Correspondence

Diaphragmatic paralysis due to spinal muscular atrophy

Sir,

We read with interest the paper on diaphragmatic paralysis due to spinal muscular atrophy by McWilliam *et al.*¹ Their report of patients with diaphragmatic paralysis in association with a clinical picture suggestive of spinal muscular atrophy is of particular interest, since we have also been aware of this association over the past five years.

A girl born in 1981 was admitted to hospital at the age of 2 months with respiratory difficulty and poor feeding. At the time of presentation she was profoundly hypotonic and areflexic. A chest radiograph showed elevation of both diaphragms and there was poor diaphragmatic movement bilaterally on radiographic screening. Despite plication of the right hemidiaphragm (which was most severely affected) she gradually deteriorated and died at the age of 5 months of a staphylococcal pneumonia. Postoperatively she remained ventilator-dependent and showed progressive hypotonia and muscle wasting, typical of spinal muscular atrophy. A diaphragmatic muscle biopsy obtained at thoracotomy showed partial denervation atrophy, and at necropsy skeletal muscle biopsy showed similar changes and there were reduced numbers of anterior horn cells in the spinal cord sections.

A second infant, a boy, was admitted at the age of 8 weeks after a rapid respiratory deterioration. He had a two week history of snuffles, cough, and poor feeding. He was extremely hypotonic and areflexic, and it was noted from the family history that a sibling had died at the age of 9 weeks of an undiagnosed respiratory illness. The chest radiograph showed elevation of the right dome of the diaphragm. Efforts to wean him from ventilation including plication of the right diaphragm were unsuccessful. The child died at the age of 9 weeks with progressive peripheral muscle wasting and respiratory failure. Biopsy of the diaphragm taken at thoracotomy showed partial denervation atrophy, and examination of skeletal muscle at necropsy confirmed these findings.

In the light of our experience with these patients, post mortem muscle histology was performed on two further infants in whom a clinical diagnosis of spinal muscular atrophy had been made. In both these cases the diaphragm muscle had seemed thin and showed changes of denervation atrophy, although radiological diaphragmatic movement had been evident in life.

Mellins *et al.*² first described the association between diaphragmatic paralysis and spinal muscular atrophy. The report by McWilliam *et al.*¹ together with our experience, would support the view that this association is not as rare as hitherto believed. The proposal that this condition should be considered in cases of sudden infant death seems appropriate. In two of our infants there was an acute onset

of respiratory symptoms. Furthermore, we would emphasise that spinal muscular atrophy should be considered in all infants with eventration of the diaphragm, and that diaphragmatic muscle biopsy should be taken at the time of surgical plication. Denervation changes were present in diaphragmatic muscle biopsies in all our patients (two obtained before death), although in one infant skeletal muscle biopsy from the vasculus lateralis showed normal histology. In addition to diaphragmatic denervation atrophy, this patient showed loss of anterior horn cells in the lower thoracolumbar region on serial section of the spinal cord.

References

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- ² Mellins RB, Hays AP, Gold AP, Burdon WE, Bowdler JD. Respiratory distress as the initial manifestation of Werdnig-Hoffman disease. *Pediatrics* 1974;**53**:33-40.

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Dr McWilliam comments:

I was most interested to hear of three further cases of this disorder which I regard as a distinct genetic variant of spinal muscular atrophy rather than an association of diaphragmatic paralysis with spinal muscular atrophy type 1. The two cases described raise the important issues of early diagnosis and subsequent management. Our experience suggests that with appropriate electrophysiological investigations (motor nerve conduction studies and comprehensive electromyography) diagnosis is possible without the need for histological examination of the diaphragm. With awareness of the diagnosis I would suggest that neither ventilatory support nor plication of the diaphragm are appropriate. I certainly agree that this diagnosis should be considered in all cases of diaphragmatic paralysis or eventration, particularly as hypotonia, if present, may be considered secondary to the respiratory disorder and therefore dismissed.

