A case of respiratory muscle weakness due to cytochrome c oxidase enzyme deficiency

A 27 yr old woman was admitted to another hospital after 3 months of progressive dyspnoea on exertion. She was short of breath on walking up <1 flight of stairs. She also complained of coughing and some wheezing. Previous treatment included numerous courses of antibiotics and systemic corticosteroids without benefit. The patient had no prior illnesses; she was on no other medications, and had no known environmental exposures. She had never smoked cigarettes or abused alcohol or drugs. Her family history was noncontributory.

Physical examination revealed the blood pressure to be 127/64 mmHg, heart rate 98 beats·min⁻¹, respiratory rate 23 breathes·min⁻¹. The patient was afebrile and in mild respiratory distress. There was evidence of pulmonary hypertension. A chest examination revealed limited thoracic movement and diminished breath sounds without wheezing or cracks. The patient had 3+ peripheral oedema. The neuromuscular exam was normal, including eye movements. Initial arterial blood gas analysis on room air: pH 7.36, O₂ tension in arterial blood (Pₐ, O₂) 4.1 kPa (31 mmHg), CO₂ tension in arterial blood (Pₐ, CO₂) 9.4 kPa (71 mmHg). The routine laboratory evaluation was unremarkable. The chest radiograph revealed cardiomegaly with central pulmonary vascular engorgement. Supplemental oxygen was administered, and the Pₐ, O₂ rose to 9.0 kPa (68 mmHg); however, the Pₐ, CO₂ progressively rose, ultimately requiring ventilatory support. Evaluation of the pulmonary hypertension included the following: cardiac ultrasound showed marked right atrial and ventricular enlargement, with moderate tricuspid regurgitation and normal left ventricular function. There was no evidence of intracardiac shunts. The ventilation-perfusion lung scan and lower extremity duplex ultrasound were normal. Right heart catheterization revealed a pulmonary artery pressure of 97/52 mmHg, cardiac output/index 73.5 L·min⁻¹, pulmonary capillary wedge pressure 18 mmHg, central venous pressure 27 mmHg, systemic vascular resistance 881 dyne·s⁻¹·cm⁻⁵, pulmonary vascular resistance 576 dyne·s⁻¹·cm⁻⁵. The patient was successfully extubated 2 days later and transferred to our hospital.

Further evaluation at our hospital included: arterial blood gases, which showed pH 7.27, Pₐ, O₂ 11.0 kPa (83 mmHg), Pₐ, CO₂ 10.5 kPa (79 mmHg) on 5 L·min⁻¹ O₂. Pulmonary function tests (PFTs): forced vital capacity (FVC) 1.02 L (28% pred), 1.02 L (28% pred), forced expiratory volume in one second (FEV₁) 0.89 L (28% pred), FEV₁/FVC% 87% pred, carbon monoxide diffusing capacity of the lung (DL( CO) ) 11.88 mL·min⁻¹·mmHg⁻¹ (46% pred), and carbon monoxide transfer coefficient (KCO) (DL( CO)/alveolar volume (VA) 6.18 mL·min⁻¹·mmHg⁻¹·L⁻¹ (130% pred). A high-resolution computed tomography (CT) scan of her lungs showed no evidence of any intraparenchymal disease. A sleep study ruled out obstructive sleep apnoea. The patient was successfully treated with bilevel positive airway pressure therapy.

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* University of Michigan Medical Center, Division of Pulmonary and Critical Care Medicine, and ** Depts of Pathology and Neurology, Ann Arbor, MI, USA.

Correspondence: A. O'Brien, Division of Pulmonary and Critical Care Medicine, Box 0360, 3916 Taubman Center, University of Michigan Medical Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA.

