Motor neuron disease presenting as acute respiratory failure: a clinical and pathological study

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Abstract

Respiratory failure is rarely a presenting symptom of motor neuron disease. Seven patients with motor neuron disease who presented with acute respiratory failure of unknown cause and required mechanical ventilation were studied. They all had symptoms and signs suggestive of diaphragmatic weakness. Respiratory involvement seemed disproportionately severe, as six were ambulatory and only three noted limb weakness. Only one had tongue weakness and none had swallowing difficulty. Electrophysiological studies showed widespread denervation and, in particular, diaphragmatic involvement to explain the severe respiratory failure. Weaning from the ventilator was unsuccessful in all cases. The four patients examined at necropsy showed severe loss of anterior horns cells in the cervical cord, with only minimal upper motor neuron involvement. Motor neuron disease should be recognised as a cause of acute respiratory failure, secondary to diaphragmatic paralysis from involvement of phrenic motor neurons.

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Although respiratory failure is common in the advanced stages of motor neuron disease and is the major cause of mortality, it is rarely a presenting symptom. Early deterioration in respiratory function is almost invariably gradual, with an accelerated decline during the 12 to 15 months preceding death.^{1,2} Motor neuron disease presenting as acute respiratory failure of unknown cause is rare.³⁻¹⁰ We report here the clinical features of seven such patients, with pathological findings in four cases. The diagnostic and management difficulties are discussed.

Methods

CASE SERIES

The patients were seen at Victoria and University Hospitals, London, Ontario, and Centre Hospitalier, Sherbrooke, Quebec between January 1991 and April 1995.

Case 1

A 69 year old man collapsed at home and was

in severe hypercapnic respiratory failure. He was intubated in the emergency department. For 11 months previously he had had increasing shortness of breath on exertion, orthopnoea, difficulty climbing stairs, and a weight loss of 9 kg. Investigations for an underlying malignancy were negative.

On examination he was on a ventilator but able to communicate by writing. Cranial nerve examination showed bifacial weakness, the tongue was moderately weak but without wasting or fasciculation. Motor examination disclosed fasciculations in the proximal muscles, mild wasting of the deltoids, intrinsic muscles of the hands and feet, and diffuse mild to moderate weakness in all limbs. Deep tendon reflexes were brisk and plantar responses were flexor on the right and extensor on the left. Sensation was normal. There was indrawing of the abdomen with inspiration.

Blood gases before intubation, while on an oxygen rebreathing mask, showed pH 7.12, PaO₂ 133 mm Hg, PaCO₂ 115 mm Hg, HCO₃⁻ 41 mmol/l. A chest radiograph showed elevation of both hemidiaphragms and atelectasis. Vital capacity was 700 ml and the maximum inspiratory pressure was -20 cm water (normal > -50 cm water).

He declined further ventilatory support and died of hypercapnic respiratory failure three days after extubation.

CASES 2 TO 7

The table summarises the clinical features. In none of these patients was a neuromuscular disorder suspected before their presentation to the emergency department as acute respiratory failure, although all had respiratory symptoms such as dyspnoea or orthopnoea for variable periods (table). Blood gases before intubation all showed severe hypercapnia. Although all the patients were ventilated, they were alert and usually able to communicate by writing. Motor examination showed mild or moderate wasting and weakness in the limb muscles in all patients. Fasciculations were present in patients 1 and 7. Phrenic nerve conduction studies invariably showed very reduced responses. Needle EMG showed widespread denervation in all patients, most severe in the diaphragm.

PATHOLOGICAL FINDINGS

Necropsy examinations were performed in patients 1, 2, 3, and 7. The gross appearances of the cerebral cortex, cerebellum, and brainstem were normal, except for mild diffuse

