**Pulmonology/Respiratory**

Respiratory Insufficiency Respiratory insufficiency is regarded as fairly common in mitochondrial diseases, however there have not been any studies to date to assess the true prevalence of respiratory dysfunction in children or adults with differing genetic mitochondrial diseases. There are very few anecdotal case reports describing specific mitochondrial syndromes with unusual outcomes due to severe respiratory failure such as in MERRF patients. Most of these cases resulted from disease deterioration and worsened respiratory status following a pneumonia or other respiratory tract infections requiring intubation. More case reports have discussed similar findings in patients presumed to have mitochondrial disease based on clinical criteria or partial electron transport abnormalities and may have contributed to the believe that respiratory insufficiency was a common finding in mitochondrial disease (Byrne et al. 1985; Cros et al.1992).

Respiratory insufficiency can result from muscular weakness and shallow breathing that can lead to atelectasis, r estrictive lung disease with possible complete or partial collapse of a lung. They can also be caused by lung disease from chronic aspiration due to a swallowing dysfunction. Acute decompensation can be a result of apnea during an episode of seizure or brainstem involvement in certain subtypes of mitochondrial diseases or following a stroke.

Nocturnal hypoventilation is usually the earliest sign of respiratory insufficiency, and may progress to daytime hypoventilation and the need for respiratory support including mechanical ventilation. Monitoring respiratory insufficiency with pulmonary function testing (PFTs) should be done on a regular basis for those at risk, in order to identify pulmonary involvement, requirement for respiratory equipment, and to initiate noninvasive ventilation as early as possible to improve l o n g t e r m p r o g n o s i s a n d q u a l i t y o f l i f e ( W o l f e L F , 2 0 1 2 ) .

Oxygen in Mitochondrial disease It has been long debated whether oxygen therapy could improve mitochondrial function. Though there are anecdotal reports that hyperbaric oxygen therapy may be beneficial in some patients with certain mitochondrial conditions, there is no scientific evidence to date that would positively indicate the use of this therapy as a treatment for mitochondrial disease. There are also as many anecdotal reports of patients doing poorly on hyperbaric oxygen treatment that further studies are needed in this area before any recommendations could be made for mitochondrial disease patients. Currently it is not endorsed for patients with mitochondrial disease by the Scientific and Medical Advisory Board of the United Mitochondrial Disease Foundation. (h ttp://www.umdf.org/atf/cf/%7B858ACD34­ECC3­472A­8794­39B92E103561%7D/HBOT.pdf)

Most recently, a publication in the journal Science suggested that chronic treatment of cultured cells and zebrafish models with low oxygen may limit mitochondrial toxicity. In a mouse model of Leigh disease showed marked improvement in survival, body weight, body temperature, behavior, neuropathology, and disease biomarkers. This study further highlights the need for future research to determine whether hypoxia or hyperoxia exposure can be a beneficial treatment for human diseases associated with mitochondrial dysfunction (Jain et al 2016).

Sleep disorders Sleep disorders are an under­recognized but frequent cause of morbidity in patients with primary mitochondrial disease. Neurological involvement in primary mitochondrial disease may lead to abnormal sleep behavior, which has most likely been an underreported symptom in this population. Many patients with mitochondrial disease report fatigue and exercise intolerance, which overlap with symptoms seen in sleep disorders. Thus, investigating and treating sleep disorders in this population may lead to improvement in disabling symptoms. Although the clinical history may suggest a sleep disturbance, a polysomnogram can identify a specific diagnosis and treatment. Other causes of poor sleep may include pain, behavior, and medication side effects.

A recent review article summarized the polysomnography results on 54 patients with a proven or suspected diagnosis of primary mitochondrial disease between the years 1976­2014. Many patients reportedly had hypotonia and/or neuromuscular weakness. Most had central sleep apnea, 5 had obstructive sleep apnea, and 24 had decreased ventilatory drive in response to hypoxia and/ or hypercapnia; presumed to be due to cellular energy failure and decreased respiratory muscle tone during REM sleep. Central nervous system involvement may also play a role, especially brainstem involvement seen in Leigh syndrome or MELAS. Patients with Leigh syndrome have also been observed to have abnormal respiration, due to involvement of the dorsal root ganglion proximal to the solitary tract nucleus (Ramezani, 2014).