Perinatal hepatitis B virus detection by hepatitis B virus-DNA analysis

Sir,

We read with interest the paper by De Virgiliis *et al.*¹ comparing this new technique with hepatitis B antigen

and antibody determination in assessing the risks of perinatal transmission of hepatitis B. It is well known that hepatitis Be antigen correlates well with the presence of complete viral particles in the serum, active viral replication, and high infectivity in the perinatal period and at other times. The authors find hepatitis B virus-DNA, detected by spot hybridisation technique not only in four hepatitis Be antigen positive sera but also in 10 of 89 maternal sera containing hepatitis Be antibody, and in the summary state that the technique is useful in identifying mothers who might transmit infection to their offspring. This study does not confirm, however, that the presence of hepatitis B virus-DNA without hepatitis Be antigen positivity indicates a state of infectivity of these mothers. Evidence of hepatitis B virus infection was found in one of 10 infants from hepatitis Be antigen negative, hepatitis B virus-DNA positive mothers, and in none of 82 infants from hepatitis Be antigen negative, hepatitis B virus-DNA negative mothers, giving a P value by Fisher's exact test of 0.108.

All the infants in the study received hepatitis B immunoglobulin at birth and at 3 and 6 months of age. Since this immunoprophylaxis has been shown to influence the rate of infection of infants, further studies will be required to assess the infective implications of hepatitis B virus-DNA in maternal serum containing no hepatitis e antigen. A more meaningful and potentially helpful conclusion may be obtained in infants of hepatitis Be antigen negative mothers for whom hepatitis B immunoglobulin is not available.

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Dr De Virgiliis and co-workers comment:

We thank Drs Mowat and Mieli-Vergani for the interest they have shown in our short report.¹

The detection of hepatitis Be antibody in the serum of chronic hepatitis B surface antigen carriers does not coincide with the disappearance of hepatitis B virus-DNA, which is the expression both of high hepatitis B virus replication and infectivity.² This finding explains the transmission of hepatitis B virus and the occurrence of fulminant hepatitis in infants born to hepatitis Be antibody positive mothers.^{3,4}

Accordingly, several pregnant women with hepatitis Be antibody in our series showed serum values of hepatitis B virus-DNA similar to those who were hepatitis Be antigen positive. Hepatitis B immunoglobulin administration in all our newborns from hepatitis B surface antigen positive mothers has obviously reduced the risk of the transmission of infection making statistical analysis useless. Nevertheless we have noticed hepatitis B virus infection in three infants, all born to hepatitis B virus-DNA positive mothers. One of these was hepatitis Be antibody positive and the other two were hepatitis Be antigen positive. We agree with Drs Mowat and Mieli-Vergani that a clinical study without hepatitis B immunoglobulin administration

would allow a more useful analysis (as already stated in our paper) but we do not believe this to be ethical.

References

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Inspiratory:expiratory ratio and pulmonary interstitial emphysema

Sir,

Dr Greenough and colleagues' study¹ has emphasised that mechanical ventilation at rates of 100 per minute can exacerbate established pulmonary interstitial emphysema. They speculated that at fast rates of mechanical ventilation insufficient expiratory time may cause further accumulation of trapped air.

In one of the studies cited² Ng and Easa described two patients. In the first, early pulmonary interstitial emphysema deteriorated during mechanical ventilation at 100 per minute while in the second pulmonary interstitial emphysema appeared during mechanical ventilation at the same rate. In both there was complete resolution of early pulmonary interstitial emphysema after hand ventilation with a resuscitation bag using peak pressures of 10 to 15 cm H₂O and end expiratory pressures of 3 to 5 cm H₂O for 2 to 36 hours. The authors stressed that infants receiving high ventilator pressures or with pulmonary interstitial emphysema of several days' duration might not respond so well. Neither study^{1,2} reported the inspiratory:expiratory ratio used.

We have investigated the effects of hand versus mechanical ventilation on the proximal airway pressure waveform. We used (a) a Penlon bag with a refill valve (circuit compressible volume less than 50 ml) and (b) a Sechrist IV100B time cycled, pressure limited, continuous flow ventilator with a Fisher Paykel MR 500 humidifier (circuit compressible volume 500 ml). The ventilator respiratory rate was set at 120 per minute and the inspiratory:expiratory ratio at 1:1. Each was connected to a neonatal lung simulator (Specialised Laboratory Equipment, Croydon) set to give compliance 0.5 ml/cm H₂O and resistance 100 cm H₂O/l/per sec at a flow of 6 l/min. Pressure traces were recorded on paper using a Hewlett Packard 8805C transducer. Typical traces are shown in the Figure. Hand ventilation gave an inspiratory:expiratory ratio which was always less than 1:3.6 at rates of 120 to 150 per minute.

If an inspiratory:expiratory ratio considerably greater