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Clinical features

Patient	Age Sex	Duration of respiratory symptoms	Other symptoms at presentation	Mobility at presentation	Precipitating factor for acute respiratory failure	Deep tendon reflexes	Plantar response	Abdominal paradox	Diaphragms on chest radiograph	Diagnosis	Outcome
1	69M	11 months	Leg weakness 11 months	Ambulatory	Atelectasis	Brisk	Right flexor, left extensor	Present	Elevated	ALS	Died, respiratory failure
2	55F	5 weeks	Hand weakness 15 months	Ambulatory	Atelectasis, COPD	Reduced to absent	Flexor	Present	Not elevated	PMA	Died, respiratory failure
3	70M	3 weeks	None	Ambulatory	Pulmonary infection, COPD	Normal	Flexor	Absent	Not elevated	PMA	Died, unrelated condition
4	77F	2 weeks	Leg weakness 12 months	Non-ambulatory	Pulmonary infection, COPD	Reduced	Flexor	Present	Not elevated	PMA	Died, respiratory failure
5	68M	12 months	None	Ambulatory	None identified	Brisk	Right flexor, left extensor	Present	Not elevated	ALS	Alive, on home ventilator
6	48F	3 months	None	Ambulatory	None identified	Reduced to absent	Flexor	Present	Not elevated	PMA	Died, respiratory failure
7	72M	2 months	None	Ambulatory	None identified	Brisk	Extensor	Present	Not elevated	ALS	Died, respiratory failure

ALS = amyotrophic lateral sclerosis; COPD = chronic obstructive pulmonary disease; PMA = progressive muscular atrophy.

A

B

(A) Loss of anterior horn cells—patient 1. Photomicrograph from the cervical anterior horn showing an area devoid of motor neurons (bottom and right), background gliosis and residual anterior horn cells (top and left), one of which is degenerating (arrow); haematoxylin, eosin, solochrome; bar = 50 μ m. (B) Nerve root axonal swelling—patient 1. An axonal swelling is shown in this photomicrograph from the anterolateral funiculus; haematoxylin, eosin, solochrome; bar = 10 μ m.

atrophy in patient 7. The anterior spinal nerve roots seemed normal in patient 1, but were atrophic in patients 2, 3, and 7. In all patients, microscopic examination of the motor cortex was normal. Cranial motor neurons were generally well preserved, although a few Bunina bodies were found in patient 1 and mild neuronal loss was seen in the nuclei ambiguus and the hypoglossal nuclei in patient 7. Microscopic examination of the spinal cord all showed pronounced loss of anterior horn cells, scattered axonal swellings, and gliosis (figure). There was no obvious predilection for the cervical cord in patients 1 and 2. In patient 3, the upper cervical segments seemed more involved than the lower cervical, thoracic, and lumbar segments. In patient 7, there was severe involvement of the cervical cord but only minimal changes in the thoracic and lumbar segments. In the corticospinal tracts mild loss of myelinated fibres occurred and a few macrophages were found in patients 1, 2, and 3, but there were no detectable changes in patient 7.

Morphometric analysis of the spinal cord was performed in patient 7. The segments C5 to T2, T6, and L3 were analysed. Ten μ m thick sections were cut from each segment at four levels separated by 100 μ m and stained with cresyl violet. The grey matter from each section and its anterior horn cells were drawn on paper with a camera lucida. Each drawing of the anterior horn was divided in the parasagittal plane into medial, intermediate, and lateral thirds and the anterior horn cells in each third were counted. There was a 30% to 43% decrease in the number of anterior horn cells in the C5 to T2 segments compared with a control patient without neurological disease (Mann-Whitney *U* test: $P < 0.0001$). However, there seems to be no difference in the involvement of the medial neurons compared with the lateral neurons in the cervical segments.

Discussion

CLINICAL FEATURES

All of our patients developed hypercapnic respiratory failure requiring assisted ventilation, before the diagnosis of motor neuron disease. Although they were previously seen by internists or neurologists, their clinical findings were subtle and were overlooked by the examining physicians. In all cases the respiratory failure was initially attributed to other causes, such as pneumonia, exacerbation of chronic obstructive pulmonary disease, heart failure, or sleep apnoea.

