



***MITO 101 – Pulmonary Complications of Mitochondrial Disorders***

**Anastassios C. Koumbourlis, M.D., M.P.H.**

Chief, Pulmonary Medicine  
Schneider Children's Hospital  
Associate Professor of Clinical Pediatrics  
Albert Einstein College of Medicine

A.C. Koumbourlis, M.D., M.P.H.  
Division of Pulmonary Medicine  
Schneider Children's Hospital  
865 Northern Boulevard, Ste. 103  
Great Neck, NY 11040  
Phone: (516) 622-5280  
FAX: (516) 622-5285  
e-mail: [Akoumbou@ij.edu](mailto:Akoumbou@ij.edu)

## INTRODUCTION

Although mitochondrial disorders typically do not affect the lungs directly, (1,2) respiratory symptoms are fairly common in mitochondrial diseases as a result of the malfunction of other organ systems.

## PATHOGENESIS

Among the organ systems whose dysfunction may affect the lungs, the most important are the following:

**I: Musculoskeletal system:** Hypotonia or muscle weakness have been reported in up to 80% of patients with mitochondrial diseases due to either peripheral causes (e.g. myopathy) or central causes (e.g. encephalopathy).(3-6) Depending on the muscles involved and the severity of the weakness, patients can develop various complications such as:

- **Acute and/or chronic bronchitis:** respiratory muscle weakness invariably impairs coughing and, as a result, the ability of the patient to clear secretions from the lower airways. Retention of secretions eventually leads to chronic airway inflammation and facilitates the colonization of the airways with pathogens that cause infection and further production of mucus.
- **Impaired swallowing and aspiration:** aspiration is a common feature seen both in patients with encephalopathy due to impaired gagging and in patients who develop weakness of the oropharyngeal muscles. Chronic aspiration is one of the most common causes of chronic bronchitis and of recurrent pneumonias.
- **Nocturnal hypoventilation and sleep apnea:** hypoventilation can be the result of upper airway obstruction due to oropharyngeal muscle weakness or to brainstem dysfunction in cases of severe encephalopathy.(7) Hypoventilation will eventually lead to the development of oxyhemoglobin desaturation and hypercarbia.
- **Progressive respiratory insufficiency/failure:** weakness of the respiratory muscles leads to shallow breathing and gradual atelectasis that can lead to complete lung collapse. The development of thoracic deformities, especially scoliosis, further exacerbates the problem by limiting the expansion of the rib cage during inspiration. Significant atelectasis is one of the main causes of progressive respiratory insufficiency and eventual respiratory failure.

The above complications are not unique to mitochondrial disorders and can be seen in a variety of disorders that cause muscle weakness (e.g. spinal muscular atrophy, muscular dystrophy, amyotrophic lateral sclerosis etc).

**II. Gastrointestinal dysfunction:** Gastroesophageal dysmotility, delayed gastric emptying, gastroesophageal reflux, and vomiting are often associated with mitochondrial disorders.(8) Gastroesophageal reflux in particular has been implicated as a cause of many respiratory conditions such as chronic rhinosinusitis, hoarseness, chronic cough, and asthma, as well as recurrent pneumonia if and when it is associated with aspiration.(9,10) Abdominal distention and "bloating" may impair chest wall mechanics due to the pressure exerted below the diaphragm. Considering that most of the patients will also have weakness of other respiratory muscles, the cumulative effects on respiration may be quite serious.

**III. Cardiovascular system:** Cardiac dysfunction usually present as dilated cardiomyopathy, hypertrophic cardiomyopathy, or left ventricular non-compaction, which - if untreated - will lead to congestive heart failure and pulmonary edema. The latter prevents gas exchange in the alveoli and makes the lungs non-compliant, which, in the context of respiratory muscle weakness, can easily lead to respiratory failure.

**IV. Central Nervous System:** Encephalopathy is a common manifestation of the various mitochondrial disorders and it may be associated with respiratory symptoms that may be acute (e.g. apnea during an episode of seizure) or chronic (e.g. inability to swallow, absence of gag, or true apnea in case of brain stem involvement).

