Fig (a) Variability of fibre size with some central nuclei and increased connective tissue. Phagocytosis. (peroneus brevis; HE × 400). (b) Scattered necrotic fibres in deltoid muscle. (HE × 400).

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Adult onset of nemaline myopathy presenting as diaphragmatic paralysis

Sir: Nemaline myopathy is a relatively benign congenital myopathy presenting in children as nonprogressive or slowly progressive muscle weakness. The neonatal form, however, may manifest as respiratory distress. Several cases of adult-onset nemaline myopathy have also been reported. 1–4

We report a case of adult-onset nemaline myopathy with predominantly diaphragmatic involvement. The patient presented with pulmonary symptoms and subsequently died from respiratory arrest.

A 32 year old Caucasian male was first admitted to hospital in September of 1979 for evaluation of shortness of breath and somnolence. He had been in good health until April 1979, when he began experiencing dyspnoea not clearly related to exertion or somnolence, and paroxysmal episodes of dry cough. His chest was clear to auscultation and percussion, but pulmonary

function testing revealed a restrictive pattern. Arterial blood gases showed a pO₂ of 59 mm Hg and a pCO₂ of 53 mm Hg. Right heart catheterisation revealed mild pulmonary hypertension with an systemic arterial pressure of 55 mm Hg; no evidence of intracardiac shunt was found. A presumptive diagnosis of interstitial lung disease was made and the patient was discharged on oral corticosteroids, diuretics and the cough syrup, hydromorphone.

One month later, the patient suffered temporary respiratory arrest thought secondary to inadvertent hydromorphone overdose. In view of his lack of response to treatment, the patient was hospitalised for further evaluation. During this second admission, physical examination revealed an obese, somnolent white male with a resting tachycardia of 125 beats/minute and rapid shallow breathing at 25/minute. The lungs were again clear.

A chest radiograph was normal. Forced vital capacity (FVC) was 1-73 (23% of predicted), forced expiratory volume (FEV₁) was 1-2 (29% of predicted), and the FEV₁/FVC ratio was 70%. Arterial blood gases on room air revealed a pH of 7-46, a pCO₂ of 50 mm Hg, and a pO₂ of 50 mm Hg. During voluntary hyperventilation the pCO₂ decreased to 20 mm Hg. During a 12 minute treadmill test, pCO₂ decreased from 63 to 40 mm Hg, and the pO₂ increased from 59 to 63 mm Hg. Polysomnography revealed normal sleep stages with no nocturnal apnea, but marked arterial oxygen desaturation to 48%; the pCO₂ rose to a high of 75 mm Hg. Fiberoptic bronchoscopy was normal. To exclude bronchiectasis, bronchography was planned, but after premedication the patient experienced respiratory arrest. He was resuscitated, but developed neurological sequelae characterised by generalised seizures and speech and memory dysfunction. Prolonged mechanical ventilation was required because of persistent hypoventilation despite successive treatment with protriptyline, acetazolamide and methylphenidate. A tracheostomy was eventually performed.

In March of 1980, 11 months after the onset of his symptoms, the patient was transferred to our institution for evaluation of distal muscle wasting, a question of a new left parietal lobe infarct, poorly controlled seizures, and prolonged respiratory failure labelled as primary alveolar hypoventilation.

Careful history revealed the presence of subtle symptoms of underlying neuromuscular disease since childhood. He had always walked on his toes and stumbled a lot. He had had several Achilles tendon lengthening procedures without benefit. He had never been athletic and led a relatively sedentary lifestyle as a security guard. His calf muscles had always been weak, but there had been no recent progression. Physical examination revealed a febrile, respirator-dependent, mildly obese, very somnolent young man. A tracheostomy tube was in place. Lung examination revealed scattered rhonchi. There was a prominent P₂ and a grade II/VI systolic ejection murmur in the pulmonary area. Thoracoabdominal dissociation was noted when the patient breathed without ventilator assistance. Neurological examination revealed generalised muscle weakness with mild hypotonia, symmetrical distal muscle wasting, and pes equinovarus with shortening of the Achilles tendons. Deep tendon reflexes were physiologic and sensory testing was normal. Haemoglobin was 16-5 gm%, hematocrit 54%, erythrocyte sedimentation rate 7 mm/h, and CK 88 U (normal <200 U). Rheumatoid factor and antinuclear antibodies were absent and thyroid function tests were normal.

A chest radiograph revealed small lung volumes, with bilateral diaphragmatic elevation. An electrocardiogram showed sinus tachycardia and incomplete RBBB. EEG and CT scan of the head showed focal changes in the left parietal lobe region consistent with infarction. The FVC was 1-65 l. Maximal occluded inspiratory and expiratory pressures were both less than 50 cm H₂O. Static lung compliance measured on the ventilator was 100 cc/cm H₂O. The lung elastic recoil (Pₐ) measured at near total lung capacity was >21 cm H₂O. The ventilatory response to CO₂ measured after rebreathing technique was flat. An electromyogram revealed diffuse short-duration, low amplitude motor unit action potentials consistent with myopathy. A quadriceps muscle biopsy demonstrated small rod bodies characteristic of nemaline myopathy.

The patient’s seizures were controlled when therapeutic phenytoin levels were achieved, his fever resolved with broad spectrum antibiotics and gas exchange improved to where he maintained a pCO₂ between 50 to 60 mm Hg with spontaneous respirations. Continued nocturnal ventilatory support was recommended in view of the severe respiratory muscle weakness and the previous respiratory arrests. However, the patient became increasingly depressed, declined the recommendations and insisted on having the tracheostomy closed. He remained stable for 6 months but experienced another respiratory arrest and expired after a brief hospitalisation elsewhere.

