, in the remaining 16 seronegative patients by a positive cholinesterase inhibitor test.

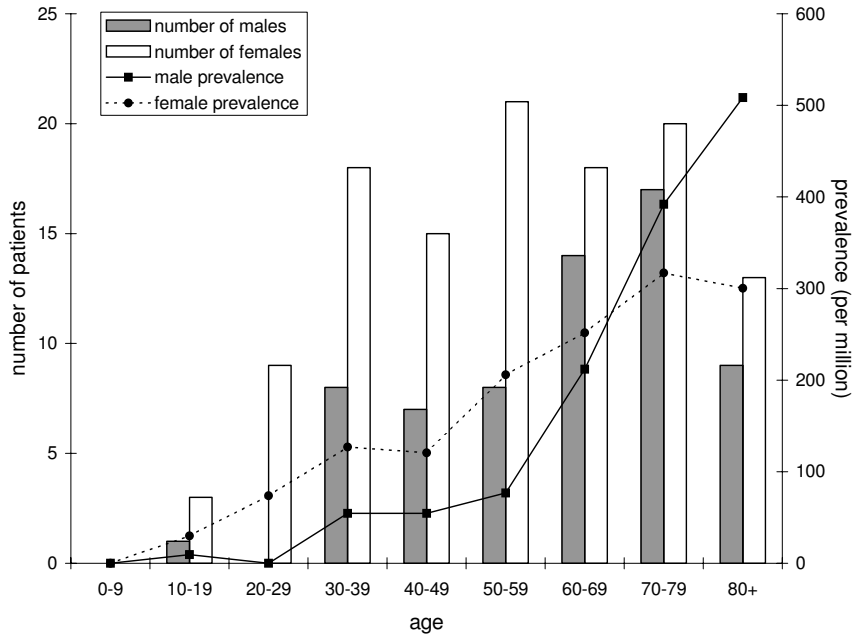

Figure 1. Number of patients and age and sex specific prevalence of MG on January 1, 2000

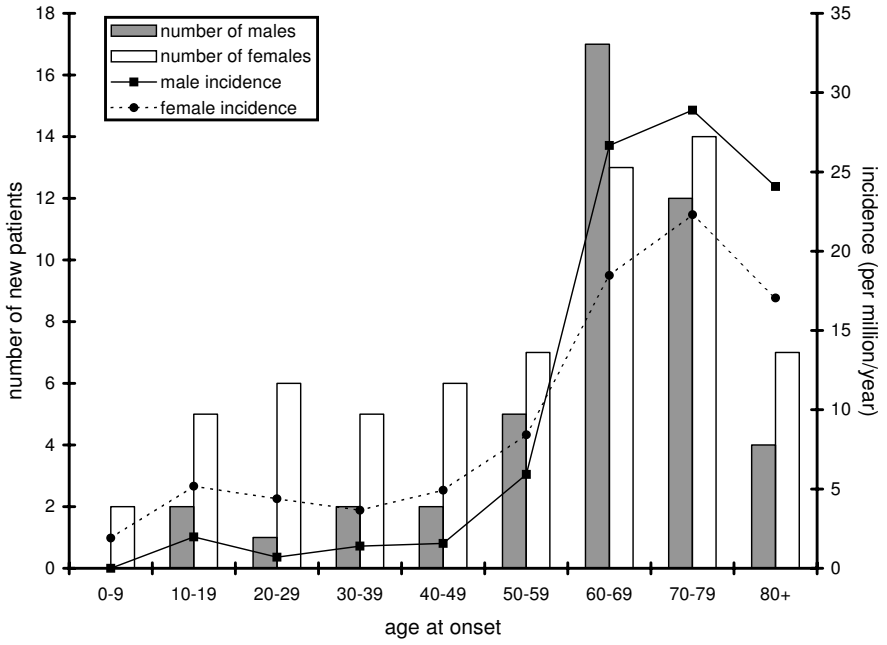

Figure 2. Age and sex specific onset and annual incidence of MG per million population during the study period

During the study period, a thymoma was diagnosed 32 times, the annual incidence being 1.90 x 10^{-6} (95% CI 1.30-2.68). Ten of these patients (31%) had MG. Mean age of diagnosis of thymoma of these ten patients was 57 ± 15 years, and the mean age of diagnosis of thymoma patients without MG 62 ± 12 years (t=1.12, p=0.27).
LEMS was diagnosed eight times in the study period, the annual incidence being 0.48 x 10^{-6} (95% CI 0.20-0.94), i.e. 14 times lower than the incidence of MG. Two patients had been diagnosed before 1990. Seven patients with LEMS had a SCLC, six of whom died during the study period. The one patient surviving on January 1, 2000 had a disease duration of seven years. The incidence for SCLC associated LEMS was 0.42 x 10^{-6}/year (95% CI 0.17-0.86). No other tumours than SCLC were found. By January 1, 2000, four patients with LEMS were living within the defined region, giving a point prevalence of 2.32 x 10^{-6} (95% CI 0.63-5.94), being 46 times lower than the prevalence of MG.
SCLC was diagnosed in 1593 patients, resulting in an annual incidence of 94.7 x 10^{-6} (95% CI 80.0-109.3). In seven of these patients (0.44%; 95% CI 0.18-0.90) LEMS was