## CLINICAL PRESENTATION

The respiratory manifestations of mitochondrial disorders tend to be chronic (persistent or recurrent) but non-specific, and they often deteriorate in the absence of a clearly defined respiratory illness. Potential manifestations include the following:

- **Noisy breathing:** usually consisting of continuous “gargling” sounds due to the retention of secretions in the oropharynx.
- **Hoarseness and/or stridor:** these are typical manifestations of laryngeal irritation and edema caused mostly by chronic gastroesophageal reflux.
- **Chronic “chest congestion”, cough (with or without wheezing) of unknown etiology:** the congestion usually reflects the inability of the patient to clear secretions from the lower airways as well as the chronic airway inflammation that is often associated with airway reactivity.
- **Unusual breathing patterns:** abnormal breathing can be caused either by respiratory muscle weakness and/or by encephalopathy with brainstem dysfunction. Depending on the type and degree of respiratory muscle weakness, patients may present with mouth breathing, shallow breathing, or glossopharyngeal breathing (“frog breathing”). It should be noted that, due to their muscle weakness, patients may not have typical signs of respiratory distress such as chest wall retractions.
- **Sleep disturbances:** manifested by snoring; apneic pauses during sleep; excessive fatigue and sleepiness during daytime.
- **Exercise Intolerance:** it usually presents as early and/or disproportionate feeling of fatigue even with minor activities involving skeletal muscles (e.g. chewing) but the severity varies among patients.(11) The mechanisms causing the fatigue are complex but key among them is the inability of the mitochondria of the skeletal muscles to utilize the oxygen for the production of energy required for physical activity. Because the impairment is at the mitochondrial level, the amount of available oxygen to them becomes irrelevant. Thus, neither the delivery of more oxygenated blood to the muscles, usually achieved by increases in heart rate (often to levels much higher than those seen in healthy individuals), nor the administration of supplemental oxygen have any effect. As a result, the muscles are forced to rely primarily on non-aerobic sources of energy such as glycolysis (the breakdown of carbohydrates). The anaerobic metabolism results into the production of large amounts of lactic acid and of carbon dioxide(CO<sub>2</sub>).<sup>(12)</sup> The latter is a powerful stimulus for increased ventilation in an effort to blow off the excess CO<sub>2</sub>. The sudden need to increase ventilation often creates the feeling of “air-hunger” on the affected patients.

## DIAGNOSTIC STUDIES

The following tests should be considered in patients with suspected or documented mitochondrial disorders:

- **Chest X-ray** (to determine presence and severity of atelectasis as well as evidence of chronic lung changes such as hyperinflation and bronchiectasis)
- **Pulmonary Function Testing (PFTs)**. Ideally, the patients should undergo a full evaluation with lung volume measurements (to determine whether there is loss of lung volume), spirometry (to determine whether there is obstructive lung disease) and measurement of the maximal inspiratory and expiratory pressures (MIP & MEP) as well as of the "cough flow" to assess the respiratory muscle strength. Most or all of these tests can usually be performed by children as young as 5 years of age, but they may not be feasible for children (or adults) with CNS involvement and development delay.
- **Modified Barium Swallow**: to evaluate the presence and severity of swallowing dysfunction and of aspiration.
- **Pulse oximetry and capnography**: spot checks when the patient is awake, and overnight tracings during sleep for patients known or suspected to have or to be developing respiratory insufficiency. A formal sleep study is advisable when there is evidence of abnormality.
- **Flexible Fiberoptic Bronchoscopy**: it should be considered when the presence of aspiration has not been established and/or when one needs to know whether the lower airways are colonized with pathogens.

