Respiratory muscle weakness in the Lambert-Eaton myasthenic syndrome

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ABSTRACT Respiratory muscle function was assessed in six patients with the Lambert-Eaton myasthenic syndrome. Five had histologically proved small cell carcinoma of the lung; the sixth later developed metastases from an unknown primary site. Two patients had ventilatory failure, one without respiratory symptoms; another, who had emphysema, had dyspnoea and orthopnoea. The remaining three patients had no respiratory symptoms. Four patients had limb muscle weakness as judged by the maximal voluntary contraction of the quadriceps muscle (range for all subjects 32–100% predicted). Transdiaphragmatic pressure (Pdi) was measured during a maximal unoccluded sniff (Pdi: sniff), a maximal sustained inspiratory effort against a closed airway (Pdi: Pimax), and phrenic nerve stimulation (Pdi: twitch). Mild to moderate diaphragmatic weakness was present in all six patients in proportion to the degree of leg weakness (Pdi: sniff 30–64% predicted; r = 0.6; Pdi:Pimax 6–69% predicted, r = 0.8); this was associated with very low or absent Pdi:twitch during phrenic nerve stimulation. Four patients had weakness of the expiratory muscles. Improvement in muscle strength was documented in two patients after tumour chemotherapy and specific treatment with 3,4-diaminopyridine and prednisolone; one patient was still alive five years from first diagnosis. It is concluded that the respiratory muscles may be implicated in this condition more often than has previously been recognised. As the lack of mobility may cause respiratory symptoms to be minimised, the presence of respiratory muscle weakness may remain undiagnosed unless formal measurement of respiratory muscle function is made.

Introduction

The Lambert-Eaton myasthenic syndrome is an autoimmune disorder of neuromuscular transmission, in which IgG antibodies to presynaptic calcium channels lead to their down regulation, thereby reducing calcium dependent, nerve impulse evoked acetylcholine release. About 60% of patients with the Lambert-Eaton myasthenic syndrome have an underlying small cell carcinoma of the lungs. The syndrome gives rise to a predominantly proximal muscle weakness, which early in the disease improves transiently after sustained contraction (post-tetanic potentiation). It also causes depression or absence of tendon reflexes, autonomic disorders (dry mouth, constipation, impotence) and, as in other disorders of neuromuscular transmission, abnormal sensitivity to muscle relaxant drugs.

Ventilatory failure has been reported in patients with the Lambert-Eaton myasthenic syndrome after muscle relaxant drugs, and there are a few isolated case reports of spontaneous ventilatory failure in this syndrome. Lesser degrees of respiratory muscle weakness have not been documented. We therefore studied six patients with the syndrome to investigate the extent to which respiratory muscles are affected.

Patients

We studied six unselected patients, five male and one female (table 1) with clinical and electrophysiological findings typical of the Lambert-Eaton myasthenic syndrome (table 2). The diagnosis was initially made at the National Hospital for Nervous Diseases, London, and the patients were subsequently referred to the Brompton Hospital for investigation of underlying malignancy. Five patients were consecutive referrals to the Brompton Hospital with newly diagnosed Lambert-Eaton myasthenic syndrome, and the sixth (patient 5) was under review when the study was started. Cerebellar symptoms were prominent in two patients (Nos 1 and 6), who had no evidence of intracerebral metastases on computed tomograms.
One patient (No 2) had severe autonomic manifestations. Five patients had histologically proved small cell carcinoma of the lung. In the sixth patient (No 2) no evidence of malignancy had been found at the time of study.

One patient (No 1) had not noticed any respiratory symptoms but was found to be in ventilatory failure at the time of study, arterial oxygen (Pao2) and carbon dioxide (Paco2) tensions being 6.9 and 6.5 kPa. Patient 4 presented with ventilatory failure (Pao2 with 4 l/min oxygen 7.4 kPa, Paco2 7.3 kPa), with progressively severe dyspnoea and a vital capacity of only 1.2 l. Respiratory muscle strength was not formally assessed until he had received 10 days' treatment with prednisolone, 3,4-diaminopyridine (a drug that increases transmitter release from motor nerve terminals), antitumour chemotherapy, intensive physiotherapy, and drugs for coexisting inappropriate antidiuretic hormone secretion. By this time his vital capacity had improved to 1.9 litres and his Paco2 (while he was breathing oxygen 6 l/min) to 10.1 kPa and Pco2 to 5.9 kPa. Arterial blood gas tensions were not measured in the other three patients.

