Thorax 1988;**43**:478–479

Short reports

Diaphragm weakness in Charcot-Marie-Tooth disease

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ABSTRACT Two patients are described with Charcot-Marie-Tooth disease and chronic peripheral neuropathy. Both had dyspnoea, orthopnoea, and evidence of severe diaphragm weakness. Expiratory muscle function was well preserved and abnormalities of gas exchange during sleep were only minor.

Charcot-Marie-Tooth disease comprises a group of inherited disorders characterised by chronic degeneration of peripheral nerves and nerve roots, resulting in distal muscle atrophy. Respiratory muscle weakness is not a generally recognised feature. One previous report described diaphragmatic dysfunction in two siblings with the disease,[1] although non-insulin dependent diabetes was also present. We describe two patients with severe diaphragmatic dysfunction not explained by any additional pathology.

Patients

Patient 1 was a 58 year old man with severe, generalised, predominantly motor neuropathy, with some loss of sensation in the legs. Elevation of both hemidiaphragms on the chest radiograph and paradoxical diaphragm motion detected by fluoroscopy had first been noted five years previously. At that time vital capacity was 1 litre, having been 2 l several years previously. His chest radiograph and spirometric results had not changed when he was referred to us five years later. He complained of breathlessness on exertion, although his exercise capacity was severely limited by his neurological condition. He described severe breathlessness on slipping down in bed.

Patient 2 was a 48 year old man who had severe weakness of all four limbs, with a progressive deterioration in walking ability over the previous three years. He had distal loss of light touch and pinprick sensation and joint position sense in all four limbs. He had experienced urgency of micturition for the past 18 years and more recently some frequency of defaecation. He had become progressively more short of breath on exertion, with orthopnoea for the previous two years. Both hemidiaphragms were raised on the chest radiograph.

Neither patient had symptoms of nocturnal hypoventilation, and daytime blood gas tensions were normal.

Investigations

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured with a rolling seal spirometer. Vital capacity (VC) was measured in both the seated and the supine posture and the postural fall was expressed as a percentage of the seated value (dVC). Twelve second maximum voluntary ventilation (MVV) and dynamic lung compliance during tidal breathing were measured with a spirometer and oesophageal balloon. Absolute lung volumes were measured in a constant volume whole body plethysmograph. All volumes were corrected to BTPS. Transfer factor for carbon monoxide (TLCO) and the transfer coefficient (KCO) were estimated by the single breath helium dilution method.

Global respiratory muscle strength was assessed from maximum static expiratory (PEmax) and inspiratory (PImax) mouth pressures.[2] Diaphragm strength was assessed by measuring transdiaphragmatic pressure (Pdi) during a maximum static inspiration against a closed airway (PdiPImax) and during a maximal sniff (sniff Pdi).[3] Phrenic nerve stimulation was carried out with techniques developed in our laboratory,[4] and phrenic nerve conduction time was measured as the time from the initial stimulation to the beginning of the M wave of the diaphragm action potential.[4]

Maximum voluntary quadriceps force (MVC quads) was measured for isometric contractions of each leg in a specially designed chair to provide an index of peripheral muscle strength; results were compared with the normal range established in this laboratory.

Both patients were studied on two consecutive nights, in their normal sleeping positions (lying on one side, with the head supported with two pillows). The electrocardiogram, electroencephalogram, and electro-oculogram were recorded from surface electrodes. Oxygen saturation (Sao_2) was measured with an ear oximeter (Hewlett Packard), and transcutaneous carbon dioxide tension ($Tcco_2$) with a capnometer (Hewlett Packard). Gas flow was recorded by thermistors, and thoracoabdominal movement was detected with magnetometers. Sleep stages were identified and the total duration of wakefulness, rapid eye movement sleep (REM) and non-REM sleep were calculated according to standard criteria.[5]

Results (tables 1 and 2)

Routine haematological and biochemical tests gave normal results.

Both patients had a moderately severe restrictive ventilatory defect with an abnormally large fall in vital capacity on becoming supine, suggesting bilateral diaphragm weakness.[3] MVC quads was reduced, a finding consistent with severe quadriceps weakness. PEmax was just outside the normal range in patient 1 (75 (normal >80) cm H_2O) and normal in patient 2. PImax was reduced in both patients.

