The Lambert-Eaton myasthenic syndrome

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Chapter 4

Difference in distribution of muscle weakness between myasthenia gravis and the Lambert-Eaton myasthenic syndrome

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J Neurol Neurosurg Psychiatry 2002;73:766-768

Abstract

Myasthenia gravis (MG) and the Lambert-Eaton myasthenic syndrome (LEMS) may have a similar distribution of muscle weakness. Deciding for the diagnosis MG or LEMS on clinical grounds may therefore be difficult. We compared the localization of initial muscle weakness and distribution of weakness at the time of maximum severity between 101 patients with MG and 38 patients with LEMS. In MG, initial weakness involved extraocular muscles in 59%, bulbar muscles in 29%, and limb muscles in 12% of the patients. In LEMS no patient had ocular weakness, 5% bulbar weakness and 95% weakness of the limbs as first symptom ($p<0.001$). At the point of maximum severity, weakness in MG was purely ocular in 25%, oculobulbar in 5%, restricted to the limbs in 2% and present in both oculobulbar muscles and limbs in 68% of the patients. At this point, none of the LEMS patients had weakness restricted to extraocular or bulbar muscles ($p=0.002$). The legs were affected in all LEMS patients, whereas in 12 patients with generalized MG limb weakness was restricted to the arms ($p=0.024$). In conclusion, in a patient suspected to have a myasthenic syndrome, whose first symptom is ocular weakness, LEMS is virtually excluded. Furthermore, limb weakness confined to the arms is only found in generalized MG, and not in LEMS. Generally, muscle weakness in MG tends to develop in a craniocaudal direction, and in the opposite direction in LEMS.

Introduction

Myasthenia gravis (MG) and the Lambert-Eaton myasthenic syndrome (LEMS) are both acquired autoimmune disorders characterized by a defective neuromuscular transmission. Several clinical differences between MG and LEMS are known; for example, decreased tendon reflexes and autonomic dysfunction are features of LEMS but not of MG.[1] Nevertheless, MG is the most common alternative diagnosis in patients with LEMS. [1] It may be difficult to decide on a diagnosis of MG or LEMS on clinical grounds, as the distribution of muscle weakness may be similar in the two diseases. Although there are no studies comparing the distribution of muscle weakness between the disorders, some reports have stressed involvement of the cranial muscles in MG and predominant limb muscle weakness in LEMS.[1-3] To study the diagnostic value of this observation, we compared the localization of muscle weakness during the disease course in patients with MG and LEMS.

Methods

We carried out a retrospective survey of all patients with a diagnosis of MG in our hospital between 1990 and 2000. Patient records were collected using the Leiden neuromuscular database. Records of patients with a diagnosis of LEMS between 1998 and 2000 were collected from all eight university hospitals in the Netherlands, as part of a national research project. All patients had been examined by at least one of the authors (ARW, JJV, PWW). Patient records were reviewed using a structured checklist to record all signs and symptoms and results of laboratory and electromyographic testing. The inclusion criteria for patients with MG were acquired variable muscle weakness, and at least one of the following: (1) the presence of anti-acetylcholine receptor (AChR) antibodies, (2) a decrement larger than 10% on repetitive nerve stimulation without incremental response, or (3) an unequivocal positive response to an acetylcholinesterase inhibitor test. Inclusion criteria for LEMS were acquired variable muscle weakness, and either the presence of serum anti-voltage gated calcium channel (VGCC) antibodies, or an increment larger than 100% on high-frequency repetitive nerve stimulation or after maximum voluntary contraction.[4] Patients with incomplete clinical data were excluded from analysis.

The localization of initial weakness was classified as ocular (ptosis, diplopia), bulbar (dysphagia, dysarthria), or limb weakness. Distribution of weakness at the time of maximum disease severity was classified as (1) purely ocular, (2) purely oculobulbar, (3) generalized, e.g. ocular or bulbar and limb muscle weakness, or (4) limb muscle weakness. When weakness of the limbs was present, we classified its localization as both arms and legs, arms only or legs only.

Statistical comparison of data between the two groups was done with a χ^2-test. Positive likelihood ratios of the localizations of initial weakness for a diagnosis of MG were calculated.

Results

Patients and confirmation of diagnosis

In all, 172 patients diagnosed with MG or LEMS were found. Twenty-one patients were excluded because they did not fulfil our inclusion criteria, and 12 patients because of incomplete clinical data. After exclusion, data from 101 patients with MG and 38 patients with LEMS were analysed (table 1). The diagnosis of MG was confirmed by presence of anti-AChR antibodies in 72 of 97 patients tested (74%). In 18 of the 25 seronegative patients (60%) EMG confirmed the diagnosis. All seronegative patients with MG and without EMG abnormalities (11 patients) had an unequivocal positive response to an acetylcholinesterase inhibitor test. The diagnosis of LEMS was confirmed by EMG in all patients with LEMS. They all had an increment of CMAP amplitude of more than 100% on repetitive nerve stimulation. All patients with LEMS were tested for anti-AChR antibodies, and were negative for these antibodies.