Patient 5 was studied three years after diagnosis. His carcinoma of the lung had responded to chemotherapy and the limb muscle weakness had partially responded to continuous treatment with prednisolone and 3,4-diaminopyridine. His severe dyspnoea and orthopnoea had been attributed to emphysema, and coexisting respiratory muscle weakness had not been suspected. Arterial blood gas analysis showed mild hypoxaemia (Pao2 8.2 kPa, 93.9% saturation), with a normal Paco2 (4.7 kPa).

All six patients had undetectable serum acetylcholine receptor antibodies and no response to intravenous edrophonium (Tensilon). There was no evidence of any electrolyte disturbance at the time of study. No patient had received muscle relaxant drugs or aminoglycoside antibiotics.

Methods

Forced expiratory volume in one second (FEV1), vital capacity (VC), and forced vital capacity (FVC) were measured with a rolling seal spirometer (Spiroflow, PK Morgan). Total lung capacity (TLC) was measured in subjects 1 and 5 with a constant volume whole body plethysmograph. All volumes were corrected to BTPS.

The maximal contractile force of each quadriceps femoris muscle was measured by means of a specially designed chair. Each maximal voluntary contraction was maintained for at least four seconds to ensure no further increment in force; the highest value sustained for one second was recorded.

Respiratory pressures were measured with differential pressure transducers (Validyne Model MP 45-1, Validyne Corporation, Northridge, California). Global expiratory and inspiratory muscle strength was assessed from the maximum pressures generated at the mouth (Pm) during maximal occluded expiratory efforts from TLC (Pm:Pmax) and inspiratory efforts from RV (Pm:Pmax). Global inspiratory muscle strength was also assessed from the measurement of oesophageal pressure during a maximal sniff from FRC (Poes:sniff),11,12 a balloon catheter system being used to record oesophageal pressure. Diaphragm strength was assessed from the transdiaphragmatic pressure (Pdi) measured during a maximal sustained inspiratory effort against a closed airway (Pdi:Pmax) and during a maximal unoccluded sniff (Pdi:sniff).12,13

All voluntary manoeuvres were repeated with a pause for a rest of at least 10 seconds between each attempt until three reproducible maximum values were obtained.

Table 1  Details of patients with the Lambert-Eaton myasthenic syndrome at time of initial study

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Dyspnoea (MRC scale)</th>
<th>Orthopnoea</th>
<th>Vital capacity (l) (% pred)</th>
<th>FEV1/FVC %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>M</td>
<td>154</td>
<td>65</td>
<td>1</td>
<td>-</td>
<td>1-9 (68)</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>F</td>
<td>163</td>
<td>67</td>
<td>1</td>
<td>+</td>
<td>2-6 (89)</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>168</td>
<td>57</td>
<td>1</td>
<td>-</td>
<td>2-4 (63)</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>M</td>
<td>184</td>
<td>68</td>
<td>4</td>
<td>+ +</td>
<td>2-7 (57)</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>M</td>
<td>170</td>
<td>64</td>
<td>4</td>
<td>+ +</td>
<td>2-9 (76)</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>M</td>
<td>185</td>
<td>92</td>
<td>1</td>
<td>-</td>
<td>4-1 (87)</td>
<td>66</td>
</tr>
</tbody>
</table>

Table 2  Results of electrophysiological studies*

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Mean conduction velocity† (m/s)</th>
<th>MAP amplitude (mv)</th>
<th>MAP amplitude after 15 s MVC (% increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>1-6</td>
<td>7-5 (369)</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>2-6</td>
<td>5-0 (92)</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>0-6</td>
<td>10-5 (1650)</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>5-0</td>
<td>13-0 (205)</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>1-8</td>
<td>5-5 (205)</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>1-3</td>
<td>7-0 (438)</td>
</tr>
<tr>
<td>Normal</td>
<td>&gt;8-6</td>
<td>&gt;8-8</td>
<td>(&lt;9)</td>
</tr>
</tbody>
</table>

*Recorded with surface electrodes on abductor digiti minimi.
†Measured in the median or ulnar nerve.
MAP—mass action potential; MVC—maximum voluntary contraction.
Phrenic nerve stimulation was performed as described by Newsom-Davis. The diaphragmatic mass action potential evoked from each hemidiaphragm by a single square wave impulse, 0·1 ms in duration, frequency 1 Hz, was recorded on each side of the chest with surface electrodes placed in the 7th and 8th intercostal spaces, near to the costal margin. Phrenic nerve conduction time was measured as the time between the stimulus artefact and the beginning of the mass action potential. Each phrenic nerve was then stimulated in turn to record the Pdi generated by the stimulated twitch contraction (Pdi:twitch). The stimulation voltage was increased until there was no further increase in Pdi or mass action potential amplitude, and was then increased by a further 10%, to ensure supramaximal voltage. Twitch pressures were recorded with the patient at FRC, as judged by magnetometer tracings and the resting pressures, and with the glottis closed. Ten to 20 twitches were obtained for each position and the average of the largest 10 twitches was used for analysis.