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out sleep apnoea, but there were repetitive significant falls in the $S_a\text{O}_2$ during sleep, even with supplemental oxygen. Given the presence of a restrictive ventilatory defect without parenchymal lung disease, further studies focusing on neuromuscular weakness indicated the following: 1) potassium, magnesium, calcium, creatinine kinase, thyroid function tests and lactic acid were measured and were normal; 2) the maximum inspiratory pressure (MIP), measured at residual volume (RV), was -20 cmH$_2$O; 3) a decreased diaphragmatic motion was observed on fluoroscopy; 4) low-amplitude phrenic nerve evoked-responses were noted; 5) electromyography (EMG) of the diaphragm and extremity muscles was normal, as were nerve conduction studies, including tests of neuromuscular transmission; 6) a muscle biopsy revealed coarse mitochondrial staining with ragged red-like fibres (fig. 1), elevated intracellular lipids (fig. 2), and misshapen mitochondria with disoriented cristae in electron micrographs, all suggestive of a mitochondrial metabolic myopathy. Further biochemical studies revealed a partial cytochrome c oxidase (COX) enzyme deficiency (table 1). As part of the evaluation, the patient also underwent a cardiopulmonary exercise study. This demonstrated the presence of a mixed ventilatory and circulatory defect, consistent with her respiratory muscle weakness and impaired oxygen utilization in the peripheral musculature.

Therapy included noninvasive ventilatory support with BiPAP (Respironics Inc, Murrysville, PA, USA), oxygen support and diuretics. This resulted in a progressive decrease in $P_a\text{CO}_2$ (from $>10.6$ kPa (80 mm Hg) to $<6.7$ kPa (50 mmHg)), and a gradual improvement in her FEV$_1$ and FVC by 20%. The patient was also symptomatically improved, noticing increased energy and decreased dyspnoea on exertion. A follow-up in the clinic 2 months later revealed a $P_a\text{O}_2$ of 10.9 kPa (82 mmHg), $P_a\text{CO}_2$ of 6.0 kPa (45 mmHg) on room air, and no evidence of pulmonary hypertension or right ventricular dilatation on a repeat cardiac ultrasound. Her MIP, measured at RV, was -118 cmH$_2$O, and her maximum expiratory pressure (MEP), measured at total lung capacity (TLC), was 110 cmH$_2$O. At 12 months, using BiPAP 12 h·day$^{-1}$ (inspiratory positive airway pressure 15 cmH$_2$O, expiratory positive airway pressure 5 cmH$_2$O), her pulmonary function tests demonstrated a FVC 1.66 L (42% pred), FEV$_1$ 1.38 L (44% pred), FEV$_1$/FVC 83% pred, and her $S_a\text{O}_2$ saturation on room air was 99%. The patient reported walking 1 mile·day$^{-1}$ and working 40 h·week$^{-1}$.

**Discussion**

COX is one of four enzyme complexes in the mitochondrial respiratory chain (Complex IV) that transfer electrons from energy-rich molecules, such as nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH$_2$), to molecular oxygen. COX is located in the inner membrane of mitochondria. It is a complex enzyme composed of 13 subunits, three of which are coded by mitochondrial deoxyribonucleic acid (DNA). The other 10 subunits are encoded by nuclear DNA. Because of its complexity, deficiency of this enzyme results in a variety of clinical presentations. They can be classified into two major groups: one with predominantly muscle involvement (myopathies), and the other with multisystem involvement predominantly affecting the brain (encephalomyopathies). The patients with predominant muscle involvement usually present soon after birth with severe generalized weakness, respiratory distress and lactic acidosis. Some of them progressively deteriorate and die of respiratory failure before 1 yr (fatal infantile myopathy). Others have renal involvement, or may initially have severe weakness and require ventilatory support, later improving spontaneously and usually normalizing by 2–3 yrs of age (benign infantile myopathy). The presence of tissue-specific and developmentally regulated COX isoenzymes is a possible explanation for this return of COX activity [1–3].

