SHORT REPORT

Amyloid myopathy presenting with respiratory failure

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Abstract
Amyloidosis is a rare cause of myopathy. Its prominent or presenting feature may be respiratory failure. Physiological measurement of transdiaphragmatic pressure and biopsy specimens of muscle show the pathological mechanism to be diaphragm weakness due to amyloid infiltration of the diaphragm rather than parenchymal lung involvement. Thus amyloid myopathy even without the typical macroglossia and muscle pseudohypertrophy should be considered as one of the neurological causes of respiratory failure.

Respiratory muscle weakness is recognised as the presenting feature in few neurological disorders, including motor neuron disease,1 Guillain-Barre syndrome, polymyositis,2 myasthenia gravis, acid maltase deficiency,3 and (rarely) porphyria.4 Amyloid myopathy, first described by Lubarsch in 1929,5 is a rare condition in which amyloid is deposited in the muscle. It is usually characterised by muscle weakness, pseudohypertrophy, and macroglossia,6,7 but is not yet commonly recognised as a cause of respiratory failure. Although two incompletely described cases have been reported,8,9 in neither case was the extent of diaphragm weakness documented. We describe a patient with amyloid myopathy presenting with respiratory failure who had physiologically documented weakness of the diaphragm.

Case report
A 73 year old woman was admitted with a six month history of breathing difficulty followed by progressive weakness, weight loss, and malaise. She had dysphonia at rest, most noticeable when supine. Weakness of arms and legs was gradual in onset and eventually impaired housework, getting out of a bath, and rising from a chair. She had no bulbar symptoms until just before admission, when her voice became weak and swallowing impaired. She had a history of non-insulin dependent diabetes mellitus and hypertension. Seventeen years before admission, she had had carcinoma of the breast treated by mastectomy and local irradiation. There was no family history of neuromuscular or other neurological diseases. Medications on admission consisted of ranitidine, metoclopramide, cefotaxime, propranolol/acetaminophen, and prochlorperazine.

On examination she was anxious and alert. Her respiratory rate was 32/min, heart rate 100/min, temperature 37°C, blood pressure 120/70, and the vital lung capacity was 700 ml. The apex beat was not displaced, and S4 was audible. She had an apical systolic murmur (2/6). The lungs were dull to percussion at both bases. There was no enlargement of liver or spleen. Her mental state was normal. There was no ptosis, ophthalmoplegia, or facial weakness. Though her voice was weak, her palate moved fully and symmetrically, and the gag reflex was normal. The tongue was strong, neither wasted, hypertrophic, nor fasciculating. Neck flexors and extensors were of normal strength. Limb muscle bulk was normal, and there were no fasciculations or myotonia. Proximal muscles were distinctly weak (MRC scale 3/5 proximally and 4+ distally), more in the legs than in the arms. Deep tendon reflexes were normal and symmetric. Plantar responses were flexor. Sensation and coordination were normal.

Blood gas determinations on 3 l of oxygen/min showed pH 7.36, pCO2 38 mm Hg, pO2 95 mm Hg, bicarbonate 22 mmol/l. Routine serum chemistries, electrolytes, glucose, serum enzymes, and liver function tests yielded normal results with the exception of a serum creatinine concentration of 20 mg/l. Initial serum creatine kinase was 244 IU/l but dropped to 84 on admission (normal for females <135 IU/l). The erythrocyte sedimentation rate was 66 mm/hr. There was a normochromic, normocytic anaemia (haemoglobin 9 g/l) and lymphopenia (7%), with an otherwise normal complete blood count and differential. Thyroid function tests and serum B12 concentration were normal. An edrophonium test and anti-acetylcholine receptor antibody were negative. An echocardiogram showed mild concentric hypertrophy of the left ventricle and a poor ejection fraction estimated at 20–25%. Chest x ray photographs showed small bilateral pleural effusions, which proved sterile and contained no malignant cells. A skeletal survey showed
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Table: Diaphragmatic performance in amyloid myopathy

<table>
<thead>
<tr>
<th>Patient trial</th>
<th>RR</th>
<th>Vt</th>
<th>Peso</th>
<th>PPast</th>
<th>Pdi</th>
<th>Pdimax</th>
<th>Pdi/Pdimax</th>
<th>Ti/Ttot</th>
<th>TTI</th>
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<tr>
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<td>165</td>
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<td>9.6</td>
<td>20</td>
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<td>160</td>
<td>7.4</td>
<td>−1.5</td>
<td>8.9</td>
<td>13</td>
<td>0.69</td>
<td>0.23</td>
<td>0.16</td>
</tr>
<tr>
<td>Normal</td>
<td>16–20</td>
<td>450–600</td>
<td>NA</td>
<td>NA</td>
<td>15–25*</td>
<td>80–120*</td>
<td>&lt;0.4**</td>
<td>&lt;0.4**</td>
<td>&lt;0.16**</td>
</tr>
</tbody>
</table>

*Normal values; † Normal values. Abbreviations used: RR (respiratory rate), Vt (tidal volume, ml), Peso (oesophageal pressure, cm H2O), PPast (gastric pressure, cm H2O), Pdi (transdiaphragmatic pressure, cm H2O), Pdimax (maximum transdiaphragmatic pressure, cm H2O), Pdi/Pdimax (critical fraction of diaphragm), Ti/Ttot (inspiratory time fraction), TTI (tension time fraction: [Pdi/Pdimax] × [Ti/Ttot]), NA (not available).

