Respiratory Failure Revealing Mitochondrial Myopathy in Adults* 

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Two patients, a 70-yr-old black woman and a 56-yr-old black man, presented with respiratory failure unexplained by intrinsic lung disease. Both had been dependent on a respirator for several weeks. No abnormalities of the central or peripheral nervous system or long-standing muscle weakness was noted. The findings from ophthalmologic and cardiac evaluations were normal. The serum creatinine kinase concentration was mildly elevated in case 1, and needle electromyography showed myopathic potentials in case 2. In both instances, muscle biopsy established the diagnosis of mitochondrial myopathy. Biochemical studies of muscle extracts showed partial deficiency of complex 3 in patient 2 and of complex 4 in patient 1. Both patients were weaned from the ventilator after long periods of ventilatory assistance. These observations document a hitherto undescribed presentation of adult-onset mitochondrial myopathy.

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A number of neuromuscular disorders may be complicated by respiratory insufficiency, but ventilatory failure is rarely the presenting manifestation.1,2 There are reports of respiratory failure revealing acid maltase deficiency in adults3 but not adult-onset mitochondrial myopathy. Our cases represent a new clinical presentation of mitochondrial disease to add to the already complex clinical patterns characteristic of these disorders. Mitochondrial myopathy should therefore be ruled out in respiratory failure thought to be due to dysfunction of the neuromuscular system.

The spectrum of clinical manifestations in mitochondrial disease is extremely broad, from pure muscle disease to complex multisystem disorders. The manifestations confined to striated muscle vary greatly and may include myalgia, exercise intolerance, proximal muscle weakness, external ophthalmoplegia, or facioscapulohumeral syndrome.4 The clinical course is also extremely variable, from rapidly progressive to static deficits, with even remitting forms, as in the benign infantile mitochondrial myopathy due to reversible cytochrome c oxidase deficiency.5 Mitochondrial multisystem disorders predominantly involve brain and muscle. Among them, several syndromes have been recognized: the Kearns-Sayre syndrome,6 myoclonic epilepsy with ragged red fibers (MERRF),7 and a syndrome of mitochondrial myopathy, encephalopathy, lactacidosis, and stroke-like episodes (MELAS).8 A mitochondrial disease affecting muscle and kidney has also been reported in association with cytochrome c oxidase deficiency.8

Many biochemical defects have been identified in mitochondrial disease.9 However, there is considerable variability in the clinical syndromes associated with any one of these defects. As research in the biochemistry and the molecular genetics of these disorders progresses,10,11 new classifications will undoubtedly be developed; however, at this time, clinicians must be well aware of the protean manifestations of mitochondrial disease. We report herein a hitherto undescribed presentation of mitochondrial disease in adults, isolated respiratory failure.

CASE REPORTS

CASE 1

A 56-yr-old black man had a 15-yr history of recurrent respiratory difficulties attributed to emphysema. During those years, he had made several visits to emergency rooms but had never been admitted. The patient had been receiving prednisone (10 mg daily) for a year at the time of admission. There was no personal or family history suggesting neuromuscular disease.

The patient developed increasing shortness of breath over a 3-wk period, which eventually culminated in acute respiratory failure. On admission, arterial blood gas analysis showed the following: pH of 7.36, PaCO2 of 59 mm Hg, and PaO2 of 48 mm Hg on FiO2 of 0.21; and Pa(a)-O2 of 32 mm Hg, suggesting chronic respiratory failure and hypoxemia due probably to a combination of V/Q mismatching and alveolar hypoventilation. The patient was treated with intravenous aminophylline, epinephrine, and steroids. Despite aggressive therapy, his arterial blood gas levels continued to deteriorate; he was intubated, and ventilatory assistance was begun.

After 3 wk, the patient could not be weaned from the ventilator despite multiple attempts. He was on maximum doses of bronchodilators. There were no signs of infection or abundant respiratory secretions. There were no electrolyte, metabolic, hemodynamic, or nutritional abnormalities to explain the failure to wean. On the ventilator and CPAP of 5 cm H2O with FiO2 of 0.25, arterial blood gas analysis showed a pH of 7.19, PaCO2 of 78 mm Hg, and PaO2 of 168 mm Hg, suggesting alveolar hypoventilation with adequate oxygenation. At this point a neurology consultation was obtained to evaluate a neuromuscular cause of this failure to wean. No paresis or limitation of extraocular movements was noted. There were mild...
proximal muscle weakness and wasting, both of recent onset, which were thought to be iatrogenic (steroid therapy). The tendon reflexes were normal. No cerebellar signs or signs of long tract involvement were noted. Findings from the funduscopic examination were unremarkable.

