The Lambert-Eaton myasthenic syndrome

Wirtz, P.W.

Chapter 7

Associated autoimmune diseases in patients with the Lambert-Eaton myasthenic syndrome and their families

P.W. Wirtz, J. Bradshaw, A.R. Wintzen, J.J. Verschuuren

Department of Neurology, Leiden University Medical Centre
Leiden, The Netherlands

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Abstract

In view of the clustering of autoimmune diseases (AID), we studied the frequency and nature of additional AID in patients with the Lambert-Eaton myasthenic syndrome (LEMS) and their family members, in both small cell lung carcinoma (SCLC) related and non-tumour (NT) related cases. Additional AID in patients with LEMS were assessed by interviewing the patient and studying the medical record. Family histories up to second-degree family members were established by interviewing patients, controls and family members. Forty-four patients with LEMS were assessed, of whom eighteen (41%) had SCLC. In the NT group seven patients (27%) had an additional AID, in the SCLC group two (11%) (p=0.20). Thyroid disorder (five patients) and insulin dependent diabetes mellitus (two patients) were the most common AID. AID were significantly more frequent in families of patients with NT-LEMS (64%) than in control families (27%) (p=0.002), which was not found in SCLC-LEMS (36%, p=0.53). Affected family members were linked to the NT-LEMS patient through the maternal line in all cases. In conclusion, AID were more frequently found in LEMS patients without a tumour and their families, which could not be shown for SCLC-LEMS. This suggests that NT-LEMS shares immunogenetic factors with other AID. In families of NT-LEMS, a remarkable preponderance of maternal inheritance was seen, as has been reported previously in myasthenia gravis.

Introduction

The Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disease (AID), in which antibodies against voltage-gated calcium channels cause muscle weakness and autonomic dysfunction. In more than half of the patients a small cell lung carcinoma (SCLC) is found, which is thought to be the initiating factor of LEMS by expressing voltage-gated calcium channels in an immune stimulating environment.[1-3] It has been suggested that both patients and their family members often have other AID, especially in patients without underlying malignancy.[2] However, this suggestion has not been investigated by a systematic family study in patients with LEMS. Furthermore, it is not known whether this relation, if real, would apply for LEMS patients with SCLC as well as for patients without SCLC. To examine the frequency and nature of AID in LEMS patients and their families, 44 LEMS patients and 39 related families were studied.

Patients and methods

The patients with LEMS assessed in this study had all been examined consecutively by the same physician (PWW) as part of a nationwide research project. All included patients had a definite diagnosis of LEMS based upon electrophysiological features or serum P/Q-type calcium channel antibodies,[4] in addition to variable muscle weakness. EMG criteria were a low compound muscle action potential amplitude as well as an increase of this amplitude of more than 100% following high frequency repetitive nerve stimulation or following maximal voluntary contraction.[5] This study was approved by the Medical Ethical Committee of the Leiden University Medical Centre. All patients gave informed consent before inclusion.

We assessed additional AID in patients by interviewing and examining the patient and studying the medical records. AID were considered established if there was adequate clinical and laboratory data to confirm the diagnosis. The control group consisted of spouses, partners or friends of the patients, and their families, who were selected by the patients themselves. The presence of AID in families of patients or controls was systematically explored as following: 1. family histories up to second degree family members were established by interviewing each patient or control and any accompanying family members, 2. a pedigree was made in which family members with AID were indicated, 3. a list of AID was used to check if any AID were forgotten, and 4. each recorded pedigree was sent to the index patient or control for verification and, if necessary, correction. The list of AID included

- Addison's disease,
- insulin dependent diabetes mellitus (IDDM),

- myasthenia gravis (MG),
- pernicious anaemia,
- psoriasis,
- rheumatoid arthritis,
- systemic or discoid lupus erythematosus,
- thyroid disorders,
- vitiligo.

No attempt was made to confirm the family history through medical records. Information about offspring was not included, as often the partners and their families served as controls.