Localization of initial weakness

Localization of initial weakness was significantly different between MG and LEMS (χ^2=82.93, p<0.001) (Figure 1). The positive likelihood ratios for having MG and not LEMS was infinite for ocular onset, 5.5 for bulbar onset and 0.12 for onset in the limbs.

Table 1. Characteristics of patients with myasthenia gravis (MG) and the Lambert-Eaton myasthenic syndrome (LEMS)

	MG (n=101)	LEMS (n=38)
man:woman (% man)	36:65 (36)	22:16 (58)
mean age at onset (range)	41 years (5-78)	50 years (11-76)
associated tumour*	13 (13%)	14 (37%)
median interval between disease onset and tumour diagnosis (range)	8 months (0-62)	3 months (1-54)
disease-specific antibody positive†	72/97 (74%)	32/36 (89%)
immunosuppression or chemotherapy	58 (58%)	21 (55%)‡
mean follow-up (range)	9 years (1-42 years)	7 years (1-38 years)

*thymoma in MG, small cell lung carcinoma in LEMS

†anti-acetylcholine receptor antibodies in MG, or anti-P/Q-type voltage gated calcium channel antibodies in LEMS

‡all 14 patients with LEMS and SCLC received chemotherapy

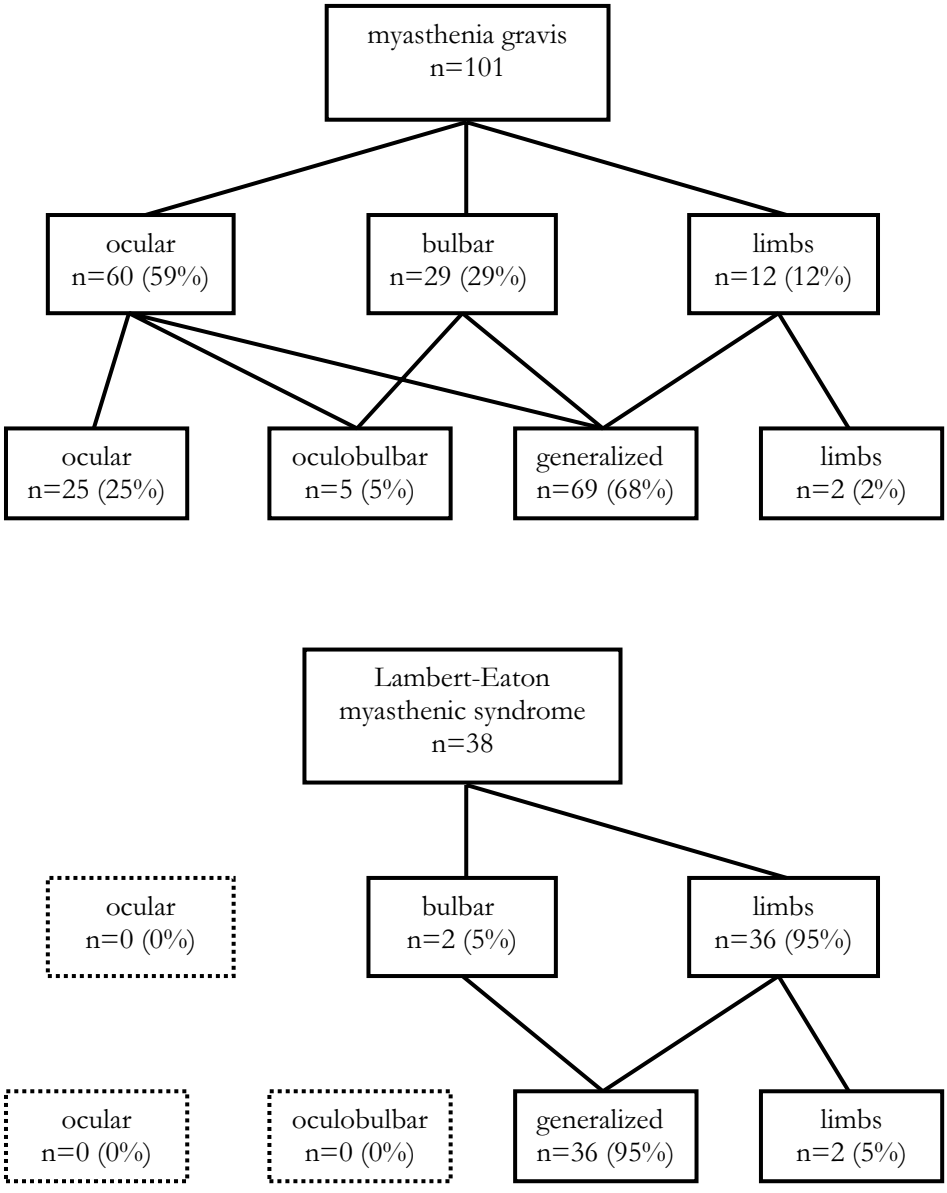

Figure 1. Localization of initial weakness (2nd box level) and weakness at time of maximum severity (3rd box level) in myasthenia gravis and the Lambert-Eaton myasthenic syndrome

Distribution of muscle weakness at maximum disease severity

At the point of maximum disease severity, 69 patients with MG (68%) had generalized MG. Among the 62 patients with MG whose disease began with ocular weakness, the weakness weakness remained purely ocular in 25 (40%). Among 29 patients with bulbar onset, muscle weakness remained restricted to oculobulbar muscles in three patients (10%). No purely bulbar weakness was detected among these three. In two patients, both women, symptoms remained restricted to limb muscles. Both these patients had anti-acetylcholine receptor antibodies and a young age at onset (19 and 20 years), with a follow-up of seven and two years, respectively. In the LEMS group, two male patients had weakness restricted to the limbs at the point of maximum disease severity. The first had an age at onset of 18 years, no tumour and a follow-up of 38 years; the second had an age at onset of 49 years and died of a small cell lung carcinoma 16 months after the onset of symptoms of LEMS. Unlike MG, we did not find any LEMS patient with pure ocular or mixed oculobulbar weakness without involvement of limbs at the point of maximum disease severity (χ^2=15.26, p=0.002). Among 70 patients with MG and weakness of limbs, three (3%) had weakness restricted to the legs and 12 (12%) to the arms; in patients with LEMS, weakness of the extremities was restricted to the legs in 3 patients (8%), while no LEMS patient had weakness restricted to arms (χ^2=7.49, p=0.024).

In the 25 seronegative patients with MG, localization of initial weakness did not significantly differ from the whole MG group, but at maximum disease severity, weakness restricted to ocular muscles was seen in 14 patients (56%) and generalized weakness in the other 11 patients (44%).