Neuromuscular weakness predisposes people to sleep disordered breathing and 45% of children with mitochondrial disease have been identified as having neuromuscular weakness. In a recent retrospective study regarding sleep disordered breathing in children aged 15 months ­ 18 years old with mitochondrial disease (based on modified Walker criteria), 18 children had a polysomnogram between 2007­2012. In this cohort, 61% (n=11) had excessive daytime hypersomnolence or fatigue, 44% (n=8) had snoring, 17% (n=3) had sleep movements, 60% (n=6) had obstructive sleep apnea, 20% (n=2) had nocturnal hypoventilation, and 40% (n=4) had documented hypoxemia. In addition, 56% (n=10) had sleep disordered breathing, associated with hypotonia and/or overweight, compared to 1.2­13.9% in the general population (Mosquera RA, 2014).

Oropharyngeal Dysfunction Hyersialorrhea is common in patients who have central nervous system (CNS) involvement affecting oropharyngeal strength or coordination, but it can also be caused by GERD, constipation and medical side effects. Referral to otolaryngology and/or speech therapy may be very helpful. Treatment may be necessary to prevent aspiration pneumonia, improve hygiene, and reduce social stigma. Oral anti­cholinergic medications may be helpful but have undesired side effects such as worsening constipation, urinary retention and cardiac disturbances and should be used with caution in patients with baseline symptoms or other autonomic dysfunction. Sublingual botox injection may be helpful but requires a specialist (Erasmus 2012, Rodwell 2012) .

Patients with primary mitochondrial disease are at risk for development of aspiration pneumonia, due to oropharyngeal weakness or discoordination, compounded by GERD. Treatment requires gastroenterology and pulmonology consultation. The use of a gastrostomy tube (G tube) and consideration for fundoplication can decrease aspiration risk. Aspiration may be silent and still be a leading cause of morbidity and mortality. Signs that should prompt concern of aspiration risk include abnormal speech, poor gag reflex, weak cough, poor feeding, and reduced clearance of secretions. A J tube may be required if aspiration persists with a G tube.

Community acquired pneumonia is an additional concern, especially in those with neuromuscular weakness and respiratory involvement. Vigilant hand­washing, preventative vaccinations and avoidance of sick contacts can reduce infection. Pneumonia and hospitalization can be a cause of neurological decline and overall disease decompensation.

Vaccinations Vaccination recommendations for mitochondrial diseases usually follow guidelines for inborn errors of metabolism. Patients with stable or slowly progressive mitochondrial diseases c an receive the recommended schedule of vaccinations. Cautious observation following administration is recommended to detect any morbidity caused by catabolic stress (fever, vomiting, decreased PO intake). Vaccination with a live vaccine, may be contraindicated if patient has a significant immunodeficiency and would require a personalized evaluation. ( Menni et al. Vaccine 2012) In general ch ildren with inborn errors of metabolism receiving a normal immunization schedule did not have any increased risk for serious adverse events during the month after vaccination which provides reassurance that routine vaccination of children with inborn errors of metabolism is safe. (Klein et al Pediatrics 2011) (Short report Arch Dis Child 2011;96:99–100)

*Special Considerations: Leigh syndrome*

Leigh syndrome (LS) is the most common childhood presentation of mitochondrial disease, with more than 75 monogenic etiologies reported, and prevalence of 1:40,000 (Lake 2016). LS is characterized by a progressive neurological decline, with decompensation often triggered by intercurrent illness during which time an acute deterioration may cause respiratory failure. Symptoms are variable but typically include hypotonia, spasticity, movement disorder, cerebellar ataxia, peripheral neuropathy and muscle weakness, progressing in a stepwise fashion. Neuroimaging may reveal typical bilateral symmetric T2­hyperintensities in the basal ganglia and brainstem (Rahman 1996).