Prevalence of AID in patients were compared with their prevalence in the general population, which was based on figures of the Statistics Netherlands, a department of the Ministry of Economic Affairs,[6] and figures from Dutch epidemiological studies.[7-9] The overall prevalence of AID in the general population was calculated by adding these prevalences found in the literature and were corrected for sex distribution. Prevalence of AID in families was compared using a χ^2 or Fisher's exact test when appropriate. Median values were compared using the Mann Whitney test. A p-value less than 0.05 was considered significant.

Results

Patient characteristics

Forty-four patients with LEMS were analysed, of whom 25 (59%) were males. Eighteen (41%) patients had a SCLC. In the group with SCLC only four patients (22%) were female, whereas there were 15 female patients in the group without a tumour (58%) (p=0.02). The median age at onset of LEMS was higher in the SCLC group (57 vs. 52 years; p=0.04). The median age at examination was 58 years (range 32-91) and not significantly different between the two groups.

Additional AID in patients with LEMS

Nine patients (20%) had a (history of) an AID in addition to LEMS (table 1), thyroid disorder being the most common (five patients, 11%), followed by
IDDM (two patients, 5%). One patient had more than one additional AID. In the NT group seven patients (27%) had an additional AID; five female (33% of female NT) and two male patients (18% of male NT)(p=0.66). In the SCLC group two patients (11%), both females (50 % of female SCLC), had an additional AID, whereas none of

Table 1. Additional autoimmune diseases in 44 patients with the Lambert-Eaton myasthenic syndrome

Sex	SCLC	Age at onset of LEMS (years)	Additional autoimmune disorder
F	-	30	Thyroid disorder + discoid lupus erythematosus
F	-	46	Myasthenia gravis
F	-	53	Insulin dependent diabetes mellitus
F	-	54	Thyroid disorder
F	-	56	Thyroid disorder
M	-	33	Rheumatoid arthritis
M	-	53	Insulin-dependent diabetes mellitus
F	+	35	Thyroid disorder
F	+	59	Thyroid disorder

SCLC small cell lung carcinoma; *LEMS* Lambert-Eaton myasthenic syndrome; *F* female; *M* male

the male patients with SCLC had suffered an AID other than LEMS (p=0.04). The higher frequency of AID in NT-LEMS than in SCLC-LEMS was not significant (p=0.20). Median age at onset of LEMS in patients with additional AID did not differ significantly from that of patients without additional AID. All additional AID were diagnosed before onset of LEMS. AID were more frequent in LEMS patients than in the general population, but this difference was significant only in the NT-LEMS patients (table 2).

AID in family members

Adequate family history could be taken from 39 of these patients (14 SCLC-LEMS, M:F=11:3, and 25 NT-LEMS, M:F=11:14); five patients did not give consent for this part of the study. In total 247 first degree and 301 second degree family members of patients were studied. We studied the families of 51 controls (M:F=20:31, median age 62 years, range 30-82). Results are shown in table 3. AID in families were more frequently found in NT-LEMS families than in control families, this difference being significant when only first-degree (p=0.014), as well as when both first- and second-degree family members were considered (p=0.002). These differences were not

Table 2. Autoimmune diseases in the Lambert-Eaton myasthenic syndrome and the general population

	no tumour	population[a]	SCLC	population[a]
Thyroid disorder	0.12	0.015	0.11	0.009
IDDM	0.078	0.0047	-	-
RA	0.038	0.0082	-	-
MG	0.038	99×10^{-6}	-	-
Total AID	0.27 (0.12-0.48)[b]	0.029	0.11 (0.01-0.36)[b]	0.022

SCLC small cell lung carcinoma; *IDDM* insulin dependent diabetes mellitus; *RA* rheumatoid arthritis; *MG* myasthenia gravis; *AID* autoimmune disorder

[a]corrected for sex distribution in patient group, based on references 16, 18, 19 and 21

[b]95% confidence interval

significant in SCLC-LEMS (p=0.71 and p=0.53). Most frequently reported AID in family members were IDDM (21 family members), thyroid disease (12), and rheumatoid arthritis (11). Other reported disorders in family members were psoriasis (2), systemic lupus erythematosus (1) and vitiligo (1). In NT-LEMS, affected family members were linked to the LEMS patient through the maternal line in 12 patients, through both the maternal and paternal line in three patients, but never through the