Discussion

We found differences in distribution of muscle weakness between patients with LEMS and MG which will help the clinician to distinguish between these disorders. At the onset of MG, ocular symptoms were by far the most common (59% of the patients), whereas an ocular onset did not occur in patients with LEMS. We are not aware of other studies comparing clinical characteristics between patients with MG and LEMS, but several studies describing only patients with MG have found extraocular muscle weakness to be the most common initial symptom,[5-7] while in a clinical description of 50 LEMS patients none had an ocular onset.[1] Thus a patient presenting with purely ocular weakness in whom a myasthenic syndrome is suspected is very unlikely to have LEMS.

At the point of maximum disease severity, more than half the patients with MG and ocular onset had developed generalized weakness, whereas in almost all patients with LEMS, limb weakness was followed by oculobulbar weakness. Thus, although both diseases tend to progress towards generalized weakness, weakness in MG generally spreads in craniocaudal direction, while in LEMS it spreads in the opposite direction. The 60% generalization rate of ocular MG that we found is in agreement with previous studies.[5,8] Two patients with MG had weakness which remained confined to the extremities during the disease course; this has been designated the chronic "limb-girdle" form of MG.[9] In patients with limb muscle weakness, the weakness remained restricted to the arms in some patients with MG, but not in LEMS patients, who all had weakness of the legs, most often accompanied by arm weakness, at the point of maximum disease severity. This suggests that a myasthenic patient in whom limb weakness is confined to the arms only, has MG and not LEMS.

Several factors have been suggested to explain the prominent involvement of extraocular muscles in MG. These muscles are different from skeletal muscles, having higher firing frequencies, tonic muscle fibers which are absent in skeletal muscles, and different acetylcholine receptor expression patterns. All these properties may predispose them to neuromuscular blockade in MG.[10,11] We observed that ptosis in LEMS patients was mostly mild, and was never of the severity seen in some patients with MG. Although diplopia was a common complaint in patients with both disorders, an apparent external ophtalmoplegia was only seen in patients with MG. These differences in severity of extraocular weakness between MG and LEMS have also been observed by others.[1] Comparisons of these two diseases may therefore be helpful in further elucidating the mechanisms whereby MG causes such prominent eye muscle weakness.

Acknowledgements

We thank J.G. van Dijk, Leiden University Medical Centre, for critically reading the manuscript. P.W.W. was supported by a grant of the Prinses Beatrix Fonds.

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