Two Cases of Mitochondrial Myopathy with Predominant Respiratory Dysfunction

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Although it is well known that the respiratory failure is a major cause of death in most patients with chronic neuromuscular disease, predominant respiratory dysfunction without severe involvement of limb muscles is an unusual complication of mitochondrial myopathy in adult age. We experienced two cases of mitochondrial myopathy with severe involvement of respiratory function and only mild involvement of limb muscles. One is a 16 year old female and another is a 22 year old male. The diagnosis is based on morphologic characteristics of "ragged red fibers" under the light microscope and abnormal mitochondrias on the electron microscope in the muscle biopsy.

Key Words: Mitochondrial myopathy, respiratory dysfunction

The mitochondrial myopathies are a clinically and histochemically heterogenous group of disorders, sharing the common features of structural mitochondrial abnormalities on skeletal muscle biopsy (Morgan-Hughes, 1982). There are a few reports of patients with mitochondrial myopathy developing early respiratory failure and only mild involvement of limb muscles. The physiological basis for this complication is unclear yet, but may relate to the reduced ventilatory drive rather than severe respiratory muscle weakness (Byren, 1985; Barohn, 1990).

There have been several case reports on mitochondrial myopathy in Korea, but without early respiratory failure (Sunwoo, 1983; Myung, 1988). Here we report two cases of mitochondrial myopathy who developed predominant respiratory dysfunction with only mild limb muscle weakness.

CASE REPORT

Case 1.

A 16-year old female was admitted to Severance Hospital in December 1988 because of cough, dyspnea and altered mental state. She had not paid any attention to her health until five days previously when she developed a febrile condition with coughing and dyspnea; one day before admission she became cyanotic and stuporous.

Her birth history was not remarkable and she was able to walk at 2 years of her age. Her school performance was relatively normal except mild exertional dyspnea during physical exercise since 10 years of her age. The family history was not remarkable except that her younger brother had suddenly died of an unknown cause at the age of 5 years.

On admission her body temperature was 38°C, pulse rate 90/min and blood pressure 110/80 mmHg. Her height was 145 cm and weight 39.5 Kg. She was pale and thin, looked acutely ill and in stuporous mental state. The heart sound was regular without murmur and the breathing sound was decreased in the right lower lung field. On crude neurological examination, there was no definite

Received November 13, 1990
Accepted December 31, 1990
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lateralizing or focal signs except mild generalized muscle wasting and hyporeflexia. No limitation of joint movement was noticed. Chest X-ray revealed pneumonic consolidation at the right upper and middle lobe. Arterial gas analysis showed PH 7.29, PO$_2$ 41 mmHg, PCO$_2$ 69 mmHg and HCO$_3$ 41 mEq/L, compatible with acute respiratory failure. The peripheral white blood cell count was 13,500/mm$^3$ with 80% of segmented neutrophils. The blood chemistry showed total bilirubin 1.0 mg/dl, alkaline phosphate 90 IU/L, BUN 3.0 mg/dl, and Creatine 0.5 mg/dl. The erythrocyte sedimentation rate was 17 mm/hour. The echocardiogram and electrocardiogram did not show any specific abnormalities.

Immediate intubation followed by artificial ventilatory support was done with administration of antibiotics. She became alert soon after the ventilatory care. A few days later, her condition had markedly improved and she was able to comb and wash her face herself. A neurological examination was repeated; the cranial nerve functions were normal without evidence of ptosis or external ophthalmoplegia. There was mild weakness of the limb muscles, but she could hold up her legs and arms for a while. There was general hyporeflexia, but no sensory deficits or cerebellar dysfunctions was noticed. In contrast to the clinical improvement, the peculiar finding in this case is that the respiratory support had to be maintained even after clearing the pneumonic consolidation on the chest X-ray. An additional laboratory study was performed; thyroid function and oral glucose tolerance test were normal. ANA was negative. The lactic acid in serum and CSF were 3.62 mm/l and 1.24 mm/l (normal range 0.5-2.25 mm/L) respectively.

The electrophysiological studies revealed normal nerve conduction studies but myopathic electromyographic findings. The muscle biopsy was performed in the right gastrocnemis muscles which showed the findings of mitochondrial myopathy; lightmicroscopy showed scattered vacuolar degeneration of myofibers and regenerating myofibers. More than 10% of muscle fibers were ragged red fibers in modified Gomori trichrome stain (Fig. 1). Electron microscopy revealed subsarcolemmal accumulation of slightly enlarged mitochondria with disoriented cristae (Fig. 2).

She was given steroid, carnitine, vitamin-K, vitamin-C, riboflavin and coenzyme Q$_{10}$ with transient clinical response. She was able to walk without any
Fig. 2. Electronmicrograph showing subsarcolemal accumulation of slightly enlarged mitochondria (× 15,000).