Table 3. Frequency of autoimmune disorders in families of patients with Lambert-Eaton myasthenic syndrome

	no tumour	SCLC	controls
no. families	25	14	51
total number of relatives	380	168	730
mean pedigree size	15	12	14
AID in 1st degree family	11 (44%)[a]	3 (21%)	9 (18%)
families with AID (1st and 2nd)	16 (64%)[b]	5 (36%)	14 (27%)
families with thyroid disorder	5 (20%)	2 (14%)	5 (10%)
families with IDDM	8 (32%)[c]	2 (14%)	6 (12%)
families with rheumatoid arthritis	5 (20%)	2 (14%)	6 (12%)
families with SLE	0 (0%)	1 (7%)	0 (0%)
families with pernicious anaemia	0 (0%)	0 (0%)	1 (2%)

SCLC small cell lung carcinoma; *AID* autoimmune disorder; *IDDM* insulin dependent diabetes mellitus; *SLE* systemic lupus erythematosus

[a]OR=3.7 (95%CI=1.3-10.7); p=0.014 (compared to controls)

[b]OR=4.7 (95%CI=1.7-13.1); p=0.002 (compared to controls)

[c]OR=3.5 (95%CI=1.1-11.7); p=0.033 (compared to controls)

paternal line only (Figure 1). In SCLC-LEMS, this link was through the maternal line in four cases and the paternal line in one case.

Discussion

We have shown evidence for an increased frequency of additional AID in patients with LEMS without a tumour and in their family members, which was not apparent in LEMS patients with an underlying SCLC. This suggests that NT-LEMS has a common immunogenetic background with other AID, and could point to a difference in immunogenetic background between NT- and SCLC-LEMS.

Frequency of AID in patients with LEMS

The frequency of AID in patients with NT-LEMS was clearly higher than in the general population. In a study of 50 LEMS patients 24% of tumour related cases and 28% of idiopathic cases had an additional immunological disorder, which is in line with our results with regard to NT-LEMS, whereas the frequency in our SCLC patients was lower.[2] Another study of 73 LEMS patients reported AID in 19% of 42 NT patients, and no additional AID in 31 SCLC patients.[10] Organ-specific autoantibodies, other than anti-VGCC antibodies, were also reported to be present more frequently in NT patients than in a control group, which was not shown in SCLC patients.[11] Other epidemiological studies on autoimmune diseases gave an overall prevalence of AID of 2.0%-2.3% in their control populations,[12,13] which was similar to the percentages we calculated.

Frequency of AID in family members

An increased frequency of AID was also found in the family members of patients with NT-LEMS, but not in those of patients with SCLC. A family history of AID in LEMS patients was reported in only one previous study, in which 1/25 SCLC (2.5%) and 6/25 NT patients (24%) had a family history of organ-specific AID.[2] These frequencies were probably so low because data were obtained from a retrospective review of the case records. Most frequently found AID in both patients and family members were thyroid disease and IDDM, probably reflecting their high prevalence compared with other AID.[14] Moreover, the association of NT-LEMS with the HLA-DR3DQ2 haplotype is also found in IDDM and Grave's disease, and could therefore play a role in the clustering of these AID within LEMS patients and their families.[15-18] In SCLC-LEMS, no such association is found.[19] Although certain gene regions, including HLA, are likely to cause susceptibility to more than one AID, which could explain the clustering of diseases within the same families and individuals, it has been shown in several AID that HLA alone cannot account for familial clustering of them.[14,20]

Figure 1. Family history of autoimmune disease in patients with the Lambert-Eaton myasthenic syndrome without a tumour. Squares represent males and circles females. Patients with the Lambert-Eaton myasthenic syndrome (proband) are shown as filled symbols, family members with an autoimmune disease as hatched symbols. DM, insulin dependent diabetes mellitus; LEMS, Lambert-Eaton myasthenic syndrome; pso, psoriasis; RA, rheumatoid arthritis; TD, thyroid disorder; vit, vitiligo.