Brainstem lesions may cause respiratory symptoms including apnea, hypo­ or hyperventilation, and irregular respiration as well as difficulty swallowing and risk of aspiration (Thorburn 2014). In 13 patients with LS in whom the mtDNA mutation was identified, 69% had bulbar problems, 85% respiratory disturbance; in the 22 patients with LS in whom the mutation was not identified, 36% had bulbar problems and 64% had respiratory disturbance. Onset of symptoms in LS is usually between 3­12 months, with 50% dying by age 3 due to respiratory or cardiac failure (Rahman 2015). Anesthesia may worsen respiratory symptoms and precipitate respiratory failure, therefore careful monitoring is required in the perioperative period.

The genotype­phenotype correlations are increasingly understood with advancements in next­generation sequencing and molecular diagnosis of these patients. For example, in a recent review of SURF1 deficiency, 78% of the 44 patients were found to have central respiratory failure, with a median age of 31 months. Most presented in the first year of life with feeding problems, episodic regression, ophthalmoplegia, movement disorder, and early death. Of the 36/44 who died, the cause was central respiratory failure in 29/36 (80%) (Wedatilake, 2013).

In a large multicenter retrospective study of patients with Leigh syndrome followed at eight European mitochondrial disease centers, 130 patients were identified with Leigh syndrome. 77 patients had identified pathogenic mutations, and the remainder did not have a molecular diagnosis but met clinical criteria. 80% of patients presented by age 2, with a median age of onset of symptoms at 7 months. The most common symptoms were neurological (hypotonia, abnormal reflexes, dystonia) and ophthalmological (nystagmus, strabismus, optic atrophy); with seizure in 40%. About 44% of the patients required hospitalization (intensive care in 39.2% of those hospitalized) in the previous year due to disease exacerbation from infection in 60.8% and respiratory problems in 13.5%. Respiratory issues were present in 37.7% and included hyperventilation/abnormal breathing in 20%, apnea (16.1%), obstructive or restrictive lung disease (13.8%), and central hypoventilation (10%). Respiratory complications were attributed to both brainstem lesions as well as respiratory muscle weakness. Predictors of poor prognosis include disease onset prior to 6 months, failure to thrive, epileptic seizures, brainstem lesions, and need for intensive care; 39% of the patients died by age 21 years, with a median age of 2.4 years (Sofou 2014).

In a longitudinal study of 39 Leigh syndrome patients in South Korea, c linical outcome was assessed by a functional outcome score based on ambulation, feeding and respiration and correlated with neuroradiology and molecular defect (Lee 2016). Respiratory status was scored based on need for mechanical ventilation (1 point) vs no need for assistance (2 points), based on a scoring system described in children with mitochondrial disease (Debray, 2007). Patients were followed over 4 years, with 74% having progressive neurological deterioration and 3 died due to sepsis or respiratory arrest. In this cohort, 88% (29) could breathe without a ventilator, and 12% (4) needed ventilatory support via tracheostomy due to apnea or respiratory insufficiency. Poor prognosis was associated with early onset of disease (prior to one year old) and lesions in addition to basal ganglia involvement on initial neuroimaging. Those with brainstem lesions had clinical features consistent with dysphagia (15%), dysphagia and dysarthria (13%), and apnea (5%).

While retrospective natural history studies of Leigh syndrome, improved genotype­phenotype correlations, and ongoing prospective studies are leading to identification of predictors of disease severity and long­term prognosis, respiratory complications have been shown to be a leading cause of morbidity and mortality for this mitochondrial disease phenotype.