Relevant laboratory results included negative ANA and rheumatoid factor, mildly elevated serum creatine kinase (CK) (three times normal), normal serum lactic acid (less than 0.5 mEq/L), normal results on thyroid function tests, and mildly elevated CSF protein (0.59 g/L) with 1 cell per milliliter. A CT scan of the head was normal. Conduction studies of the peroneal, tibial, median, and sural nerves were normal. F responses in the peroneal, tibial, and median nerves were normal as well. Needle electromyography of the deltoid, biceps, vastus lateralis, and anterior tibia muscles was unremarkable. Repetitive stimulation of the median nerve showed no decremental response in the abductor pollicis brevis muscle. A muscle biopsy was obtained from the sternocleidomastoid muscle at the time of tracheostomy.

The patient remained dependent on the ventilator for 5 mo. He was eventually extubated but died a week later. Permission for autopsy was not granted.

**Case 2**

A 70-yr-old black woman initially admitted to the orthopedic service for an elective total knee replacement. As part of the preoperative evaluation, she was noted to have markedly abnormal arterial blood gas levels (pH of 7.33, PaCO₂ of 76 mm Hg, and PaO₂ of 34 mm Hg on FIO₂ of 0.21 with normal P(A-a)O₂ of 25 mm Hg). This suggested alveolar hypoventilation as the cause of her hypoxemia and respiratory acidosis. The patient was in no respiratory distress and was able to walk two city blocks without shortness of breath. She never smoked and had never suffered from any lung or neuromuscular disease. She had a history of hypertension for many years, with evidence of a hypertensive cardiomyopathy, and had had a bout of congestive heart failure the previous year. The patient was receiving digoxin (Lanoxin), furosemide, propranolol, and tocamide hydrochloride. On examination, her blood pressure was normal, her lungs were clear, and she showed no signs of congestive heart failure. The chest x-ray film was normal. Pulmonary function studies performed then revealed an FVC of 1.53 L (77 percent of predicted value), FEV₁ of 1.10 L/s (70 percent of predicted value), and FEV₁/FVC of 72 percent. This suggested a mild restrictive ventilatory impairment. The surgery was cancelled; and the patient was discharged, and further outpatient work-up was arranged.

The patient was lost to follow-up until May 1987, when she presented to the emergency room with a 2-day history of altered mental status, shortness of breath, and fever. She was lethargic and had signs of a pneumonia. Her arterial blood gas analysis this time showed a pH of 7.32, PaCO₂ of 88 mm Hg, and PaO₂ of 28 mm Hg on FIO₂ of 0.21, and P(A-a)O₂ of 17 mm Hg, again suggesting that alveolar hypoventilation was the cause of her hypoxia and respiratory acidosis. A CT scan of the head showed cerebral atrophy. A chest x-ray film showed an infiltrate in the left lower lobe. A lung V/Q scan was interpreted as low probability for pulmonary emboli.

The acute episode required intubation and ventilatory assistance. The patient could not be weaned from the ventilator for 6 wk despite multiple attempts. The pneumonia had cleared. There were no electrolyte, metabolic, or nutritional abnormalities to explain the failure to wean. A neurologic consultation was obtained to assess the possibility of neurogenic ventilatory failure. Neurologic examination revealed absence of ptosis, full extraocular movements, and an absence of cerebellar signs, long tract dysfunction, or muscle weakness. Tendon reflexes were normal throughout. An edrophonium test was normal. Mental status and the results of neurologic examinations performed at some distance from the acute episode were entirely normal. Findings from a complete ophthalmologic evaluation were normal.

Laboratory investigations revealed normal levels of serum CK, glucose, BUN, lactate, and pyruvate. The results of thyroid function tests were normal. Stimulation of the phrenic nerve at the neck elicited normal responses bilaterally. Motor conduction of the peroneal and median nerves (with F response studies) and sensory conduction of the median and sural nerves were normal. Repetitive stimulation of the spinal accessory nerve showed no decrement of the compound response evoked in the upper trapezius muscle. Needles electromyography revealed brief, low-amplitude, and polyphasic motor unit potentials in the cervical and lumbar paraspinal muscles and in the vastus lateralis muscles bilaterally, with normal recruitment pattern, suggesting primary muscle disease. A biopsy of the deltoid muscle was obtained.

The patient's respiratory function improved gradually, and artificial ventilation was discontinued 6 wk after admission. The patient was followed up to a year after this episode. She had returned to her usual state of health and had developed no additional respiratory problem.

**Histopathologic Studies**

In both cases, the muscle specimen was processed with a battery of routine histochemical reactions and embedded in epoxy resin (Epon) for electron microscopy.