## MANAGEMENT & TREATMENT

Because of the subtlety and variability of the respiratory complications, it is strongly advisable for patients with mitochondrial disorders to have a pulmonary evaluation in order to determine the exact needs and prescribe and monitor the various interventions. Despite the differences in pathogenesis, the goals of management are very similar to those in other conditions involving muscle weakness(13):

- **Prevention of atelectasis**: early introduction of non-invasive ventilation (e.g. CPAP or BiPAP)
- **Improved clearance of lower airway secretions**: introduction of various techniques of airway clearance including chest physical therapy; "huffing"; "PEP valves"; Vest; Cough-assist device. Which one of these techniques should the patient use depends on the severity of the problem and the cooperativeness of the patient.
- **Early and aggressive treatment of complicating factors**: these include conditions that may promote or increase the production of secretions such as GE Reflux, and the various respiratory infections. Although the latter may often be of viral origin, antibiotics may be helpful.
- **Escalation of treatment and long-term treatment**: whether and to what extent the various treatments should be escalated (e.g. employing tracheostomy and chronic mechanical ventilation) has to be decided in the context of the patient's overall condition and prognosis.

## REFERENCES

1. DiMauro S, Schon EA. The mitochondrial respiratory chain and its disorders. In, Mitochondrial Medicine. DiMauro S, Hirano M, Schon EA. Eds. Informa Healthcare, Abington, K, pp7-26
2. Di Mauro S, Schon EA. Mitochondrial respiratory chain disease. *N Engl J Med* 2003;348:2656-2668
3. Scaglia F, Towbin JA, Craigen WJ, Belmont JW, O'Brian Smith E, Neish SR, et al. Clinical spectrum, morbidity, and mortality in 113 pediatric patients with mitochondrial disease. *Pediatrics* 2004;114-925-931
4. DiMauro S. Mitochondrial myopathies. *Curr Opin Rheumatol* 2006;18:636-641
5. Oskoui M, Davidzon D, Pascual J, Erazo R, Gurgel-Giannetti J, Krishna S, et al. Clinical spectrum of mitochondrial DNA depletion due to mutations in the thymidine kinase 2 gene. *Arch Neurol.* 2006; 63:1122-1126
6. Debray FG, Lambert M, Chevalier I, Ribitaille Y, Decarie JC, Shoubridge EA, et al. Long-term outcome and clinical spectrum of 73 pediatric patients with Mitochondrial diseases. *Pediatrics* 2007; 119:722-733
7. Huntsman RJ, Sinclair DB, Bhargava R, Chan A: Atypical Presentations of Leigh Syndrome: A case series and Review. *Pediatr Neurol* 2005;32:334-340
8. Gössler A, Schalamon J, Huber-Zeyringer A, Höllwarth ME. Gastroesophageal reflux and behavior in neurologically impaired children. *J Pediatr Surg.* 2007;42(9):1486-90.
9. Gorenstein A, Levine A, Boaz M, Mandelberg A, Serour F. Severity of acid gastroesophageal reflux assessed by pH metry: is it associated with respiratory disease? *Pediatr Pulmonol.* 2003; 36(4):330-4.
10. Yüksel H, Yilmaz O, Kirmaz C, Aydoğdu S, Kasirga E. Frequency of gastroesophageal reflux disease in nonatopic children with asthma-like airway disease. *Respir Med.* 2006 Mar;100(3):393-8.
11. Andreu AL, Hanna MG, Reichmann H, Bruno C, Penn AS, Tanji K et al. Exercise intolerance due to mutations in the cytochrome *b* gene of mitochondrial DNA. *N Engl J Med* 1999;341:1037-44
12. Taivassalo T, Dysgaard Jensen T, Kennaway N, DiMauro S, Vissing J and Haller RG. The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients. *Brain* 2003; 126:413-423
13. Finder JD, Birnkrant D, Carl J, Farber HJ, Gozal D, Iannaccone ST, Kovesi T, Kravitz RM, Panitch H, Schramm C, Schroth M, Sharma G, Sievers L, Silvestri JM, Sterni L; American Thoracic Society. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. *Am J Respir Crit Care Med.* 2004;170(4):456-65.