**Table 1. – Muscle biopsy biochemical enzyme assay**

<table>
<thead>
<tr>
<th>Assay data</th>
<th>Results</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory enzymes µmol·min$^{-1}$g$^{-1}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytochrome c oxidase</td>
<td>1.18</td>
<td>&gt;1.41</td>
</tr>
<tr>
<td>Succinate-cytochrome c reductase</td>
<td>0.72</td>
<td>&gt;0.35</td>
</tr>
<tr>
<td>NADH dehydrogenase</td>
<td>28.18</td>
<td>&gt;14.22</td>
</tr>
<tr>
<td>NADH-cytochrome c reductase</td>
<td>0.73</td>
<td>&gt;0.52</td>
</tr>
<tr>
<td>Reference enzymes µmol·min$^{-1}$g$^{-1}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinate dehydrogenase</td>
<td>1.65</td>
<td>0.47–1.53</td>
</tr>
<tr>
<td>Citrate synthase</td>
<td>8.01</td>
<td>7.33–12.43</td>
</tr>
<tr>
<td>Carnitine free nmol·mg$^{-1}$</td>
<td>14.58</td>
<td>&gt;9.00</td>
</tr>
<tr>
<td>Carnitine total nmol·mg$^{-1}$</td>
<td>16.16</td>
<td>&gt;10.25</td>
</tr>
</tbody>
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![Fig. 1. – Photomicrograph of muscle biopsy, showing coarse cytoplasmic staining and thickened sarcolemma of muscle fibres (nicotinamide adenine dinucleotide stain). (Internal scale bar = 30 µm.)(Image 50x123 to 281x485)](image1.png)

![Fig. 2. – Photomicrograph of muscle biopsy. Muscle fibres contain increased numbers of large lipid granule (Oil-Red-O stain). (Internal scale bar = 30 µm.)](image2.png)
Mitochondrial enzyme deficiencies are rare. Rarer still is the symptom onset in adults with no preceding respiratory symptoms, as in our patient. Most cases of COX deficiency are detected in infancy [4, 5], though there have been case reports in older children [6]. Presentation during adulthood has been previously reported [7–11], usually with either preceding lifelong respiratory symptoms or other chronic symptoms. Ragged red fibres are typically seen in muscle biopsies of patients with mitochondrial myopathies (related to sub-sarcoclemmal accumulation of abnormal mitochondria), though their presence is not absolute [8, 9]. Ragged red fibres were seen in our patient, as evidenced by the very coarse, clumped mitochondrial staining in the majority of type I and type II muscle fibres. The normal extremity muscle EMG initially suggested a nonneuromuscular aetiology of respiratory failure. This has been previously reported, however [7, 9].

Sleep is thought to play a pivotal role in the evolution of respiratory failure in patients with neuromuscular disorders [12]. In general, the onset of respiratory failure begins as hypoventilation during rapid eye movement (REM) sleep. The resultant severe hypoxemia contributes to depression of the respiratory drive and arousability. This hypoventilation gradually extends into nonREM sleep and finally is also present during the awake state [13]. The weak respiratory muscles contribute partly or wholly to this sleep-disordered breathing, though other possible contributing factors include upper airway dysfunction, or impaired ventilatory control mechanisms due to brainstem involvement by the primary disease process. Treatment of this sleep-disordered breathing in patients with neuromuscular weakness with noninvasive positive pressure ventilation has been shown to improve awake daytime blood gas tensions and respiratory muscle strength significantly, thus altering the natural history of the disease [14]. This improvement may be secondary to releasing respiratory muscle fatigue or to improved central respiratory drive.

Our patient had both nocturnal and daytime hypoventilation. She was treated with BiPAP, initially on a continuous basis and eventually only at night. She showed an excellent response to this therapy, with improvements in her blood gas tensions, spirometry, and respiratory muscle strength significantly, thus altering the natural history of the disease [14]. This improvement may be secondary to releasing respiratory muscle fatigue or to improved central respiratory drive.

There are many instructive features in this patient. Firstly, neuromuscular weakness can cause respiratory failure and pulmonary arterial hypertension. Secondly, the need to consider neuromuscular aetiologies in patients with dyspnoea is reinforced. Finally, the effectiveness of bilevel positive airway pressure therapy in respiratory failure due to a myopathy is illustrated.

References