At necropsy, multiple muscle samples from the extremities and diaphragm were examined by histochemical and electron microscopic studies. All muscles showed evidence of nemaline, with the heaviest concentration of nemaline rods being in the diaphragm. Virtually all diaphragmatic muscle fibres harboured large collections of rod bodies. The central nervous system was normal except for an old parietal lobe infarction. The lungs revealed patchy atelectasia, mild emphysematous changes, hyperaemia, and a recent small infarction. There was no evidence of interstitial disease.

Respiratory failure due to selective diaphragmatic weakness has been previously described as a presenting symptom of neuromuscular disease in acid maltase deficiency, motor neuron disease, limbgirdle muscular dystrophy, and myotonic dystrophy. Diaphragmatic involvement with abundance of nemaline in muscle fibres in neonatal and childhood nemaline myopathy is well described. There are a few reports of adult-onset nemaline myopathy with diaphragmatic involvement. One patient, similar to ours, presented with severe pulmonary symptoms and mild, non-progressive muscle weakness, and expired with ventilatory failure. Necropsy revealed nemaline in the diaphragm and skeletal muscles. Another report described an adult who experienced no pulmonary symptoms, but suffered sudden cardiac death; necropsy revealed evidence of nemaline in less than 4% of diaphragmatic muscle fibres, but in more than 56% of gastrocnemius fibres. These reports, along with our case, suggest a relationship between the degree of diaphragmatic involvement and the degree of respiratory dysfunction in patients with nemaline myopathy.

Our patient was initially suspected to have interstitial lung disease on the basis of a restrictive ventilatory defect on pulmonary function testing and small lung volumes radiographically. Only later did reduced maximal inspiratory and expiratory pressures point to respiratory muscle weakness and normal lung compliance studies weighed against parenchymal lung disease. Careful observation of thoracoabdominal movements alone could have directed attention to diaphragmatic dysfunction.

Of particular interest in our patient was the blunted response to CO₂ that initially suggested primary alveolar hypoventilation. This phenomenon has been previously reported as being fairly characteristic of patients with bilateral diaphragmatic paralysis due to a variety of neuromuscular diseases. There is a high risk of severe arterial oxygen desaturation and hypercarbia during sleep, in the absence of apnoea in these patients. This fact should be emphasised, as
our patient sustained two respiratory arrests related to the use of narcotics. Therefore, avoidance of hypnotics and narcotics in this group of patients is strongly recommended.

Recognition of the fact that adult-onset nemaline myopathy may present with pulmonary symptoms due to diaphragmatic paralysis rather than muscle weakness is of utmost importance to the clinician, since these patients, otherwise, might be subjected to unnecessary and often invasive investigations or inappropriate therapy.

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Coincidence of myotonic dystrophy and Down’s syndrome (Trisomy 21)

Sir: In 1981, Bird1 described the first case of myotonic dystrophy associated with Down’s syndrome (trisomy 21) and suggested that myotonic dystrophy could have a small but significantly increased frequency of chromosomal aberrations, bearing in mind previous descriptions of myotonic dystrophy associated with other chromosomal anomalies.2–5 The following is a report of a new case of myotonic dystrophy associated with Down’s syndrome.

A 15 year old girl was diagnosed as having Down’s syndrome (trisomy 21 with deletion of long arms) since birth. In her family, the father, a sister of the father and a sister of the patient suffered from myotonic dystrophy. At her birth, the father was 36 years of age and her mother 34, their respective karyotypes being normal. She had weak suction with cough and nasal reflux, eye anomalies, very little spontaneous mobility and muscular hypotonia. She began walking on her own at 18 months of age. At the age of four, she was prescribed corrective lenses because of visual difficulty. Menarche was at the age of 9 years.

At the age of 15 years, she was examined in our department. There was obesity, intellectual retardation, inexpressive and myopathic facies, thick lips, mongoloid palpebral clefts, cataracts in both eyes, high arched palate, caries and badly positioned teeth. She had weakness of the masticatory muscles and, to a lesser degree, distally in the extremities. There was spontaneous myotonia of the hands, which improved with exercise but was not influenced by the cold, and percussion myotonia of the tongue, forearms and hands; generalised muscular hypotonia without a clear muscular atrophy was observed; global incapacity was slight. The electromyogram showed typical myotonic discharges. The levels in blood of CK, aldolase, GOT, GPT, LDH, T3, T4, TSH, PRL, FSH, LH, GH, ACTH and cortisol were normal. An oral glucose tolerance test following ingestion of 75 g of glucose showed: fasting 68 mg/100 ml; 30 minutes 106 mg/100 ml; 1 hour 115 mg/100 ml; 2 hours 71 mg/100 ml and 3 hours 69 mg/100 ml. The IgG in serum was 700 mg/100 ml (normal 800–1200), with normal IgA and IgM. The WAIS intellectual coefficient was 40. Cerebral CT scan was normal.

Considering that the frequency of Down’s syndrome (trisomy 21) is 1 in every 600 births6 and that myotonic dystrophy has a prevalence of 2 to 5 cases per 100,000 population,7 the probability of both diseases being present in the same individual is extremely low. Besides our patient, there exists only one report of this association.8 However, the coexistence of myotonic dystrophy with another chromosomal anomaly, such as Klinefelter’s syndrome (47, XXY),2–5 has been described. In addition, Nadler et al9 reported two brothers with myotonic dystrophy and phenotypic features of Klinefelter’s syndrome before cytogenetic evaluations were available, and Sparkes and colleagues10 described a patient with Klinefelter’s syndrome and myotonic dystrophy, although there was not a family history of myotonia, frontal balding, cataracts or endocrine dysfunction.

Further descriptions of new cases are necessary to determine whether these associations are merely coincidences, or whether myotonic dystrophy is associated with an increase in frequency of chromosomal anomalies.

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