Several clinical trials have been completed with an antioxidant known as EPI­743, a novel para­benzoquinone (Edison Pharmaceuticals). In an open­label, compassionate use/FDA Expanded Access study of children with primary mitochondrial disease at risk for progressing to end­of­life care within 90 days, 11/12 showed remarkable clinical and neurological improvement and 4/12 had a diagnosis of Leigh syndrome. One of the Leigh patients with SURF1 died after completing the study, 3 had a partial relapse, and 10 had improved quality of life at the end of the study. Although initially attributed to brain stem pathology, brain stem lesions on neuroimaging did not correlate with overall functional outcome or 13 week treatment. Other outcomes included brain redox assessments using technetium­99m­hexamethylpropyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT) radionuclide imaging, which correlates with brain glutathione levels and the clinical response (Enns 2012). In an additional phase 2A study including 9 patients with Leigh syndrome ages 1­13 years were treated in an open­label study for 6 months. All showed improvements on the clinical outcomes which included the Newcastle Pediatric Mitochondrial Disease Scale, the Gross Motor Function Measure, and PedsQL Neuromuscular Module, as well as the Movement Disorder­Childhood Rating Scale (Martinelli 2012).

**Summary for the manuscript**

The lungs are usually not directly involved in the clinical manifestations of primary mitochondrial disease. However neuromuscular and the central nervous system (CNS) involvement may affect the lungs and the breathing in patients with primary mitochondrial disease which can be fairly common with disease progression (1). As such some mitochondrial syndromes with prominent CNS or muscular involvement may have more severe respiratory manifestations compared to other syndrome that affect other organ systems. Children with more severe diseases such as Leigh syndrome tend to have more severe, early and chronic respiratory complications compared to later onset forms where the respiratory problems may only arise with acute decompensations. None of the complications affecting the lungs or respiratory system is unique to mitochondrial disease, similar problems are common in many other neuromuscular and genetic disorders affecting mobility.

Hypotonia and/or muscle weakness is present in up to 80% of patients with mitochondrial disease due to central or peripheral causes (2­5). Typical pulmonary complications include: central and obstructive apnea, sleep disorders, nocturnal hypoventilation, restrictive lung disease, aspiration pneumonia, chronic or acute respiratory insufficiency and progressive respiratory failure (6). Acute decompensation may occur as a postoperative complication or result of general anesthesia. Primary cardiomyopathy may lead to congestive heart failure and pulmonary edema, especially in the setting of respiratory muscle weakness.

Respiratory symptoms may include noisy breathing, hoarseness, stridor, congestion, cough, abnormal breathing, sleep disturbances, daytime hypersomnolence, and exercise intolerance (7). Goals of management and treatment include prevention of atelectasis, improved clearance of secretions, and decisions involving escalation of care with progressive respiratory failure and decision­making in regards to need for chronic ventilation.