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Accepted 24 March 1988

Table 1 *Results of lung function tests and maximum voluntary contractions of quadriceps (MVC quads)*

		Patient 1	Patient 2
MVC quads (kgf)	R	4	0
(normal > 24)	L	8	29
FEV_1 (% pred)		38	45
FVC (% pred)		39	44
FEV_1/FVC (%)		72	86
TLC (% pred)		59	54
RV (% pred)		90	83
Dynamic compliance (l/cm H_2O)		0·03	0·04
TLCO (% pred)		44	71
KCO (% pred)		137	167
Resting Po_2 (kPa) (% sat, sitting)		10·4 (96%)	10·0 (95%)
Resting Pco_2 (kPa)		4·6	5·7

FVC—forced vital capacity; TLC—total lung capacity; RV—residual volume; TLCO—transfer factor for carbon monoxide; KCO—transfer coefficient. 1 kgf = 9·807 N.

Table 2 *Results of respiratory muscle tests*

	Patient 1	Patient 2
Sitting vital capacity (l)	1·8	1·5
Supine fall in vital capacity (%) (normal < 25%)	30	30
MVV (l/min)	31	24
Maximum respiratory pressures (cm H_2O)		
PEmax (normal > 80)	75	100
PImax (normal > 44)	20	30
PdiPImax (normal > 48)	22	15
Pdi sniff (normal > 100)	17	23
Twitch Pdi (normal > 14)	0	0
Phrenic nerve conduction time (ms) (normal < 9·5)	Not detected	

MVV—maximum voluntary ventilation; PEmax, PImax—maximum static expiratory and inspiratory mouth pressure; PdiPImax—transdiaphragmatic pressure measured during maximum static inspiration against a closed airway; Pdi sniff—transdiaphragmatic pressure measured during maximal sniff.

Severe bilateral diaphragmatic weakness was confirmed by the very low Pdi generated during both the maximal sniff and the maximal static inspiratory manoeuvre. No diaphragm electromyographic trace was detectable on either side for either patient, despite stimulation of the phrenic nerves with 120 volts. Similarly no twitch Pdi could be detected.

Sleep studies Both patients had paradoxical abdominal motion throughout the study. Patient 1 slept for 232 minutes, with 30 minutes (13% of total sleep time) of REM sleep. Sao_2 fell to 91% for a few seconds only. $Tcco_2$ was normal while he was awake, with a maximum increment overnight of 7 mm Hg. Patient 2 slept for 261 minutes with 40 minutes (15·3%) of REM sleep. Sao_2 was 95% for most of the night, with a minimum value of 93%. The maximum increment in $Tcco_2$ was 3 mm Hg, the "awake" value being normal.

Discussion

Severe diaphragmatic dysfunction was confirmed in these two patients by the finding of very low maximal Pdi. PImax was also low, but PEmax was normal or only slightly reduced, suggesting that expiratory muscles were little affected. The peripheral neuropathy was characteristic of Charcot-Marie-Tooth disease type 1,[6] and the absence of a diaphragmatic EMG trace with phrenic nerve stimulation suggests that phrenic neuropathy was present. Our two patients were breathless on exertion, but less severely than has previously been reported for patients with severe diaphragm weakness,[3] perhaps because the weakness developed gradually or because the patients were so immobile. Orthopnoea was severe, however, in both patients. The severity of volume restriction may also have been related to increased stiffness of the chest wall or lungs, which are recognised as occurring in patients with longstanding respiratory muscle weakness. The latter would be supported by the low values of dynamic compliance found during tidal breathing.

Patients with bilateral diaphragm weakness associated with a generalised neuromuscular disorder frequently develop daytime hypercapnic respiratory failure and pulmonary hypertension resulting from nocturnal alveolar hypoventilation.[7] Charcot-Marie-Tooth disease is, however, usually associated with a normal lifespan, and in the two patients reported here we found no evidence of nocturnal hypoventilation: the increment in carbon dioxide was within normal limits and the fall in oxygen saturation was only slightly greater than that in normal subjects.[8] This may be because weakness was relatively confined to the diaphragm, which may have less severe consequences than diaphragm weakness in patients with generalised weakness of the respiratory muscles.[9]

The recognition of diaphragm paralysis in Charcot-Marie-Tooth disease is important as it may explain symptoms of breathlessness and orthopnoea, which greatly concern patients. As it does not necessarily affect life expectancy, the frequency of diaphragm weakness may be greater than previously recognised. Elevation of one or both hemidiaphragms on the chest radiograph should raise suspicion of the diagnosis.

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