Diaphragmatic paralysis due to spinal muscular atrophy

An unrecognised cause of respiratory failure in infancy?

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SUMMARY An unusual form of spinal muscular atrophy presenting with respiratory failure was observed in four infants from two families. In one, whose death was attributed to pneumonia, the diagnosis was inferred retrospectively after two siblings died from an identical illness and were shown to have diaphragmatic paralysis and the typical electrophysiological and histological features of spinal muscular atrophy. Other signs of skeletal muscular weakness were absent or inconspicuous. The fourth, unrelated infant presented in an identical way but has survived for over a year on a ventilator. Two months after the onset of respiratory paralysis, more extensive skeletal muscular weakness was seen. Other infants, dying of unexplained respiratory illness, may have this disorder and some may be included in the miscellany of disorders that constitute the sudden infant death syndrome.

Bilateral diaphragmatic paralysis is rare in infancy¹ and results in severe, often lethal, respiratory failure.^{1 2} Diagnosis is difficult without radiological screening, and the respiratory difficulty may easily be ascribed to a non-neuromuscular cause.² Mellins *et al*² described two infants who presented with respiratory failure as a result of diaphragmatic paralysis due to an unusual variant of spinal muscular atrophy. Standard reference texts emphasise the relative sparing of the diaphragm more usually seen in this disease and none mentions diaphragmatic paralysis occurring before other evidence of skeletal muscular weakness. Even when spinal muscular atrophy presents, exceptionally, with respiratory difficulty, intercostal rather than diaphragmatic weakness is the rule and other signs of skeletal muscular weakness are clinically obvious.³ This report describes four patients with spinal muscular atrophy and early diaphragmatic involvement and discusses possible ways in which other, unrecognised cases may present.

Family history (patients 1, 2, and 3)

The parents of this family of four children are aged 21 and 22 years and although apparently non-consanguineous, both sets of grandparents are from the same relatively isolated district of the Dumfries

and Galloway region of Scotland and a minor degree of consanguinity cannot be excluded. A first cousin of the mother had died aged 3 months of a 'cot death' but the family history is otherwise unremarkable.

Case reports

Case 1. Born at term in September 1980 after an uneventful pregnancy, this girl died aged 9 weeks after a two day respiratory illness. Permission for necropsy was refused and the cause of death was given as pneumonia. She had been previously healthy and no neurological disorder had been suspected.

Case 2. This boy was born at term in September 1981; his birthweight was 3.5 kg. There were no perinatal problems and his early development was normal. He developed signs of respiratory difficulty at the age of 4 months and was given amoxycillin. A few days later he was admitted to his district hospital with a presumptive diagnosis of pneumonia. Diaphragmatic dysfunction was suspected when chest radiography showed an elevated right hemidiaphragm without parenchymal lung pathology. Radiological screening of the diaphragm showed paradoxical movement on the right with diminished normal

movement on the left. He was transferred to the regional paediatric intensive care unit when the need for ventilatory support became evident. On arrival he was in obvious respiratory distress, and blood gas estimation confirmed severe respiratory failure. Respiration seemed to be entirely dependent on intercostal and accessory muscles and repeat radiological screening showed no diaphragmatic movement on attempted inspiration. Assisted ventilation was instituted and examination completed thereafter. He was an alert, visually responsive infant who smiled readily and showed normal interest in his surroundings. Proximal muscle strength seemed generally normal but tendon reflexes were absent and no active foot movements were observed. Sensory examination showed no abnormalities. Bladder function was normal and there were no long tract signs. The cranial nerves were normal.

The electrophysiological findings indicated a neuronopathic disorder. All nerves were difficult to stimulate and showed marginally reduced motor and sensory conduction velocity. At the second examination, two weeks after admission, it was not possible to stimulate any nerves in the lower limbs and there had been further reduction in motor conduction velocities in the ulnar and median nerves (13 and 27 m/second). Electromyographic examination showed greatly reduced volitional activity in tibialis anterior, and in abductor hallucis no voluntary activity could be detected. No response could be elicited by phrenic nerve stimulation in the neck. Calf muscle biopsy showed denervation changes and the sural nerve, macroscopically somewhat atrophied, showed absence of large myelinated axons. Other abnormalities detected were non-specific increases in plasma lactate dehydrogenase (5312 IU/l) and creatine kinase (424 IU/l) concentrations. An unexplained finding was a persisting thrombocytosis ($568 \times 10^9/l$).