Results

Results of respiratory muscle and quadriceps strength are shown in table 3. Quadriceps maximum voluntary contractions were almost identical in the right and left legs in all six patients, ranging from 32% to 100% predicted (mean 58%). In four patients this lay outside the normal range obtained in 40 normal volunteers in our laboratory (mean - 2 SD). An increased time to achieve maximal force at each attempt was, however, noted in all six patients, and in two patients quadriceps maximum voluntary contractions showed a progressive increase over several sequential efforts until the maximal value was attained.

Pdi:sniff was below the normal range in all six patients (mean 49% predicted, range 30-64%), in proportion to the degree of quadriceps weakness (r = 0·6). Pdi:Pmax was outside the normal range in only three patients. It was nevertheless closely related to quadriceps maximum voluntary contraction (r = 0·8), and less than 70% predicted in all six patients (mean 42% predicted, range 6-69%). There was also a close correlation between each of the three measurements of global respiratory muscle strength and quadriceps maximum voluntary contraction (Pm:Pmax: r = 0·8; Pm:Pmax: r = 0·8; Pdi:sniff: r = 0·7).

During phrenic nerve stimulation, higher voltages than normal (> 160 volts) were required to produce a detectable mass action potential on the diaphragmatic electromyograph. In three patients the mass action potential was too small on one side to allow reliable estimation of conduction time. In two patients phrenic nerve conduction time was slightly prolonged on one or both sides (table 4). Pdi recorded during both unilateral and bilateral phrenic nerve stimulation at 1 Hz was very small or absent in all six patients (table 4). No fall in mass action potential amplitude or size of Pdi:twitch could be detected even when the frequency

<table>
<thead>
<tr>
<th>Patient</th>
<th>Phrenic nerve conduction times (ms)</th>
<th>Pdi:twitch (cm H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>1</td>
<td>*</td>
<td>8.0</td>
</tr>
<tr>
<td>2</td>
<td>8.5</td>
<td>7.5</td>
</tr>
<tr>
<td>3</td>
<td>9.0</td>
<td>9.0</td>
</tr>
<tr>
<td>4</td>
<td>10.5</td>
<td>*</td>
</tr>
<tr>
<td>5</td>
<td>8.0</td>
<td>*</td>
</tr>
<tr>
<td>6</td>
<td>10.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt; 9.3</td>
<td>&lt; 8.9</td>
</tr>
</tbody>
</table>

* M wave too small to allow determination of conduction time.
of phrenic nerve stimulation was increased to three
Hertz.

Vital capacity was less than 80% predicted in four
patients (table 1). Two had an FEV₁/FVC ratio of less
than 70%: patient 1 with mild irreversible airways
obstruction (TLC 79% predicted) and patient 5, who
had moderately severe emphysema (TLC 123% pre-
dicted). In patient 4 right lower lobe collapse due to
obstruction by tumour may have contributed to the
reduction in vital capacity and hypoxaemia. There was
no radiographic abnormality to explain the reduction
in vital capacity in patient 3.

**REPEAT STUDIES**

Patients 1, 4, and 6 were studied again six weeks after
the first study, having received standard chemo-
therapy for their carcinoma and specific treatment
with plasmapheresis, 3,4-diaminopyridine, and predni-
solone for the Lambert-Eaton myasthenic syn-
drome. No improvement in quadriceps or respiratory
muscle strength was documented at this time.

Patient 3 was restudied after 18 weeks of the same
treatment, excluding plasmapheresis. There was an
improvement in respiratory muscle strength as judged
by vital capacity, mouth pressures, and Pdi:Pimax
(table 5), though improvement in maximal sniff pres-
sures was less striking. The change in vital capacity
was not explained by improvements in airway or lung
disease. Diaphragm mass action potential amplitude
was much increased and supramaximal twitches were
obtained at more normal voltages. Pdi:twitch was
almost within the normal range. Quadriceps strength
was unchanged. Despite this improvement in muscle
strength the patient died within a year of diagnosis
from extension of his malignant disease, as did
patients 1 and 4.

Two further studies were performed in patient 5 in
the two years after his initial study. Limb muscle
strength has tended to improve with maintenance
treatment with 3,4-diaminopyridine and predni-
solone. Diaphragm and global inspiratory muscle
strength have improved, as judged by both occluded
and sniff manoeuvres (table 5), and an increased vital
capacity that does not appear to be explained by
improvement in lung or airways disease or by im-
provement in nutritional status. Responses to phrenic
nerve stimulation is unchanged five years after diag-
nosis. There has been no evidence of recurrence of
malignancy.