**Case 1**

In the sternomastoid muscle, light microscopy revealed normal fascicular architecture, connective tissue, and blood vessels; there was no inflammation, fiber necrosis, or regeneration. There was increased variability in muscle fiber size. The myonuclei were normal in number and location. Many fibers exhibited purplish subsarcolemmal deposits with the modified Gomori trichrome stain, the typical appearance of ragged red fibers. The NADH-tetrazolium reductase reaction revealed alterations of the normal intermyofibrillar network with dense, mostly subsarcolemmal deposits of the reaction product (Fig 1). The reactions for myofibrillar ATPase at different pH levels showed the normal pattern of fiber type distribution. The ragged red fibers were mostly type 1. Electron microscopy revealed large subsarcolemmal and intermyofibrillar mitochondrial aggregates. Some mitochondria exhibited paracristalline inclusions. Concentric laminated bodies were seen in several fibers.

**Case 2**

Light microscopic examination of a deltoid muscle biopsy showed normal fascicular architecture, connective tissue, and intramuscular vessels without inflammation. Increased variability in muscle fiber size was noted, but no necrosis or regeneration was seen. The

![Figure 1. Sternoceleidomastoid muscle biopsy (transverse frozen section). Note mild variability in fiber diameter and peripheral accumulation of reaction product in many fibers (case 1) (NADH-tetrazolium reductase, original magnification ×100).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21640/ on 06/27/2017)
myonuclei were normal. Many fibers exhibited subsarcolemmal deposits (Fig 2) which stained purplish with the modified Gomori trichrome stain. Many fibers contained nemaline bodies (Fig 3). The NADH-tetrazolium reductase reaction demonstrated marked subsarcolemmal and intermyofibrillar accumulation of the reaction product. The ATPase reactions showed the normal distribution of the two fiber types. Electron microscopy revealed multiple subsarcolemmal and intermyofibrillar mitochondrial aggregates without intramitochondrial inclusions. Z-band streaming, nemaline body formation, and areas of focal disorganization of the myofibrillar pattern were seen in many fibers.

**Biochemical Studies**

The activity of the following enzymes was measured in crude extracts prepared from frozen muscle as previously described:12 cytochrome oxidase; succinate-cytochrome c reductase; rotenone-sensitive NADH-cytochrome c reductase; citrate synthase; NADH dehydrogenase; and succinate dehydrogenase.

Patient 1 had cytochrome oxidase (complex 4) deficiency with residual enzyme activity of 29 percent of mean control value. Immunotitration of the enzyme protein of the enzyme-linked immunosorbent assay (ELISA) using polyclonal antibodies against cytochrome oxidase purified from human heart13 showed a normal amount of immunologically reactive protein (data not shown). Patient 2 had an isolated defect of succinate-cytochrome c reductase activity, suggesting complex 2 deficiency (Table 1).

**Figure 2.** Deltoid muscle biopsy (transverse frozen section). Note subsarcolemmal accumulation of eosinophilic material in most muscle fibers (case 2) (hematoxylin-eosin, original magnification ×250).

**Figure 3.** Deltoid muscle (transverse frozen section). Note large number of nemaline bodies in several muscle fibers (case 2) (modified Gomori trichrome stain, original magnification ×250).

**Discussion**

In both cases, neuromuscular disease was considered a possible cause of respiratory insufficiency, as the patients could not be weaned from the respirator after weeks of ventilatory assistance. In patient 1, mild emphysema without any superimposed pulmonary infection was not sufficient to explain protracted ventilatory failure. In patient 2, there was no preexisting lung disease or ongoing parenchymal alteration to explain respiratory failure. Although this patient had been treated for congestive heart failure a year earlier, there was no sign of cardiac decompensation during this episode. In both cases the most common neuromuscular causes of acute respiratory difficulties, the Guillain-Barré syndrome and myasthenia gravis, had been ruled out by multiple nerve conduction studies and late responses and by edrophonium test or repetitive stimulation of peripheral nerves, respectively. A muscle biopsy was performed in patient 1 because of mild proximal weakness and in patient 2 because the EMG showed myopathic features.

Muscle biopsy was the diagnostic procedure of choice to provide an answer without undue delay. It is important to stress that sections should be stained with the modified Gomori trichrome stain to easily identify the ragged red fibers.14 In patient 2, the biopsy findings included ragged red fibers and a large number of nemaline bodies in many muscle fibers. Nemaline bodies may be seen in addition to other abnormalities in a number of neuromuscular diseases, including mitochondrial myopathy.15,16 Although nemaline bodies were very abundant in patient 2’s muscle biopsy, the enzyme abnormalities noted on biochemical analysis suggest that the nemaline bodies were an epiphenomenon to the mitochondrial myopathy.

The other laboratory tests were of limited diagnostic value. The serum CK concentration was elevated in one case only, which drew attention to the possibility of muscle disease; serum pyruvate and lactate levels were normal in both patients; needle EMG revealed no spontaneous activity in either case and some brief, polyphasic motor unit potentials suggesting myopathy in case 2, which is in agreement with the relative paucity of EMG findings in mitochondrial disease.14,16,17 Our cases suggest that mitochondrial myopathy should be considered and a muscle biopsy performed once the common causes of neurogenic respiratory failure have been excluded, even if serum CK assay, serum lactate levels, and EMG are unrevealing.