Results of special studies

Transdiaphragmatic monitoring

Pulmonary function tests and transdiaphragmatic pressure monitoring were done to determine the degree of respiratory failure and the extent to which the various respiratory muscles were contributing. Vital capacity was 0.7 l, FEV1 88% of predicted, and the negative inspiratory force 33 mm Hg. A modified gastric feeding tube (Mallinkrodt Critical Care) was inserted to measure diaphragmatic function. All measurements were performed in a 30 degree upright position and were recorded on a strip chart recorded during spontaneous breathing of oxygen enriched air through an open endotracheal tube. Simultaneous intrathoracic and gastric pressure were recorded, and transdiaphragmatic pressure (Pdi) was derived by subtracting oesophageal pressure from gastric pressure. Maximal transdiaphragmatic pressure (Pdimax) was measured at the end of expiration, during maximal voluntary inspiratory effort against an occluded airway. A Fleisch pneumotach was connected to the endotracheal tube to obtain measurements of airflow, tidal volume, respiratory rate, and inspiratory time. Inspiratory effort was generated mainly by the intercostal muscles of respiration as the negative oesophageal pressure failed to show the positive correlation with gastric pressure that would be expected with effective contraction of the diaphragm. During maximal effort the patient was able to generate only 13 cm H2O negative pressure—a low maximal transdiaphragmatic pressure compared to normal (80–120 cm H2O). We recorded two trials of spontaneous breathing (table). In each instance Pdi was low but was reduced relatively less than the Pdimax. This increased the critical fraction of the diaphragm (Pdi/Pdimax) 23–73% above the threshold for maintaining independent ventilation (0.4). These values for diaphragmatic performance were poor even when compared to other patients with neuromuscular respiratory disease. Values for Pdimax exceed 40 cm H2O in patients with neuromuscular respiratory disease not requiring ventilation assistance. These results showed severe diaphragmatic muscle dysfunction with ventilatory failure.

Immunological studies

The serum protein electrophoresis showed hypoaubumenaemia (23 g/l; normal 60–80 g/l), hypogammaglobulinaemia (2 g/l; normal, 7–17 g/l), and a prominent spike in the β region. Immunofixation identified this monoclonal spike as IgG kappa. Plasmacytid lymphocytes and plasma cells comprised 4% of the peripheral white blood cells. Bone marrow aspirate showed extensive replacement of normal hematopoietic elements by plasma cells (>80%) that stained predominantly with anti-kappa antisera by the immunoperoxidase reaction. These findings indicated a plasma cell dyscrasia.

Electrodiagnostic studies

Nerve conduction studies were performed with standard techniques, and electromyography (EMG) was done with concentric bipolar electrodes. The conduction velocities and amplitudes of the sensory nerve action potentials were normal in sural and median nerves. Motor conduction studies including distal latencies and F wave latencies were also normal in four nerves without any evidence of conduction block. There were no signs of nerve entrapment. Repetitive nerve stimulation of the biceps brachii and nasalis muscles at 3 Hz produced no decremental response either before or after exercise. No post-tetanic facilitation was seen in either muscle. EMG of proximal and distal limb muscle and thoracic paraspinal and rectus abdominal muscles all showed prominent spontaneous activity including positive sharp waves, fibrillation potentials, and repetitive discharges. Motor unit potentials were excessively brief in duration, small in amplitude, and polyphasic and showed early recruitment. This was interpreted as myopathy with "irritability," as is more commonly seen in polymyositis, toxic or necrotising myopathies, and vacuolar myopathies such as acid maltase deficiency.

Muscle biopsy specimens

Frozen section histochemistry (figure 1) of a deltoid muscle specimen showed scattered foci of endomyosial and perimysial fibrosis, with related myofibre atrophy and distortion. Few necrotic muscle fibres were present. Occasional non-necrotic fibres contained vacuoles which had a complex membranous structure. There were no inflammatory infiltrates. ATPase staining showed only type II fibre atrophy but no fibre type grouping. The above features suggested a myopathy. The key histochemical finding was that the areas of perimyosial and endomyosial
fibrosis contained hyaline material that stained strongly positive with Congo red and was birefringent to polarised light. This, taken in conjunction with the other clinical and laboratory findings, enabled us to diagnose amyloid myopathy. Adult onset acid maltase deficiency was ruled out by normal periodic acid Schiff staining and by normal concentrations of glycogen, acid maltase, and neutral maltase.