**Discussion**

It has been suggested that respiratory muscle weakness
is rare in the Lambert-Eaton myasthenic syndrome—
less common than in, for example, myasthenia gravis.7
This has not been investigated, however, with specific
tests of respiratory muscle function. One report de-
cribed a single patient with the Lambert-Eaton mya-
stechnic syndrome in whom very low mouth pressures
suggested severe global respiratory muscle weakness,
and electrophysiological studies of the phrenic nerve
suggested that the diaphragm was affected.18 This is
consistent with our findings in a further six patients, in
whom respiratory muscle strength was found to cor-
relate with the strength of the quadriceps muscle.

The incidence of mild to moderate respiratory
muscle weakness in the Lambert-Eaton myasthenic
syndrome has probably been underestimated in the
past, because of the relative lack of respiratory
symptoms in patients with reduced exercise tolerance
due to limb weakness or cerebellar ataxia. In addition,
vital capacity may be preserved until quite severe
respiratory muscle weakness is present.19 The true
extent of respiratory muscle weakness in patients with
the Lambert-Eaton myasthenic syndrome can be
assessed only by formal measurement of maximum
respiratory pressures. Detection and quantification of
respiratory muscle weakness is important because
weakness may give rise to respiratory infection or progress to frank respiratory failure. If the possibility is considered early, it may allow preventive measures to be taken before such events occur.

In some of our patients there was evidence of a progressive increase in respiratory pressures during successive maximal voluntary respiratory efforts. This may reflect the post-tetanic potentiation seen in the Lambert-Eaton myasthenic syndrome, but as substantial improvement is seen in many normal subjects during successive attempts at these manoeuvres it is not clear to what extent this observation was attributable to the syndrome. Extra care must be taken with these patients to ensure that they make sufficient efforts to achieve maximum pressures.

The reduced amplitude of the diaphragm mass action potential and reduction in Pdi:twitch on electrical stimulation of the phrenic nerves confirm that the diaphragm was specifically affected by the Lambert-Eaton myasthenic syndrome in all six patients, and reflects the findings reported for other peripheral muscles in this syndrome. Phrenic nerve stimulation appeared to be even more sensitive than measurement of maximum respiratory pressures in detecting respiratory muscle weakness as shown by the reduction in Pdi:twitch and diaphragm mass action potential amplitude in patient 6 despite only marginal reduction in maximum Pdi generated during maximum inspiratory efforts. This may reflect the underlying abnormality of neuromuscular transmission in this disorder, which characteristically improves transiently during a maximum voluntary contraction.

The classical diagnostic findings in the peripheral muscles of patients with the Lambert-Eaton myasthenic syndrome are a decline in amplitude of the mass action potential when the frequency of stimulation is increased to 3 Hz, with a progressive increase in amplitude when the frequency of stimulation is increased above 10 Hz. We were unable to detect any fall in diaphragm mass action potential amplitude with stimulation of the phrenic nerves at 3 Hz in our patients. Quantitative measurement of mass action potential amplitude in the diaphragm is, however, less reliable than in peripheral muscles. We did not attempt to increase the frequency of stimulation to show the characteristic increase in action potential amplitude at a high frequency of stimulation as this is not well tolerated by patients.

The slight prolongation of phrenic nerve conduction time in two of our patients was not associated with a corresponding reduction in conduction velocity in other muscles. Conduction velocity is usually normal in muscles other than the diaphragm in patients with the Lambert-Eaton myasthenic syndrome, prolongation occurring in only two of 50 patients with the disorder in one study. The abnormal finding in two of our patients may reflect the technical difficulty of measuring phrenic nerve conduction time when mass action potential amplitude is greatly reduced.

One of the two patients with ventilatory failure (patient 1) showed only a moderate degree of respiratory muscle weakness, and did not appear to have significant coexisting lung or airways disease. Cerebellar dysfunction may have resulted in abnormal respiratory muscle activation, causing some primary alveolar hypoventilation.

Identification of respiratory muscle weakness is important in patients with the Lambert-Eaton myasthenic syndrome as results in two of our patients suggest that it may respond to specific treatment. The outlook for these patients remains poor because of the underlying carcinoma. One of our patients, however, remains well controlled with 3,4-diaminopyridine and prednisolone five years after the initial presentation.

In conclusion, our results show that the respiratory muscles are usually implicated in this condition, at least when it is associated with cancer. They emphasise the need to assess respiratory muscle strength specifically in patients with appreciable limb weakness due to the Lambert-Eaton myasthenic syndrome.

We would like to thank Dr N M F Murray for undertaking the electrophysiological studies.

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