

## MITOCHONDRIAL DISORDERS

### - A Review of Anesthetic Considerations -

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#### Introduction

Mitochondrial disorders are defined as diseases that have a defect in mitochondrial metabolism. The mitochondrion is a group of subcellular organelles with faint, threadlike granules. Mitochondria convert energy from food molecules into adenosine triphosphate (ATP), the main source of energy for most cell functions and manifest through the Krebs's citric acid cycle, fatty acid oxidation and oxidative phosphorylation (OXPHOS). OXPHOS is the main source for the formation of ATP. The mitochondrion is also involved in iron metabolism (implicated in Friedreich ataxia), amino acid biosynthesis and apoptosis. A subclass of these disorders, mitochondrial myopathies, is thought to be caused by OXPHOS defects.

#### Epidemiology

Mitochondrial diseases are caused both by mutations, acquired or inherited, within mitochondrial DNA (mtDNA) and genetic inheritance. They may also be the result of acquired mitochondrial dysfunction due to adverse effects of drugs, infections, or other environmental causes. Mitochondrial DNA inheritance behaves differently from autosomal and sexually-linked inheritance. Nuclear DNA has two copies per cell (except for sperm and egg cells), one copy being inherited from the father and the other from the mother. Mitochondrial DNA, however, is strictly inherited from the mother and each mitochondrial organelle typically contains multiple mtDNA copies. During cell division the mitochondrial DNA copies segregate randomly between the two new mitochondria, and then those new mitochondria make more copies. If only a few of the mtDNA copies inherited from the mother are defective, mitochondrial division may cause most of the defective copies to end up in just one of the new mitochondria. Mitochondrial disease may become clinically apparent once the number of affected mitochondria reaches a certain level; this phenomenon is called "threshold expression". To date, more than 200 disease-causing point mutations to the mitochondrial genome have been reported in the Mitomap database ([www.mitomap.org](http://www.mitomap.org)).

Although the structure of mtDNA was known over 40 years ago, and the consequences of impairment of the OXYPHOS pathway even earlier, mutations of the mitochondrial genome have been described more recently<sup>1,2,3</sup>. Although much has been learned over the past 2 decades, about mitochondrial disorders, the relationship between the molecular pathology of mtDNA-related diseases and the varied but often specific phenotypes associated with different mutations remains incompletely understood. The model most frequently

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used to study mitochondrial disease is the syndrome of mitochondrial encephalopathy, lactic acidosis and stroke like symptoms (MELAS) first described 25 years ago<sup>4</sup>. Of the 200 disease causing points in the mitochondrial genome, at least 30 have been associated with MELAS.

It takes about 3000 genes to make a mitochondrion<sup>5-7</sup>. Mitochondrial DNA encodes just 37 of these genes; the remaining genes are encoded in the cell nucleus and the resultant proteins are transported to the mitochondria. Only about 3% of the genes necessary to make a mitochondrion (100 of the 3000) are involved in the making of ATP. More than 95% (2900 of 3000) are involved with other functions tied to the specialized functions of the differentiated cell in which it resides. These functions change as the body develops from embryo to adult, and tissues grow, mature, and age. These non-ATP-related functions are intimately involved with most of the major metabolic pathways used by a cell to build, break down, and recycle its molecular building blocks. Cells cannot make the RNA and DNA they need to grow and function without mitochondria and the building blocks of purines and pyrimidines. Mitochondria contain the rate-limiting enzymes for pyrimidine biosynthesis (dihydroorotate dehydrogenase) and heme synthesis (d-amino levulinic acid synthetase) required to make hemoglobin. In the liver, mitochondria are specialized to detoxify ammonia in the urea cycle. Mitochondria are also required for cholesterol metabolism, for estrogen and testosterone synthesis, for neurotransmitter metabolism, and for free radical production and detoxification. Enzymes within mitochondria oxidize fat, protein, and carbohydrates to generate ATP via the electron transport chain a process known as oxidative phosphorylation. The mitochondrial complexes (I-V) that are part of this process are multimeric proteins embedded in the inner mitochondrial membrane. Mutations in any of these proteins produce many different clinical manifestations. Although the majority of these proteins are encoded by nuclear DNA thus producing Mendelian autosomal inheritance, some are encoded by mitochondrial DNA and therefore maternal inheritance is seen. The first step of the respiratory chain/OXPHOS process is the conversion of NADH to NAD and it is the most common site of mitochondrial aberrations. Its three major forms include the fatal infantile multisystem disorder, myopathy, and mitochondrial encephalopathy. The latter two forms have variable course and prognosis and other than metabolic supplements and dietary modifications to slow down progression of the disease, multivisceral organ transplantation may be the only available definitive treatment.