Supportive management was continued but no specific treatment was given. He died suddenly one month after admission to hospital, having been ventilator dependent for all but the first three days of his illness.

Necropsy findings

The immediate cause of death was aspiration of gastric contents. The macroscopic examination was otherwise normal. Histological abnormalities (Fig. 1) were confined to the peripheral nervous system, skeletal muscle, and spinal cord. Anterior horn cells were reduced in number and several showed recent degenerative change. This abnormality was seen in all sections examined but was most obvious in the cervical enlargement. The phrenic nerves showed a

Fig. 1 Ventro-medial grey matter from the cervical cord of the patient in case 2 showing (a); diminished numbers of large anterior horn cells and a 'cell ghost', and (b); an anterior horn cell undergoing neuronophagia. (Stained with luxol fast blue-cresyl violet; $\times 125$).

noticeable reduction in the number of large myelinated axons and occasional degenerating axons. This appearance was seen to a lesser degree in other peripheral nerves examined. All muscles examined showed extensive neurogenic atrophy with occasional groups of hypertrophied fibres. This appearance, without hypertrophy, was also seen in the diaphragm. A few muscles showed focal areas of necrosis with quite considerable calcium deposition.

Case 3. This girl was born in January 1983 and had no perinatal problems. Neurological examination at the age of 3 weeks showed no abnormalities apart from difficulty in eliciting the ankle jerks. Electrophysiological examination, however, was unequivocally abnormal and gave results similar to those observed in the previous sibling. Serial examinations showed deterioration, and by 10 weeks of age it was not possible to stimulate any lower limb nerves and the electromyogram showed clear

evidence of denervation with reduced volitional activity and the appearance of abnormal spontaneous activity. Despite these findings the clinical examination remained remarkably normal and the quadriceps reflexes were still present. It was no surprise when, at the age of 2 months, progressive respiratory symptoms developed.

A subtle but definite change in respiratory pattern was the earliest feature. This consisted of exaggerated intercostal movements and bouts of tachypnoea without obvious respiratory distress. Indeed, a conspicuous feature throughout the illness was the lack of any appearance of breathlessness. In the few days before death she experienced some feeding difficulty and transient episodes of cyanosis, but even 12 hours before her death she was smiling and playing quite contentedly. By this stage there was complete areflexia but signs of muscle weakness were, as in the previous sibling, minimal and confined to the distal lower limbs. Radiological screening confirmed the absence of normal diaphragmatic movement. The platelet count ($838 \times 10^9/l$), plasma creatine kinase (276 IU/l), and lactate dehydrogenase (542 IU/l) were increased but there were no specific haematological or biochemical abnormalities. The sural nerve could not be identified when biopsy was attempted but muscle histology showed evidence of denervation (Fig. 2a). In the week before death a course of plasmapheresis was given and corticosteroids administered, both without apparent effect. She died suddenly aged 11 weeks and necropsy permission was refused.

Case 4. The parents of this girl are aged 24 and 21 years and are unrelated. The father has two healthy children by a previous marriage. The gestation and birth were normal. The father later recalled that her cry was weak from birth but at first she fed normally. At the age of 4 months she was admitted to her district hospital with left upper lobe pneumonia. There was a history of tachypnoea and increasing difficulty in feeding for one month, and of recent loss of head control in the prone position. Despite treatment with ampicillin and cloxacillin she collapsed two days after admission and required oxygen and tube feeding. Because she seemed hypotonic a diagnosis of Werdnig-Hoffmann disease was considered and she was transferred to the Regional Neurological Centre. On arrival she was in severe respiratory distress with striking intercostal recession, paradoxical abdominal movement, and vigorous use of the accessory muscles including powerful neck retraction. There were active struggling movements of all four limbs, with powerful palmar and plantar grasp reflexes but she was moderately hypotonic. On oxygen treatment she

Fig. 2 (a) Calf muscle biopsy from the patient in case 3 showing atrophied and hypertrophied fibres. (Adenosine triphosphate (pH 9.4); $\times 75$).