Fig. 3. Electronmicrograph showing characteristic sickle-shaped abnormal mitochondria containing curvilinear paracrystalline inclusions (× 8,750).
support, and intermittent artificial respiratory support was temporarily good enough for her respiratory dysfunction. She was discharged against advice at the 76th hospital day and expired a month later because of relapsed respiratory failure.

**Case 2.**

A 22-year-old man was admitted to Severance Hospital in March 1989 because of severe dyspnea. He was in relatively good health until three years ago when he developed weakness and wasting of the upper extremities. His birth and development were not remarkable. There was no family history of neuromuscular disease. For three years he had noted a weakness and wasting of upper extremities. Mild ptosis, limitation of extraocular movement and dysarthria appeared 16 months ago. Mild dyspnea and chest discomfort appeared six months before entry and had become abruptly worse a few days ago.

Upon admission, his body temperature was 37.2°C, the pulse rate 130/min, blood pressure 130/90 mmHg. His height was about 173 cm. On examination, the patient was thin and pale looking. The breathing sound was diminished on both lung fields and intercostal retraction was noted. On neurologic examination, mild ptosis and limitation of lateral gaze on both eyes were observed. There were generalized mild wasting and weakness, but he was able to walk and ascend the stairs without any support. Deep tendon reflexes were nearly absent, but sensation and cerebellar function looked normal.

An arterial gas study showed PH 7.28, PCO₂ 78 mmHg, PO₂ 52 mmHg, HCO₃ 42 mEq/L, compatible with acute respiratory failure. The serum CK was 125 IU/L and the erythrocyte sedimentation rate was 3 mm/hour. The peripheral white blood cell count was 6300/mm³ with 50% of segmented neutrophils.

The electrophysiological studies revealed sensory motor polyneuropathy in the distal limbs and myopathic changes in proximal muscles. Repetitive nerve stimulation test did not show significant decremental or incremental responses, and single fiber EMG showed no significant jittering. Muscle biopsy was done at the deltoid muscle with the result being consistent with mitochondrial myopathy; light microscopy revealed ragged red fibers in modified Gomori trichrome stain. Electron microscopy showed characteristic sickle-shaped abnormal
mitochondria containing curvilinear paracrystalline inclusions (Fig. 3) and long and short rectangular paracrystalline inclusions (Fig. 4). The patient was discharged against advice on the 8th hospital day and expired a few days later.

**DISCUSSION**

The mitochondrial myopathy could be defined either due to a defect of any mitochondrial enzyme or enzyme complex including those of the respiratory chain, or disorders characterized by morphological abnormalities of muscle mitochondria (Morgan-hughes et al. 1982; Sengers et al. 1984; DiMauro et al. 1985; Przyrembel 1987). By 1970 mitochondrial myopathies were described mostly based on morphological abnormalities of the mitochondria, but recently, biochemical studies of mitochondrial myopathy demonstrated several specific errors of mitochondrial metabolism and, a biochemical classification of mitochondrial myopathy is now taking shape (Sengers et al. 1984; Petty et al. 1986; DiMauro et al. 1987).

The conventional screening tests used for detection of muscle disease such as EMG and serum CK are not particularly helpful in the diagnosis of mitochondrial myopathy (Sengers et al. 1984; Petty et al. 1986). An important though nonspecific laboratory abnormality in mitochondrial myopathies is increased blood concentration of lactic acid (Sengers et al. 1984; DiMauro et al. 1985). Lactate may also be higher in the CSF of the patients with mitochondrial encephalomyopathies, suggesting impaired function of the cerebral mitochondria (DiMauro et al. 1985). The serum CK level is usually close to normal (Sengers et al. 1984; Petty et al. 1986).

Our two cases had developed rather abrupt respiratory failure in spite of mild limb weakness. It was known that the development of acute respiratory failure in mitochondrial myopathy was common in children but unusual in adults (Minchom et al. 1983; Byren et al. 1985; Zeviani et al. 1985). Caroll et al. (1976) observed depressed respiratory responses to hypoxia and hypercapnea in four sporadic cases of mitochondrial myopathy and concluded that these findings of reduced hypoxic and hypercapnic ventilatory response appear to be out of proportion to their mild weakness. The physiologic basis for respiratory failure is incompletely understood, but appears related to reduced ventilatory drive rather than to respiratory muscle weakness (Feit et al. 1983; Byren et al. 1985; Tatsumi et al. 1988). Recently, Barohn et al. (1990) studied ventilatory drive in mitochondrial myopathy, and speculated that the depressed ventilatory drive was due to a CNS abnormality, possibly at the brainstem level. The recognition of depressed ventilatory drive as part of the spectrum of disorders is extremely important since episodes of hypoventilation may be lifethreatening, are potentially reversible, and are especially relevant considerations in patients for whom surgery or sedation are planned (Barohn et al. 1990).

**REFERENCES**


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Respiratory Dysfunction in mitochondrial Myopathy