### *Genocopies of Mitochondrial Disease*

Genocopies are diseases that are caused by the same mutation but which may not look the same clinically. Because mitochondria perform so many different functions at different sites, with mutations and developed abnormalities, hundreds of different mitochondrial diseases may occur. Each disorder produces a spectrum of abnormalities that can make differential diagnosis difficult in the early stages. Because of the complex interplay between the hundreds of genes and cells that must cooperate for metabolic stability, it is a hallmark of mitochondrial diseases that identical mtDNA mutations may not produce identical diseases.

### *Phenocopies of Mitochondrial Disease*

The converse is also true: different mutations in mtDNA and nDNA can lead to the same diseases. In genetics, these are known as phenocopies. One example is Leigh syndrome, which can be caused by about a dozen different gene defects. Leigh syndrome, originally a neuropathological description of the brain of one affected child, was described by Leigh, in 1951. It is characterized by bilaterally symmetrical MRI

abnormalities in the brain stem, cerebellum, and basal ganglia, and often accompanied by elevated lactic acid levels in the blood or cerebrospinal fluid. Leigh syndrome may be caused by the NARP mutation, the MERRF mutation, complex I deficiency, cytochrome oxidase (COX) deficiency, pyruvate dehydrogenase (PDH) deficiency, and other unmapped DNA changes. However, not all children with these DNA abnormalities go on to develop Leigh syndrome.

### *Aging and Other Factors*

Mitochondrial diseases are even more complex in adults because detectable changes in mtDNA occur with age and, conversely, the aging process itself may result from deteriorating mitochondrial function. There is a broad spectrum of metabolic, inherited and acquired disorders in adults in which abnormal mitochondrial function has been postulated or demonstrated. Growth retardation is common.

### *Incidence*

The estimated incidence of mitochondrial myopathies is about 1:4,000 but the variable symptomatology makes this number most probably an underestimate<sup>5</sup>. About 1 in 4,000 children in the United States will develop mitochondrial disease by the age of 10 years. Up to 4,000 children per year in the US are born with a type of mitochondrial disease.

## **Classification**

Mitochondrial disorders are divided roughly into ragged-red fiber disorders and non ragged-red fibers ones based on subsarcolemmal accumulations of abnormal mitochondria and their intense red appearance with histologic staining.

Ragged-red fiber disorders include:

1. Kearns-Sayre syndrome.
2. Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes (MELAS).
3. Myoclonic epilepsy with ragged red fibers (MERRF).
4. Progressive external ophthalmoplegia (PEO).
5. Pearson syndrome.

Non ragged-red fiber disorders include:

1. Leigh encephalopathy.
2. Neuropathy, Ataxia, Retinitis Pigmentosa (NARP).

Manifestations of these disorders are depicted in Table 1.

*Table 1*  
*There are many manifestations of Mitochondrial diseases, seen at different ages*

MITOCHONDRIAL DISORDER	AGE of Dx (years)	MANIFESTATIONS
Kearns-Sayre Syndrome	>5<15	progressive external ophthalmoplegia
		retinitis pigmentosa
		cardiac conduction defect
		dilated cardiomyopathy
MELAS	late childhood, early adulthood	neurological symptoms-strokes, seizures, headaches
		Lactic acidosis
		cardiac conduction defect
MERRF	childhood, young adulthood	cardiomyopathy
		seizures
		progressive mental retardation
PEO	adulthood	similar to Kearns-Sayre syndrome
Pearson Syndrome	infancy, early childhood	refractory sideroblastic anemia
	usually fatal	insulin dependent diabetes mellitus
Leigh encephalopathy	perinatal time, early infancy	exocrine pancreatic dysfunction
		diffuse encephalopathy
		dysphagia
		hypotonia
NARP	young adulthood	central respiratory insufficiency
		Weakness
		ataxia
		retinopathy
		learning disability