(b) Quadriceps biopsy from the patient in case 4 showing some fibre type grouping and two small groups of atrophied fibres (arrowed). (Adenosine triphosphate (pH 4.6) and marred by ice crystal artefact; $\times 180$).

remained tachypnoeic but became attentive with normal tone and posture, retained tendon reflexes, and normal muscle strength except for incomplete extension of the fingers of the right hand. There was a normal withdrawal and grimace to peripheral pin prick stimulation and bladder function was normal. Chest radiograph showed a high right hemidiaphragm and residual left upper lobe consolidation. An edrophonium test was negative. Because of the selective weakness of the diaphragm and intercostal muscles a myelogram was performed under general anaesthesia to rule out a compressive lesion of the cervical and thoracic cord. This and the cerebrospinal fluid examination were normal. After

the procedure, assisted ventilation was required in addition to tube feeding. Repeated clinical examination at this time showed no evidence of limb muscle wasting or weakness and electromyographic examination of the left biceps and deltoid muscles was normal. Stimulation of the left phrenic nerve in the neck elicited an evoked potential in the eighth intercostal space with a normal latency (3.4 milliseconds) but reduced amplitude (500 μ v). Radiological screening of the diaphragm showed no movement on attempted spontaneous respiration or on electrical stimulation with single supramaximal stimuli, but slight movement was seen during tetanic stimulation. The serum creatine kinase and blood lead concentrations were normal. A diagnosis of isolated respiratory muscle paralysis of unknown cause lead to a decision to continue ventilation until diaphragmatic plication or the fitting of a phrenic nerve pacemaker could be considered. Partial collapse of the left lung developed. A tracheostomy was performed, bronchoscopy showed no bronchial obstruction and the lung re-expanded with continued ventilation and antibiotic treatment. The child played actively with her parents and nurses.

After two months in hospital her limb movements gradually became less vigorous and after a further month her tendon reflexes had become absent. Wasting was apparent in the biceps, triceps, and quadriceps. Repeat electrophysiological examination at the age of 6 months showed reduced motor conduction velocities in ulnar, median, and common peroneal nerves (37, 28, and 12.5 m/second) and electromyogram showed reduced recruitment of voluntary units in quadriceps and tibialis anterior. These findings were interpreted as suggesting an anterior horn cell lesion. A biopsy of the left quadriceps muscle showed appearances consistent with this diagnosis (Fig. 2b).

At this stage a diagnosis of atypical spinal muscular atrophy was made. She was transferred at the age of 7 months to a unit nearer her home where she has, to date survived a further 15 months. At the age of 13 months her muscle involvement had become more severe but remained highly selective with extensive weakness of the upper limb muscles, but, in the lower limbs, good preservation of the hip abductors and extensors and relative preservation of the quadriceps but severe weakness of hip flexion and adduction and of the hamstrings. She lay with her hips abducted beyond 90° and her knees extended and made powerful jerking bilateral abduction movements of the lower limbs when frustrated or upset. Sensation and bladder function remained normal and there was no facial weakness. Radiographs showed no hip dislocation. She has subsequently been mobilised in a pram with a

portable ventilator and attempts are being made to obtain a suitable wheelchair with a combined portable ventilator. There seems to have been no further loss of muscle power since the age of about 15 months. She has gradually been abandoned by her parents.

Discussion

The diagnosis of spinal muscular atrophy is beyond doubt in the second patient, and in the third and fourth patients both the electrophysiological and the histological findings are highly suggestive of this.⁴⁻⁸ No other diagnosis seems tenable. Mellins *et al*² went to considerable lengths to establish that their two original cases were indeed examples of an unusual variant of spinal muscular atrophy and although we have not employed all the detailed histological studies which they used, the conclusion that the disorders are identical seems inescapable. They observed reduced motor nerve conduction velocities in their patients, a finding which has been reported subsequently in the severe form of the disorder⁹ and was also seen in our patients. Sensory abnormalities, seen in two of our patients, are unusual but have been described previously by Marshall and Duchon.¹⁰ Interestingly, they observed considerably greater diaphragmatic involvement than is generally reported, a feature which was most noticeable in their more severely affected cases.

