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## SHORT REPORT

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

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**Background:** Myasthenia gravis and the Lambert–Eaton myasthenic syndrome (LEMS) may have a similar distribution of muscle weakness. Deciding on a diagnosis of myasthenia gravis or LEMS on clinical grounds may therefore be difficult.

**Objective:** To compare the localisation of initial muscle weakness and the distribution of weakness at the time of maximum severity in patients with myasthenia gravis and LEMS.

**Subjects:** 101 patients with myasthenia gravis and 38 patients with LEMS.

**Results:** In myasthenia gravis, 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% had bulbar weakness, and 95% had weakness of the limbs as the first symptom ( $p < 0.001$ ). At the point of maximum severity, weakness in myasthenia gravis was purely ocular in 25%, oculobulbar in 5%, restricted to the limbs in 2%, and present in both oculobulbar muscles and limbs in 68%. 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 generalised myasthenia gravis limb weakness was restricted to the arms ( $p = 0.024$ ).

**Conclusions:** In a patient suspected to have a myasthenic syndrome whose first symptom is ocular weakness, LEMS is virtually excluded. Limb weakness confined to the arms is only found in generalised myasthenia gravis and not in LEMS. Muscle weakness in myasthenia gravis tends to develop in a craniocaudal direction, and in the opposite direction in LEMS.

Myasthenia gravis and the Lambert–Eaton myasthenic syndrome (LEMS) are both acquired autoimmune disorders characterised by defective neuromuscular transmission. Several clinical differences between myasthenia gravis and LEMS are known; for example, decreased tendon reflexes and autonomic dysfunction are features of LEMS but not of myasthenia gravis.<sup>1</sup> Nevertheless, myasthenia gravis is the most common alternative diagnosis in patients with LEMS.<sup>1</sup> It may be difficult to decide on a diagnosis of myasthenia gravis 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 these disorders, some reports have stressed involvement of the cranial muscles in myasthenia gravis and predominant limb muscle weakness in LEMS.<sup>1–3</sup> To

study the diagnostic value of this observation, we compared the localisation of muscle weakness during the disease course in patients with myasthenia gravis and LEMS.

## METHODS

We carried out a retrospective survey of all patients with a diagnosis of myasthenia gravis in our hospital between 1990 and 2000. Patients' 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 us (ARW, JJV, or PWW). Case records were reviewed using a structured checklist to record all signs and symptoms and the results of laboratory and electromyographic testing.

The inclusion criteria for patients with myasthenia gravis were acquired variable muscle weakness, and at least one of the following:

- the presence of anti-acetylcholine receptor (AChR) antibodies;
- a decrement larger than 10% on repetitive nerve stimulation without incremental response;
- 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.<sup>4</sup> Patients with incomplete clinical data were excluded from analysis.

The localisation 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 purely ocular, purely oculobulbar, generalised (for example, ocular or bulbar plus limb muscle weakness), or limb muscle weakness. When weakness of the limbs was present, we classified its localisation as both arms and legs, arms only, or legs only.

Statistical comparison of data between the two groups was done with a  $\chi^2$  test. Positive likelihood ratios of the localisation of initial weakness for a diagnosis of myasthenia gravis were calculated.

## RESULTS

### Patients and confirmation of diagnosis

In all, 172 patients diagnosed with myasthenia gravis or LEMS were found. Twenty one patients were excluded because they did not fulfil our inclusion criteria, and 12 because of incomplete clinical data. After exclusion, data from 101 patients with myasthenia gravis and 38 with LEMS were analysed (table 1).

**Table 1** Characteristics of patients with myasthenia gravis and the Lambert–Eaton myasthenic syndrome

	Myasthenia gravis (n=101)	Lambert–Eaton syndrome (n=38)
Male:female ratio (% male)	36:65 (36)	22:16 (58)
Age at onset (years) (mean (range))	41 (5 to 78)	50 (11 to 76)
Associated tumour*	13 (13%)	14 (37%)
Interval between disease onset and tumour diagnosis (months) (median (range))	8 (0 to 62)	3 (1 to 54)
Disease specific antibody positive†	72/97 (74%)	32/36 (89%)
Immunosuppression or chemotherapy	58/101 (58%)	21/38 (55%)‡
Follow up (years) (mean (range))	9 (1 to 42)	7 (1 to 38)

\*Thymoma in myasthenia gravis, small cell lung carcinoma in Lambert–Eaton syndrome.

†Anti-acetylcholine receptor antibodies in myasthenia gravis, or anti-P/Q-type voltage gated calcium channel antibodies in Lambert–Eaton syndrome.