Other diseases associated with mitochondrial dysfunction include:

- Diabetes mellitus and deafness (DAD)
  - this combination at an early age can be due to mitochondrial disease
- Leber's hereditary optic neuropathy (LHON)
  - visual loss beginning in young adulthood, characterized by progressive loss of central vision due to degeneration of the optic nerves and retina
- Wolff Parkinson White syndrome
- Multiple sclerosis type disease
- Myoneurogenic gastrointestinal encephalopathy (MNGIE)
  - gastrointestinal pseudo-obstruction
  - neuropathy

Conditions such as Friedreich's ataxia can affect the mitochondria, but are not associated with mitochondrial proteins. Deficiencies of each of the respiratory chain complexes can result in separate conditions such as Complex I (NADH-CoQ reductase) deficiency. Deficiencies of these complexes both individually and in combination have been associated with the aforementioned ragged-red and non ragged-red fiber disorders.

## Clinical Presentation

Because of the numerous mutations, these disorders may present with a variety of symptoms and at a different age<sup>8,9</sup>. As a rule of thumb, progressive muscle weakness and exercise intolerance are the main symptoms. Although weakness of the muscles controlling the eyes and eyelids can be a prominent feature in some patients, in others, weakness of the muscles of the face and neck with subsequent difficulty in speech and in swallowing can be the clinical manifestation. The degree of exercise intolerance varies with each individual; in some, problems with walking are the issue, in others jogging or more intense activities increase the severity of symptoms. Muscle pain and muscle injury can result in rhabdomyolysis and myoglobinuria with end result of renal insufficiency and failure.

Since deficiency in ATP production is the end result of these disorders, organs with high energy demands such as the brain, the heart and the kidneys may be involved early. Headaches, hearing deficits, seizures and learning disabilities with mental retardation can be the cerebral manifestations of ATP insufficiency (stroke-like episodes in MELAS). Cardiac conduction abnormalities requiring pacemaker placement and cardiac muscle damage with cardiomyopathy are common concerns in the cardiovascular system.

Other systems affected include the respiratory system with shortness of breath and insufficiency requiring ventilator support, the gastrointestinal system with symptoms such as unexplained vomiting and dysphagia and the endocrine system with diabetes and exocrine pancreatic insufficiency.

## Diagnosis

MitoD involve multiple systems and are usually progressive. Along with history and physical, complete neurological examination and follow up is warranted. Laboratory testing should include basic and specialized testing such as lactate, pyruvate, creatinine phosphokinase (CPK), plasma amino acid levels and urine for organic acids (Table 2). Although abnormal test results may support the diagnosis of mitoD, a single normal test cannot rule it out. The triad of lactic acidosis, seizures and stroke-like episodes is central to the diagnosis of MELAS, occurring in >90% of patients<sup>10</sup>. Lactic acidosis is determined either from serum or cerebrospinal fluid. Stroke-like episodes stress the non-ischemic origin of these events. Affected areas of the brain have an irregular distribution, consistent with a metabolic or small vessel etiology rather than disease associated with a classical vascular supply. Clinically, patients may have episodes of at least partially reversible aphasia, hemianopsia, and cortical blindness. Initially a mild sensorineural hearing loss is common. Migraine is also a common feature. An especially common systemic manifestation is diabetes mellitus, described in the earliest reports of mitochondrial disease<sup>4</sup>. There appears to be a firm association between MELAS, the m.3243A>G mutation and non insulin dependent diabetes.

*Table 2*

*Some of the common preoperative tests that should be performed in patients with mitochondrial disorders*

## LABORATORY EVALUATION

Complete Blood Count (CBC)  
Electrolytes and Glucose  
Creatinine  
Liver tests and ammonia  
Coagulation parameters  
Creatinine phosphokinase (CPK)  
Plasma lactate and pyruvate levels  
Plasma amino acids  
Urine organic acids  
Plasma acylcarnitine analysis

Despite the episodic nature, MELAS as with the other mitochondrial diseases, is progressive leading to dementia and severe neurologic deficits.