The alterations of enzymatic activities indicated partial complex 4 deficiency in patient 1 and complex 2 deficiency in patient 2. Studies of series of patients with complex 4 deficiency indicate that the corresponding phenotypes are variable, from pure myopathy to central nervous system disease.9 Complex 2...
deficiency has been suggested but not clearly documented in a few patients, and the clinical phenotypes associated with this biochemical defect remain to be defined.\(^9\) The reasons for the clinical heterogeneity of mitochondrial diseases are unclear, and further progress in molecular genetics will undoubtedly lead to a better understanding of these biochemical defects and of their consequences.\(^10\)

Two pathophysiological mechanisms could lead to respiratory failure in these patients: abnormality of the respiratory drive due to dysfunction of the respiratory centers in the brain stem, on the one hand; or weakness or fatigue of the inspiratory muscles, on the other hand. Carroll and associates\(^16\) found decreased ventilatory responses to hypoxia and hypercapnia in four patients with ophthalmoplegia and mitochondrial disease. Similar data were recently reported in several patients with mitochondrial myopathy and recurrent bouts of respiratory insufficiency.\(^19\) Carroll and colleagues\(^18\) pointed out that although dysfunction of the medullary respiratory centers was unlikely in the absence of clinical signs of damage to medullary structures, the reduced ventilatory response to hypoxia and hypercapnia seemed out of proportion to the mild degree of weakness demonstrated on pulmonary function tests (PFTs); however, it is essential to distinguish muscle weakness from muscle fatigue. Weakness is the failure to develop the required or expected force, whereas fatigue is the failure to sustain it.\(^20\)

Mitochondrial disease is often accompanied by myopathy causing marked fatigability with only mild weakness.\(^15,21,22\) Pathologic fatigue with moderate weakness of the respiratory muscles could conceivably have resulted in moderately altered PFTs, since spirometry requires only a phasic effort, whereas hypoxia and hypercapnia, which generate a sustained increase in work load, may have unmasked fatigability. Fatigue is a reversible phenomenon, yet its electrophysiologic manifestations may persist for several days following the triggering episode.\(^23,24\) Fatigue of the respiratory muscles can be assessed by physiologic methods.\(^24,25\)

Although we did not perform this type of evaluation in our patients, we suggest that in future studies the respiratory muscles should be carefully tested for low-frequency fatigue\(^23-25\) to distinguish between failure of the central drive and fatigue of the effector.

Both patients were eventually weaned from the ventilator. Assuming that muscle fatigue was a factor in their respiratory failure, ventilatory assistance provided the necessary conditions for their muscles to recover from that state. An important question concerning the long-term management of these patients arises: should the weakened and fatigable respiratory muscles be treated with rest (for example, ventilatory assistance at night with a cuirass ventilator), or should they be gradually trained (ie, breathing against resistance) to augment their endurance?\(^24\) Of note is the fact that some reports indicate that myopathic muscle is indeed trainable.\(^26,27\)

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REFERENCES


### Table 1—Mitochondrial Enzyme Activities in Crude Extracts of Muscle*

<table>
<thead>
<tr>
<th>Subject</th>
<th>COX</th>
<th>Succ-Cyt c Reductase</th>
<th>NADH-Cyt c Reductase</th>
<th>SDH</th>
<th>NADH-DH</th>
<th>Citrate Synthase</th>
</tr>
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<tbody>
<tr>
<td>Case 1</td>
<td>0.82</td>
<td>0.558</td>
<td>1.35</td>
<td>0.98</td>
<td>41.93</td>
<td>6.47</td>
</tr>
<tr>
<td>Case 2</td>
<td>1.60</td>
<td>0.132</td>
<td>0.60</td>
<td>1.40</td>
<td>48.28</td>
<td>14.06</td>
</tr>
<tr>
<td>Controls†</td>
<td>2.80</td>
<td>0.701</td>
<td>1.02</td>
<td>1.00</td>
<td>35.48</td>
<td>9.88</td>
</tr>
<tr>
<td></td>
<td>(0.52)</td>
<td>(0.228)</td>
<td>(0.377)</td>
<td>(0.526)</td>
<td>(7.07)</td>
<td>(2.55)</td>
</tr>
</tbody>
</table>

*Activities in crude extracts are expressed in micromoles of substrate utilized per minute per gram of tissue. COX, Cytochrome c oxidase; Succ-Cyt c reductase, succinate-cytochrome c reductase; NADH-Cyt c reductase, rotenone-sensitive NADH-cytochrome c reductase; SDH, succinate dehydrogenase; and NADH-DH, NADH dehydrogenase.†Numbers within parentheses are SDs; numbers within brackets are numbers of controls.
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