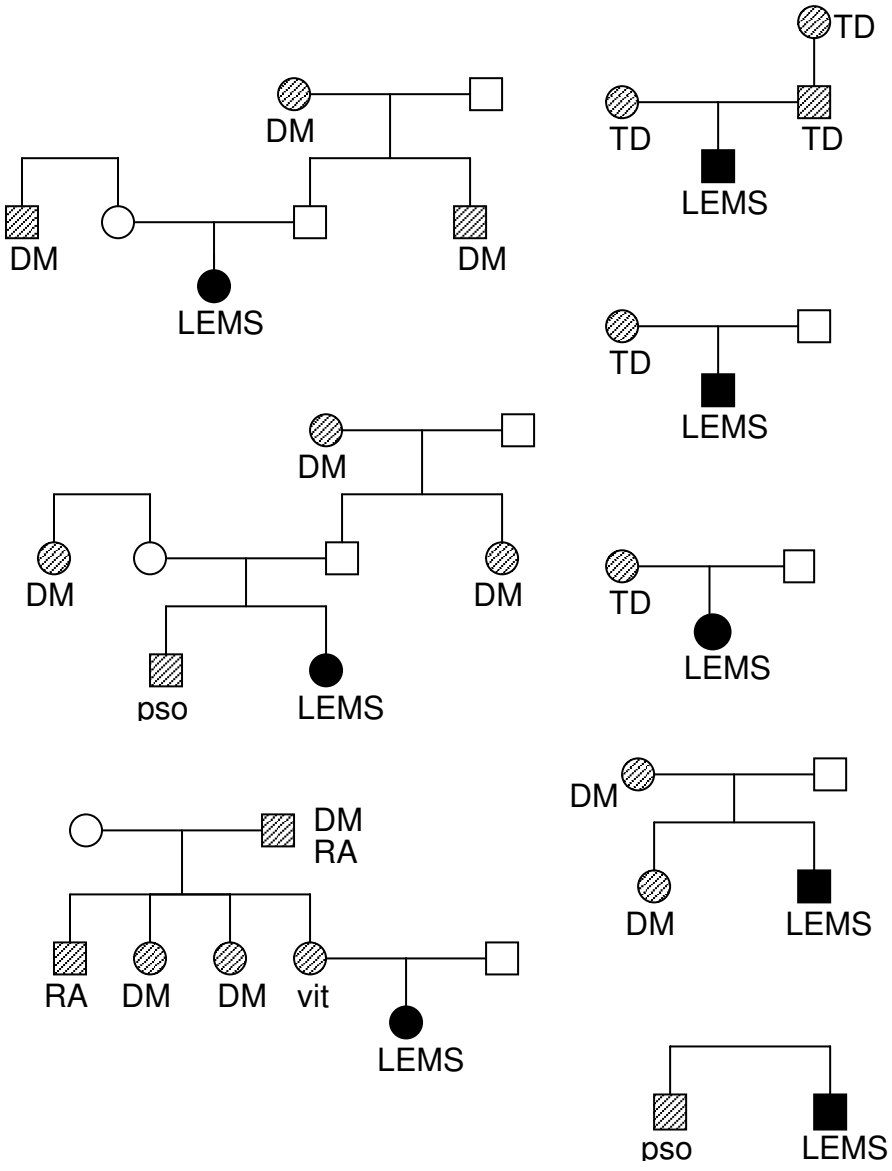
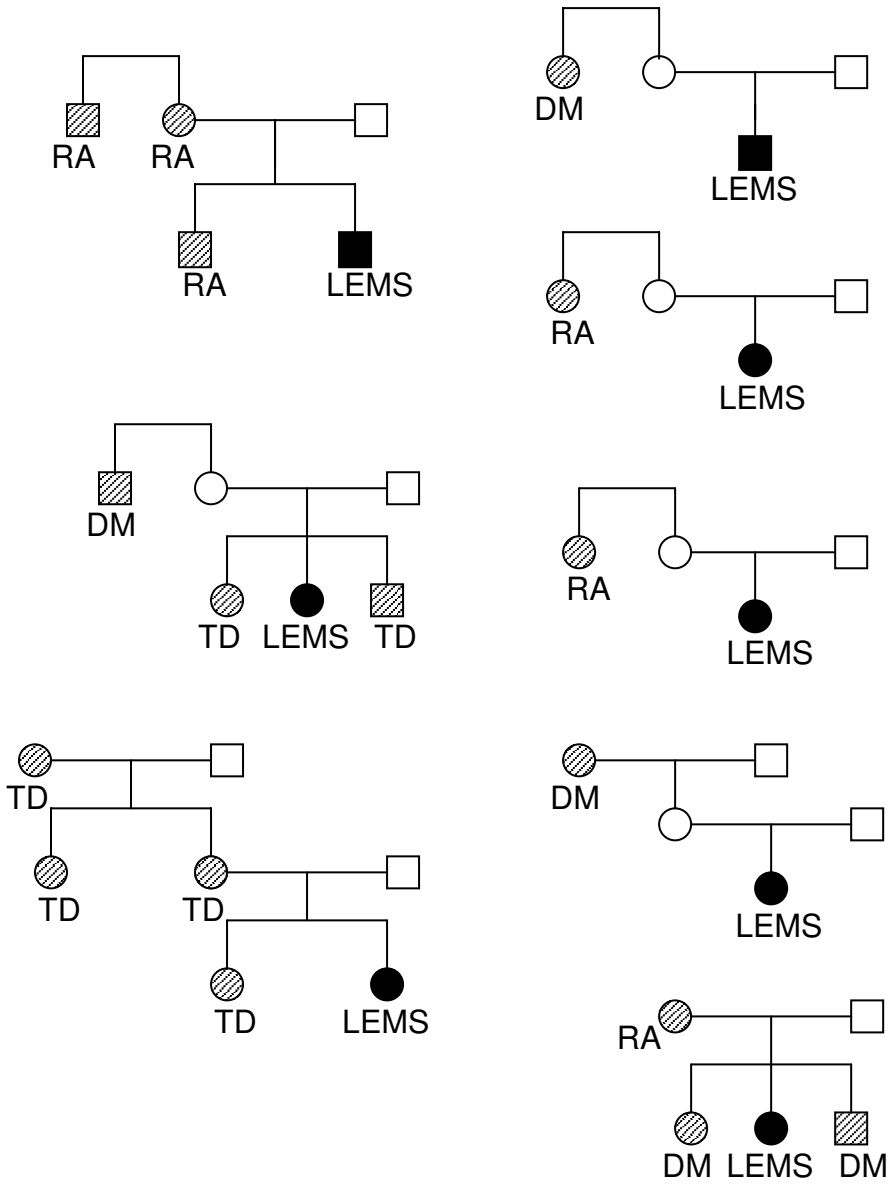