Brain imaging, audiology testing, ophthalmologic exam and electroencephalogram may identify central nervous system involvement whereas electrocardiogram and echocardiogram can detect cardiac disease<sup>11</sup>.

Skin or skeletal muscle biopsies can provide invaluable information but again they are not 100% sensitive. Fresh muscle biopsy may provide better results but not only can it be very expensive (up to \$10,000 for a complete analysis) but it is also performed in only a few centers in North America making it difficult for patients to access.

Karyotyping and genetics consultation may benefit evaluation of patients with developmental and learning disabilities.

### *Malignant Hyperthermia*

The only known myopathy disorders with true association with MH and the need for non-triggering anesthesia are:

1. Central Core disease
2. King-Denborough syndrome and
3. Evans myopathy

Although for the undiagnosed myopathic patient, a non-triggering technique should be employed, the estimated risk of malignant hyperthermia (MH) or rhabdomyolysis based on record review in a population of children with suspected neuromuscular dystrophy is less than 1%.

Two earlier reports of MH in association with mitoD have been recorded but most recent anesthesia reviews suggest that non-triggering anesthetics are not essential for the management of these disorders<sup>12,13</sup>. A wide range of anesthetics has been used including general anesthesia with volatile anesthetics, intravenous

anesthesia or regional block with local anesthetics. Mitochondrial disorders, especially MELAS, are now considered to have separate pathologies from MH.

## **Treatment**

Therapeutic options for patient with mitochondrial diseases remain limited. A recent trial of the role of dichloroacetate was terminated because of peripheral toxicity<sup>14</sup>. There are no curative therapies at present. Symptomatic management addressing cardiac, renal, growth and nutritional issues are emphasized. Other treatments are based on the use of antioxidants, respiratory chain substrates and co factors in the form of vitamins<sup>15</sup>. No consistent benefits have been observed. However, recent studies of a therapeutic role for L-arginine have been promising<sup>8</sup>. Dysfunction in COX activity and its effect on nitric oxide levels may cause the angiopathy and stroke like episodes and L-arginine may affect the uptake of glutamate and the release of GABA, increasing the production of ornithine<sup>16</sup>. Individual case reports and a prospective trial of L-arginine given orally over 2 years, significantly improved endothelial function<sup>17</sup>. Although many neurologists recommend nutritional supplements (vitamins and anti-oxidants), there is little data of their effectiveness other than Coenzyme Q supplementation. Most patients though, may have already been placed on such additives like carnitine infusion, TPN or simply high dextrose infusions, all of which should be continued intraoperatively to avoid a metabolic crisis.

## **Anesthetic Considerations**

The perioperative period carries several challenges for the anesthesiologist<sup>17-22</sup>.

**Preoperatively** history, physical and laboratory/special testing evaluation should be performed early enough for intervention as indicated. Electrolyte correction, especially that of acid-base balance may be necessary and coagulation parameters optimized. Hyperglycemia should be normalized. A specific neurologic finding may require attention or a cardiac conduction abnormality or cardiomyopathy monitored. Fasting guidelines indicate minimum of 6-8 hrs of solid meal avoidance and minimum of 2 hours for clear liquids. These patients not only are at higher risk for aspiration because of their bulbar muscle weakness and gut dysmotility, but they are also in danger of a metabolic crisis with prolonged fasting and inadequate glucose balance. Therefore a well thought out plan for their IV management should be in place. Avoidance of lactated Ringer's solution is also recommended to prevent additional lactate load.

A systematic review must be carried out as follows:

### *Neurologic*

As noted above, vision, hearing and speech may be impaired. Cognitive dysfunction is common, including language and memory difficulties. The ability to give informed consent may be impaired. Peripheral neuropathies are common.