Autosomal recessive inheritance is clearly shown in the second and third patients and it seems reasonable to infer that the first died of the same disorder. A similar family history of unidentified lethal respiratory illness was encountered in the first of the two original cases described by Mellins *et al*.² The repetition of the same clinical pattern in successively affected siblings implies a genetic entity distinct from either classic (type I) or chronic childhood (type II) spinal muscular atrophy.¹¹ The arrest of the progression in case 4, though it may prove eventually to be temporary, suggests that this form, like type II, may run an intermittent and unpredictable course.

Both of these instances illustrate how readily this disorder may be misdiagnosed as a primary respiratory illness and it is possible that other cases have also been overlooked. Neurological abnormality, even if present at the onset of respiratory difficulty, is not at all obvious and is easily missed in an infant whose illness seems to affect an entirely separate system. Neither is the abnormal respiratory pattern particularly distinctive, and in the second patient only the finding of an elevated hemidiaphragm alerted the clinician to the possibility of diaphragmatic paralysis. It is unlikely that this finding would

have provoked comment but for the absence of concomitant lung pathology more usually associated with this radiological appearance. The familial recurrence of a lethal respiratory illness is more likely to provoke thoughts of cystic fibrosis or, if this diagnosis is excluded by necropsy, a familial immune deficiency syndrome. The subtle neuropathological features of this disorder might easily be overlooked unless looked for specifically.

The rapid progression and absence of compelling symptoms until an advanced stage of respiratory failure is reached was a particularly striking feature and it has to be considered that certain cases of seemingly unexplained sudden infant death syndrome may be due to this disorder. Diaphragmatic dysfunction is most detrimental to respiratory function when the subject is in the supine position.¹²⁻¹⁴ It is probable that the loss of postural influence on intercostal muscle tone, known to occur during sleep,¹⁴ would further compound this effect. There exists, therefore, a potential mechanism whereby this disorder may present as a case of sudden infant death, a syndrome in which familial recurrence is recognised.¹⁵ An infant with diaphragmatic weakness but very little respiratory difficulty while awake might develop severe, even fatal respiratory failure during sleep in the supine position. This is precisely what seemed to happen in our third patient who was active and smiling only 12 hours before dying of respiratory failure during sleep. Such a mechanism remains conjectural at present but should be testable by appropriate histological examination in infants dying suddenly and unexpectedly, particularly if preceded by apparently trivial respiratory symptoms.

The presentation with isolated respiratory muscle weakness requiring ventilation has left our fourth patient in a predicament which may persist even for some years. If the condition had been recognised earlier the successive steps of tube feeding, ventilation, and tracheostomy might not have been taken and only the usual care given in the management of cases of Werdnig-Hoffman disease would have been offered, as in patient 3. Even a more extensive electromyographic examination or muscle biopsy at the age of 4 months, however, might not have given a firm diagnosis, and certainly a decisive plan for conservative management of future cases will depend on a strong clinical suspicion of the diagnosis being reached at an early stage. The clinical picture of progressive diaphragmatic paralysis, even in the absence of other signs, with a normal myelogram (ruling out an intrinsic spinal cord tumour or vascular malformation) can probably be accepted as diagnostic of this form of spinal muscular atrophy at this age.

Addendum

Since preparing this paper we have become aware of another example of this disorder. A 2 year old boy presented at the age of 6 weeks with increasing respiratory difficulty eventually requiring ventilation. Initial neurological examination was normal apart from bilateral diaphragmatic paralysis. One month after ventilation was instituted generalised muscle weakness with areflexia developed. Muscle biopsy and electromyogram were initially normal but at the age of 6 months showed the typical features of spinal muscular atrophy. Apart from his neck muscles, which are relatively strong, and facial and eye movements he is incapable of any voluntary movement but remains alert and communicates well with his parents.

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