**Recommendations**

* All patients with a new diagnosis of a systemic mitochondrial disease should undergo a thorough baseline objective evaluation of their respiratory status to assess for muscle weakness and other cardiopulmonary comorbidities. Score 4.53
* Initial testing should include:
  + Oxyhemoglobin saturation by pulse oximetry Score 3.94; 4.29 on repeat
  + Spirometry with FVC, FEV1, maximal mid­expiratory flow rate, maximal inspiratory and expiratory pressures and peak cough flow. These need to be performed in both the supine and upright position. If appropriate seal with a mouth piece can’t be achieved, a nasal clip or a face mask needs to be used. Score 3.74; 4 on repeat
  + Sniff Nasal Inspiratory tests to measure respiratory muscle power (Koene 2013)  Score 3.50
  + Additional testing may be required at the discretion of a pulmonologist familiar with neuromuscular diseases which can affect the pulmonary system. Score 4.65
  + Duchenne muscular dystrophy has been used as a model of mitochondrial myopathy and therefore the respiratory care guidelines may be adapted for this population (Finder 2004). Score 3.68
* Additional comorbidities should be screened for depending on the history and include:
  + Obstructive sleep apnea, bulbar weakness, risk for aspiration, gastroesophageal reflux, asthma; chronic obstructive lung disease and nutrition status. Score 4.82
  + If initial tests are normal, repeat testing should be deferred until new symptoms arise or if there is a suspicion of disease deterioration. Score 4.06
  + For patients with a well characterized respiratory involvement, testing should be repeated periodically (annually) to follow progress and predict the pulmonary function over time to guide management. Score 4.44
* Patients even with mild abnormalities should be referred to a pulmonary specialist for follow up and management. Score 4.06
* Operative care
  + Neuromuscular weakness predisposes to respiratory issues in the peri­operative period due to poor airway tone, clearance of secretions and chronic aspiration. Score 4.88
  + Prior to surgery, pulmonary assessment with a pulse oximeter at a minimum should be performed, and if SpO2 is <95%, then a blood gas to assess carbon dioxide levels should be performed. Score 4.26
  + For patients with neuromuscular weakness, preoperative use of noninvasive positive­pressure ventilation (NPPV) should be considered, especially if there is the presence of a weak cough, recurrent pneumonia, or low maximum expiratory pressure (MEP). Score 4.41
  + Post­operatively, those with neuromuscular weakness can be extubated to NPPV in order to prevent prolonged intubation, with wean as tolerated as recovery may be prolonged. Score 4.53
  + Postoperative atelectasis may require aggressive pulmonary toilet with cough assist, airway clearance, and chest physiotherapy. Score 4.79
  + Pain management should limit use of narcotics which can further suppress adequate cough and recovery (Blatter 2013). Score 4.35
* Acute Illness or Disease Worsening
  + Testing should also be offered during acute disease decompensations with exacerbated symptoms. If the disease is rapidly progressive and respiratory weakness evident on testing, a pulmonary specialist referral and more frequent monitoring is warranted. Score 4.74
  + Improving cough during periods of acute respiratory sickness can be important. Score 4.35
  + Incentive spirometry is commonly used in hospitals but manual compression, glossopharyngeal breathing and insufflations should also be attempted by a respiratory therapist in hospital or at home during the recovery period. Score 4.00
  + Chest X‐ray (CXR) and computed tomography (CT) are recommend in the acute setting to identify diaphragm abnormality, collapsed lungs, aspiration and any other pulmonary pathology.  Score 4.32
  + In some centers fluoroscopy of the diaphragm could be considered to assess features of diaphragmatic weakness. Score 3.97
* Vaccination
  + Patients with mitochondrial diseases should be offered age appropriate vaccination including the influenza vaccine as well as other relevant vaccine if there is an underlying pulmonary pathology (i.e. pneumococcal vaccine). Score 4.88
* Assisted Ventilation
  + *Non*‐*invasive ventilation (NIV)* with intermittent positive pressure ventilation through a face mask should be started in patients with documented respiratory weakness if patient has a daytime hypercapnia. The NIV can be applied intermittently during the 24h period or only at night depending of the severity of the hyercapnia and daytime symptoms (somnolence, headache..) [Wards]. Score 4.50
  + *Invasive ventilation (IV).* Patients with mitochondrial disease may require IV during periods of acute decompensations. Some patients will have a successful trial of extubation, transferring to NIV or even no support others will require a tracheostomy. For a few patients use of intermittent ventilation can be achieved even with a trachesotomy (mostly at night and during illness) but for some patients with bulbar problems or severe muscle weakness complete dependence on IV may become necessary. Score 4.47
* Aspiration prevention
  + For patients with bulbar dysfunction, choking or frequent respiratory infections a speech and swallow evaluation should be performed early on Score 4.82
  + A gastroenterologist and/or pulmonologist should be consulted for advice on how to minimize the risk of aspiration. Score 4.41
* Nocturnal hypoventilation and obstructive sleep apnea
  + Polysomnograms should be performed at baseline on every patient with a new diagnosis of a systemic mitochondrial disease to assess for sleep disturbances, central or obstructive apnea and nocturnal hypoventilation. Non‐invasive ventilation may be required and can improve daytime sleepiness, fatigue and nocturnal snoring. Score 4.00

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