### *Cardiac Manifestations*

Cardiac muscle has high-energy requirements and thus cardiac disease is common. Cardiomyopathies (especially in children where they may present as the sole anomaly) and congestive cardiac failure should be evaluated and treated. Conduction defects such as Wolff Parkinson White syndrome should be documented. Bundle branch blocks and infranodal conduction defects are not uncommon and appropriate cardiac consultation should be sought.

### *Pulmonary Changes*

Intrinsic pulmonary disease is rare. Pulmonary artery hypertension has been reported and associated with serum and cerebrospinal fluid acidosis<sup>8</sup>. Muscle biopsy in this case revealed cytochrome c oxidase-positive ragged red fibers and molecular testing demonstrated the presence of the m.3243A>G mutation.

### *Renal Abnormalities*

Renal disease occurs less commonly than cardiac or endocrine problems but may manifest as de Toni-Debre-Fanconi syndrome, nephrotic proteinuria or focal segmental glomerulosclerosis. Bartter-like syndrome, hypercalciuria and tubulointerstitial nephritis have also been reported<sup>8</sup>.

### *Gastrointestinal Involvement*

Several features have been described associated with mitochondrial diseases including constipation, gastric discomfort, hepatic pathology, pancreatitis, gastroparesis, intestinal pseudo-obstruction and malabsorption<sup>8</sup>.

### *Dermatologic Changes*

Vitiligo, scaly and pruritic rashes with diffuse erythema and reticular pigmentation have all been described<sup>8</sup>. However, skin changes appear to be relatively minor.

**Intraoperative Management:** In addition to standard ASA monitoring, arterial cannulation should be instituted for continuous hemodynamic monitoring as well as for frequent blood sampling for blood gases, electrolytes, blood glucose and lactate monitoring. Normothermia should be the goal to prevent added stress and increase in metabolic demands.

Precautions against aspiration with rapid sequence induction (RSI) and cricoid pressure may be considered in some patients, based on co-morbid conditions and degree of skeletal muscle weakness<sup>18,21</sup>. Depending on hepatic and renal insufficiency, muscle relaxants should be used cautiously. Although there is paucity of data regarding succinylcholine and mitochondrial disorders, its association with MH in one case report and possible hyperkalemic response should be considered.

Volatile anesthetics have been used in mitoD without complications but they have been shown to impair OXPHOS by inhibition of complex I. This in turn can impair CNS metabolism and cause cardiac dysfunction leading to a potential increase in sensitivity to these agents<sup>22</sup>.

Total intravenous anesthesia has been advocated by many as a safer, non-triggering anesthetic technique<sup>19</sup>. The safety of propofol has been questioned because of its lipid component possibly affecting fatty acid oxidation and because of a direct effect on the mitochondrial respiratory chain<sup>23,24</sup>. Both of these effects may predispose patients to a propofol infusion-like syndrome. This syndrome is characterized by lactic acidosis, bradycardia, rhabdomyolysis, cardiac and renal failure and although diagnosed mainly with longer duration infusions (>48hrs), in susceptible patients even short-term infusions can cause symptoms. Ketamine has not been implicated as a deleterious agent in mitoD and its analgesic properties can be an adjunct to the overall anesthetic management.

Regional anesthesia may be an attractive alternative for mitoD patients but local anesthetics have been shown to impair OXPHOS as well and may lead to inefficient ATP synthesis. Clinically, regional anesthesia has been used successfully and supporters indicate that its use may allow a decrease in opioids and thus a lower risk of respiratory depression with worsening acidosis. Also if a regional technique is used alone, volatile anesthetic sensitivity would be avoided.

**Postoperatively** minimizing metabolic stress and avoidance of increases in metabolic demand should be the ultimate goal including avoiding shivering, providing adequate analgesia, maintaining normoglycemia and a normal respiratory status. Even with a diligent perioperative plan, mitoD patients may require close monitoring in an intensive care setting.

## Conclusion

Although uncommon, mitoD can pose many challenges for the anesthesiologist. There is no “safest” anesthetic technique; the choice of anesthetic should be individualized to the patient’s needs. Consultation with experts in the field and the subspecialists in a multidisciplinary approach can provide excellent assistance with co-morbid issues and allow for good prognosis even in complex patients with multiorgan disease.

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