Twelve patients with motor neuron disease presenting as acute respiratory failure have been reported in detail³⁻¹⁰ and two in abstract form.¹¹ There are other reports of motor neuron disease with dyspnoea as a presenting symptom.^{4 5 7 12-14} All our patients had symptoms and signs of diaphragmatic weakness. They complained of dyspnoea, sometimes associated with orthopnoea. Examination invariably showed poor chest expansion. Paradoxical indrawing of the abdomen during inspiration is a useful sign of bilateral diaphragmatic weakness and was present in six of our seven patients. In all patients there was limb involvement with a variable combination of wasting, weakness, and fasciculation. Pulmonary function tests typically showed a restrictive pattern and blood gas analysis invariably showed hypercapnia. Elevation of the diaphragm on chest radiography was present in only one of our seven patients. Electrophysiological results were important in clearly establishing diffuse anterior horn cell disease, and in particular, involvement of the diaphragm, to explain the severe respiratory failure.

Although the main cause of respiratory failure in all our patients was diaphragmatic weakness, other factors often contribute to the acute decompensation. In patients 1 and 2 there was atelectasis, a complication of retained secretions due to respiratory muscle weakness. In patients 3 and 4, acute respiratory failure seemed to be precipitated by minor pulmonary infections and mild chronic obstructive pulmonary disease, which may have decreased respiratory reserve.

Diaphragmatic weakness in our patients seemed to be disproportionately severe compared with limb involvement. Six of our seven patients were walking at the time of presentation, and patient 5 continued to walk one year later. Four of our patients did not complain of any limb weakness. Only one (patient 1) had mild tongue weakness and none had swallowing difficulty.

Three of our patients (1, 5, and 7) had amyotrophic lateral sclerosis and four (2, 3, 4, and 6) had progressive muscular atrophy, with only lower motor neuron signs. Of the 12 reported patients,³⁻¹⁰ seven can be classified as amyotrophic lateral sclerosis and five as progressive muscular atrophy. As progressive muscular atrophy represents less than 10% of cases of motor neuron disease,¹⁵ its representation may be increased among this group of patients.

PATHOLOGICAL FEATURES

All four patients showed severe anterior horn cell loss in the spinal cord. With normal microscopy of the motor cortex and correspondingly only slight or no loss of myelinated axons from the corticospinal tract, upper motor neuron involvement in these patients was mild or non-existent. This supports our conclusion based on clinical and electrophysiological studies that respiratory failure is due to degeneration of phrenic motor neurons, rather than upper motor neuron involvement.

Although one report described selective involvement of the phrenic nuclei¹⁰ located in the ventromedial cell column of C3 to C5, we did not find such predilection in our four patients, even with morphometric analysis in patient 7. However, the cervical cord was severely involved in all of our patients. Our findings were similar to those for three other patients reported.^{3 6} Given the clinical and electrophysiological features of our patients, it is likely that the phrenic motor neurons were more severely involved than motor neurons of limb muscles. The reason for the failure to show this pathologically is unclear. Some phrenic motor neurons may be involved but have not yet progressed to neuronal loss. Also, microscopy may be less sensitive than clinical examination and electrophysiology in detecting small but clinically significant differences.

OUTCOME

None of our seven patients was successfully weaned from the ventilator. Six died, four after having declined further respiratory support and one from an unrelated condition (small bowel perforation). Patient 5 is alive but dependent on a home ventilator. Among the cases reported, only one became independent of a ventilator,⁴ six required nocturnal ventilatory support,^{4-7 9} two remained fully dependent on a ventilator, and three died on full ventilation.^{3 6 10} Thus, weaning from the ventilator is difficult for these patients. However, a reasonable quality of life can be maintained in some patients with ventilatory support.

ETHICAL ISSUES

All our patients presented challenging ethical issues. As their neuromuscular disorder was previously undiagnosed, the question of life support had not been discussed and yet they had been precipitated into lifetime dependency on a ventilator. As they had normal cognitive functions and were able to communicate, we discussed the diagnosis and prognosis with the patients and their families in a frank and compassionate manner. The patients were given ample time to consider their options. Four of our patients chose to discontinue ventilatory support. We offered long term ventilation, which can greatly improve the quality of life in selected cases with motor neuron disease,^{5 13} especially those with respiratory muscle weakness without severe bulbar involvement.⁵ Patient 5 in our series is such an example. However, long

term ventilation requires an exceptional commitment from the patient and family.

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