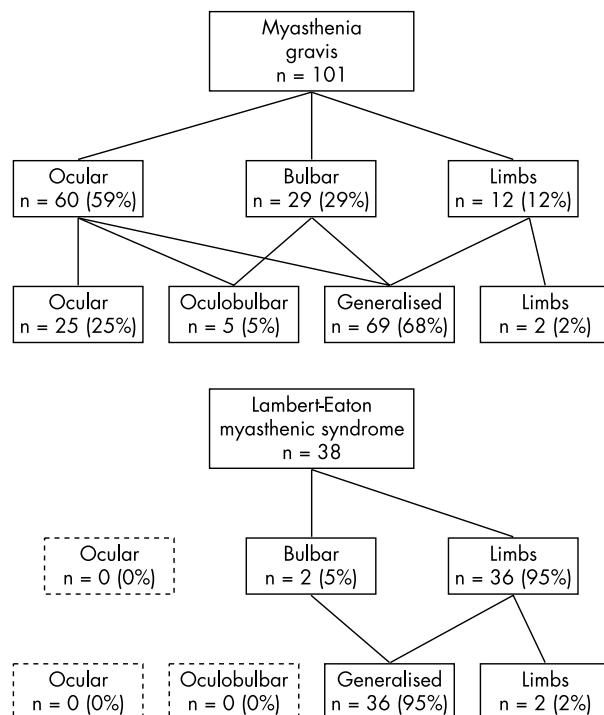
‡All 14 patients with Lambert–Eaton syndrome and small cell lung carcinoma received chemotherapy.

The diagnosis of myasthenia gravis was confirmed by the presence of anti-AChR antibodies in 72 of 97 patients tested (74%). In 18 of the 25 seronegative patients (60%) the diagnosis was confirmed by electromyography (EMG). All seronegative patients with myasthenia gravis and without EMG abnormalities (n=11) had an unequivocal positive response to an acetylcholinesterase inhibitor test.

The diagnosis of LEMS was confirmed by EMG in all patients. 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.

#### Localisation of initial weakness

The localisation of initial weakness was significantly different between myasthenia gravis and LEMS ( $\chi^2 = 82.93$ ,  $p < 0.001$ ) (fig 1). The positive likelihood ratio for having myasthenia gravis and not LEMS was infinite for ocular onset, 5.5 for bulbar onset, and 0.12 for onset in the limbs.



**Figure 1** Localisation 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 myasthenia gravis (68%) had generalised myasthenia gravis. Among the 62 patients with myasthenia gravis whose disease began with ocular weakness, the weakness remained purely ocular in 25 (40%). Among 29 patients with bulbar onset, muscle weakness remained restricted to the oculobulbar muscles in three (10%). No purely bulbar weakness was detected in these three patients. In two patients, both women, symptoms remained restricted to the limb muscles. Both these patients had anti-AChR 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 myasthenia gravis, we did not find any LEMS patient with pure ocular or mixed oculobulbar weakness without involvement of the limbs at the point of maximum disease severity ( $\chi^2 = 15.26$ ,  $p = 0.002$ ).

Among 70 patients with myasthenia gravis and weakness of the 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 three patients (8%), while no LEMS patient had weakness restricted to the arms ( $\chi^2 = 7.49$ ,  $p = 0.024$ ).

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

#### DISCUSSION

We found differences in the distribution of muscle weakness between patients with LEMS and myasthenia gravis which will help the clinician to distinguish between these disorders. At the onset of myasthenia gravis, 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 myasthenia gravis and LEMS, but several studies describing only patients with myasthenia gravis have found extraocular muscle weakness to be the most common initial symptom,<sup>5-7</sup> while in a clinical description of 50 LEMS patients none had an ocular onset.<sup>1</sup> 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 myasthenia gravis and ocular onset had developed generalised weakness, whereas in almost all patients with LEMS, limb weakness was followed by oculobulbar weakness. Thus, although both diseases tend to progress towards generalised weakness, weakness in myasthenia gravis generally spreads in a craniocaudal direction, while in LEMS it spreads in the opposite direction. The 60% generalisation rate of ocular myasthenia gravis that we found is in agreement with previous studies.<sup>5,8</sup> Two patients with myasthenia gravis had weakness which remained confined to the extremities during the disease course; this has been designated the chronic "limb girdle" form of myasthenia gravis.<sup>9</sup> In patients with limb muscle weakness, the weakness remained restricted to the arms in some patients with myasthenia gravis, 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 has myasthenia gravis and not LEMS.

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

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