Necropsy examination
At necropsy amyloid was found in the diaphragm (figure 2), intercostal and psoas muscles, tongue, heart, and in the muscular layers of the ileum and jejunum. The diaphragm itself was not considerably thickened and, in fact, no pseudohypertrophy was noted except in the heart. No amyloid was deposited in the endoneurium or perineurium of the lumbo-sacral plexus or intramuscular nerves, nor was the vasa nervorum affected. Though there was a mild degree of amyloid deposition perivascularly in the lungs, there was no amyloid in lung parenchyma or the tracheobronchial tree, so that the only part of the respiratory system affected was the respiratory muscles.

Discussion
This patient had a myopathy as suggested clinically by proximal muscle weakness and documented electrophysiologically in many muscle groups. The most impressive feature of this myopathy is that it presented with prominent respiratory failure. The muscle biopsy and necropsy material, which stained strongly positive with Congo red and was birefringent to polarised light, confirmed the diagnosis of amyloid myopathy. Other causes of the syndrome of neuromuscular weakness with respiratory failure were ruled out. The mechanism of respiratory failure in amyloidosis is of interest and in this case was shown by physiological testing. The amyloid cardiomyopathy that was present, with small pleural effusions and mild cardiac failure, could have compromised her respiratory function but was physiologically trivial compared to the severe respiratory failure. Amyloid deposition throughout the tracheobronchial tree and lung parenchyma could also cause pulmonary insufficiency. The necropsy, however, showed that the lung itself was free of amyloid. Routine pulmonary function tests are not sufficiently sensitive or specific to differentiate neuromuscular from other causes of respiratory failure. For this reason diaphragm function testing was performed to localise the cause of her respiratory failure. Transdiaphragmatic pressure measurement is the most sensitive indicator of diaphragm function10 and in this case provided definitive evidence of severe diaphragm weakness. The relatively spared negative inspiratory force indicated better preserved intercostal function. Taken together, the evidence suggests the patient’s respiratory failure and orthopnoea were directly due to infiltrative amyloid myopathy causing demonstrable weakness of the diaphragm and intercostal muscles.

There are two previously reported cases of patients with amyloid myopathy and respiratory failure, thought to be related to weakness of the respiratory muscles. In one report,8 a thickened, amyloid-filled diaphragm was found at necropsy but the authors did not know whether the respiratory failure was due to cardiac disease, intrinsic lung disease, or muscle weakness. Another described a patient who had bronchopneumonia and pleural effusions but in whom no diaphragmatic movement appeared on fluoroscopy.9 This would be regarded as good indirect evidence of poor dia-
phragm function. The mechanism by which amyloid causes muscle weakness has prompted speculation but it is still unclear. Possibly the proximity of the amyloid to the sarcolemmal membrane interferes with the propagation of the action potential along muscle fibres. Amyloid in muscle, however, is deposited in the connective tissue and has not been shown within muscle fibres or disrupting the sarcolemmal membrane in this and other cases. Amyloid has a particular predilection for blood vessels within muscle, and possibly their function is impaired, but no secondary degenerative or ischaemic changes have been seen within muscle in amyloid myopathy. Some have suggested that amyloid acts as a toxin. The vacular changes and scattered necrosis seen on muscle biopsy specimens might suggest such an effect, but there is no evidence that amyloid enters muscle fibres or any other cells. The weakness associated with amyloid deposition in muscle may actually be neurogenic in origin. In cases of amyloid myopathy, however, the peripheral nerves have been consistently normal clinically and histologically, and no significant denervation has been seen on EMG or muscle biopsy. The spontaneous EMG activity seen in these cases has been attributed to involvement of the dial intramuscular nerves, but in our material the peripheral nerves, from roots to intramuscular nerves, were surprisingly unaffected considering the magnitude of the muscle infiltration. Spontaneous EMG activity is more likely attributable to vacular myopathic changes. A more plausible hypothesis is that the pathophysiological effect of amyloid, at least in some muscles, may involve purely mechanical factors. Amyloid is associated with atrophy and distortion of adjacent muscle fibres; probably its main effect on muscle function is mechanical, perhaps resulting in a change in the length tension relation and a decrease in compliance. In the case of a thin, supple and mobile muscle such as the diaphragm, mechanical compression, atrophy, and non-compliance would be particularly damaging to the muscle’s function as a bellows.

The typical patient with amyloid myopathy has a plasma cell disorder and a history of proximal muscle weakness extending over a few months. Clinical muscle involvement in systemic amyloidosis is essentially confined to the AL type of amyloidosis as in the present case. Previous reports have regarded muscle pseudohypertrophy and macroglossia as characteristic findings, though these are not universal and were not found in our case. Respiratory failure may be a prominent or presenting feature, and consequently the diagnosis should be considered in all older patients who seem to have a neuromuscular basis for the respiratory problems. In such cases, transdiaphragmatic pressure monitoring and muscle biopsy specimens are the most appropriate ways to make a definitive diagnosis.

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