Table 2. Diagnostic tests in 202 patients with myasthenia gravis

Investigation	Performed (n, %)	Positive (n, %)*
AChR antibody assay	195 (97%)	154 (79%)
Electromyogram	125 (62%)	73 (58%)
Acetylcholinesterase inhibitor test	122 (60%)	112 (92%)

AChR acetylcholine receptor

% of patients in which test is performed

diagnosed. In six cases, LEMS was diagnosed before the detection of the tumour. In the group with SCLC, patients with LEMS averaged 57 ± 16 years of age at diagnosis of SCLC, and patients without LEMS 67 ± 10 years (t=2.80, p=0.006).

Discussion

This study presents the epidemiological features of MG, LEMS, thymoma and SCLC in one defined region. LEMS was 46 times less prevalent than MG, thereby underscoring the rarity of LEMS. However, the annual incidence of LEMS was only 14 times lower than the incidence of MG. This difference in ratios presumably reflects the poor survival of LEMS cases associated with SCLC.

The epidemiology of MG has been studied extensively. Incidence and prevalence in our study are comparable with most other recent studies, which confirms the evidence for an increasing prevalence of MG over the last decades, probably as a result of prolonged survival with the disease, improved diagnostic tools, ageing of the population and a high incidence in the very old.[5,6] In an epidemiological study of MG in 1961-1965 in Amsterdam, a city close to our region, both the annual incidence and the prevalence of MG were half that in our study (3.1 and 53 per million).[2] In the latter study age adjusted prevalence in both sexes declined in patients over 60 years,[2] whereas prevalence in our survey continued to increase with age. In our study more than half (57%) of the newly diagnosed patients had onset over the age of 60, against only 14% in the survey of Amsterdam,[2] supporting the idea of increased prevalence of MG as a result of the high incidence in an increasingly aged population.[6] Moreover, it is possible that the AChR antibody assay, which was not yet available in the sixties, has enabled detection of MG in elderly patients who would not have been diagnosed with MG otherwise.

Up to now the epidemiology of LEMS has not been studied systematically. In a retrospective study of the epidemiology of MG in Denmark, patients with LEMS were found as well, the annual incidence of LEMS being 0.17 x 10^{-6}.[7] This was lower than the incidence of 0.48 x 10^{-6} (95% CI 0.20-0.94) we found. However, the Danish study

was not designed to include patients with LEMS.[7] On the other hand, we found a frequency of only 0.44% (95% CI 0.18-0.90) of LEMS among SCLC patients, whereas this frequency was reported to be close to 3% by others.[3] The estimated 3% was derived from several, mostly prospective studies of relatively small groups of patients with SCLC, in which the patients were screened clinically or electrophysiologically for LEMS.[3] In our survey, diagnosis of LEMS could have been missed in some patients with SCLC because of attribution of weakness to the poor general physical condition, or because patients with SCLC were not routinely examined by a neurologist. Moreover, the clinical resemblance between LEMS and MG might have resulted in an erroneous diagnosis of seronegative MG in patients with LEMS. However, the frequency of seronegative patients in the MG group was not higher than generally reported,[6] nor did we encounter cases in which such confounding was suspected during revision of clinical and electromyographic features of these patients. Another possible source for underestimation could have been a lack of registration of patients, which we tried to overcome by consulting both the databases and the neurologists themselves.

In the group of patients with SCLC the mean age at which the SCLC was diagnosed was ten years lower in the patients with concurrent LEMS. An analogous difference of five years in mean age at diagnosis was seen in thymoma patients, although this did not reach significance. This difference in thymoma patients was reported previously.[8,9] Early detection of the tumour because of the presence of the neurological syndrome could partly explain the younger age, but the size of the difference in the SCLC patients also suggests that patients having a tumour at younger age are more prone to develop the associated myasthenic syndrome.

In conclusion, the results of this study confirm that the prevalence of MG has increased over the last few decades, probably because of aging of the population and improved diagnosis. This study also underscores the relative rarity of LEMS. Comparison with other studies leads us to suspect that this rarity might partly be explained by failure to diagnose LEMS in patients with SCLC. Furthermore, our results suggest that patients having a SCLC or a thymoma at younger age have a higher risk to develop LEMS or MG.

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