Figure 1 (continued).



Preponderance of maternal inheritance

In patients with MG, like LEMS an antibody-mediated disorder of the neuromuscular junction, the frequency of associated AID is reported to vary from 8% to 26%,[21] which is in line with the frequency found in LEMS. In a family study of MG, 13 of 44 (30%) patients had a family history of AID in first and second degree family members, all related to the patients through the maternal line.[22] This remarkable preponderance of maternal inheritance was also seen in our families. In MG, several explanations were considered but, as in MG, chance, biased ascertainment, female preponderance or X-linked susceptibility seem not to explain the preponderance in LEMS.[22,23] In these studies the authors suggested an effect of maternofetal interactions on the developing immune system of the fetus.[22,23] Recently, evidence has indicated that exposure of the fetus to non-inherited maternal HLA antigens has a life-long effect that could influence disease susceptibility.[24] Other explanations could be genomic imprinting with exclusive expression of the maternal allele, or mutations in mitochondrial DNA, which is almost strictly maternally inherited.

We are aware of the several limitations of this study. Due to the rarity of the disorder, we could only study a relatively small patient group. The association of NT-LEMS with other AID diseases in LEMS patients may partly be artificial, because presence of one disease is more likely to lead to detection of another. However, in all cases LEMS developed after the additional AID, which could have led to easier recognition of LEMS in patients, but not the other way about. Case ascertainment in family members was not done by checking medical records. Thus, results are presumably influenced by a recall bias or lack of knowledge of the disorders by the respondents. However, we feel that, as both patient and control group were investigated in the same manner, a comparison is legitimate.

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