Mitochondrial Diseases and Anesthesia:
A Literature Review of Current Opinions

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This course explores the considerations that the anesthesia provider has to be aware of, when caring for a patient with a mitochondrial myopathy. Even though these disorders are rare, these patients may also need surgical care, requiring that the anesthesia provider be informed of the best anesthesia options to consider. A narrative review of documented cases and their outcomes is used to generate a resource of current opinions in the anesthetic care of this patient population.

Keywords: Anesthesia, mitochondria, myopathies, ragged-red fibers, respiratory chain.

Objectives

At the completion of this course, the reader should be able to:

1. Describe the mitochondria.
2. Discuss the causes of mitochondrial dysfunction.
3. List some manifestations of mitochondrial diseases.
4. Explain the medical management of mitochondrial diseases.
5. Explain the anesthesia implications of mitochondrial diseases.

Introduction

Mitochondrial diseases relate to a wide range of complex and varied defects in the minute, intracellular organelles that essentially power the cells of the body. There is an estimated incidence of one in 4,000 live births suffering from mitochondrial diseases.[1] These diseases have varied etiologies and are difficult to classify. There are those caused by mitochondrial DNA mutations such as MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke) and MERRF (myoclonic epilepsy and ragged-red fibers) syndromes. DNA point mutation deletions such as Kearns-Sayre syndrome and primary deficiencies of the respiratory chain complexes I-V represent some of these mitochondrial diseases.

The biochemical defects that characterize these diseases are related to (1) defects of mitochondrial substrate transport, (2) defects of mitochondrial substrate utilization, (3) defects of the intracellular respiratory processes, and (4) defects of energy conservation and transduction.[2]

Patients with these diseases have variable clinical manifestations and multisystem involvement. While often clues to the disease manifest early in life, even at birth, in some cases symptoms do not become clinically apparent until late childhood or even adulthood. The course of this illness varies but gradually deteriorates leading to coma or death, usually, of respiratory failure. There is a spectrum of presenting symptoms.

Hirano and Pavlakis[3] organized the different clinical characteristics of these diseases into three categories:

I. Cardinal manifestations: onset of symptoms before age 40, clinical stroke, seizures, lactic acidosis, ragged-red fibers (which are muscle fibers that show an abnormal proliferation of mitochondria detected histochemically with modified Gomori trichrome stain) and exercise intolerance are found in over 90% of patients.

II. Frequent manifestations: dementia (90%), normal early development (90%), limb weakness (89%), short stature, hemiparesis or hemianopsia, headaches, nausea or vomiting, hearing loss, and elevated cerebral spinal fluid protein are also noted.

III. Other manifestations: myoclonus, cerebellar signs, peripheral neuropathy, pigmentary retinopathy, ophthalmoplegia, optic atrophy, nephropathy, cardiomyopathy, Wolff-Parkinson-White electrocardiographic syndrome, hirsutism, and cutaneous purpura (45%).

Laboratory, pathologic, and imaging features vary. MELAS patients present with increased values of serum

and cerebrospinal fluid lactate. In brain computerized tomography studies we can find lucencies consistent with infarcts, cortical atrophy, cerebellar atrophy and basal ganglia calcifications in these patients.

Invariably, those afflicted might require surgical interventions and anesthesia services. Given the multiple presentations and etiologies of these diseases the impact that the anesthetic modality used will have on these patients can be difficult to predict.

A narrative review of the literature will be presented focusing on the function of the mitochondria, causes of dysfunction, manifestations of mitochondrial disease, the medical management of associated disorders, and implications for the anesthetist presented with these patients in need of surgical or diagnostic interventions.

• *Function of the Mitochondria.* The mitochondria are semiautonomous organelles with a vital role in the energy production of the cell. They are also involved in the regulation of apoptosis (programmed cell death), redox potential, antiviral signaling and calcium homeostasis.[4] Its complex morphology (Figure) consists of an outer and inner membrane which create the intermembrane space and the innermost matrix space, where the tricarboxylic acid cycle (TCA), the urea cycle and the β-oxidation of fatty acids takes place. The inner membrane folds form the cristae, where the five complexes of the oxidative phosphorylation system are located.[5]

Mitochondrial respiratory chain diseases are caused by mutations of both nuclear and mitochondrial DNA. The human mitochondrion carries its own DNA (mtDNA) and is maternally inherited. It contains 37 genes that are responsible for the encoding of 13 structural subunits of oxidative phosphorylation system complexes and the 22 transfer ribonucleic acids (tRNA) and two ribosomal ribonucleic acids (rRNA) that are needed for the mitochondrial protein biosynthesis.[5] On the other hand, nuclear DNA (nDNA) is responsible for encoding more than 80 structural subunits of the oxidative phosphorylation system complexes, and the assembly proteins and enzymes required for mitochondrial biogenesis.[5] Therefore the oxidative phosphorylation system metabolic pathway is under the control of both, the nDNA and the mtDNA. Examples of mitochondrial or nuclear origin types of genes involved in the encoding of mitochondrial proteins in mitochondrial diseases are listed in Table 1.

Oxidative phosphorylation system converts substrates from glycolisis, fatty acid oxidation and tricarboxylic acid cycle to ATP through five complexes, I through V. The first four: I-IV, are responsible for electron transport chain reactions which are redox reactions that produce the energy used for the proton translocation from the mitochondria matrix to the inner membranes. Complexes I, III, and IV, create the electrochemical gradient that is needed for the synthesis of ATP by translocating protons back to the matrix using ATPase synthase (V complex).
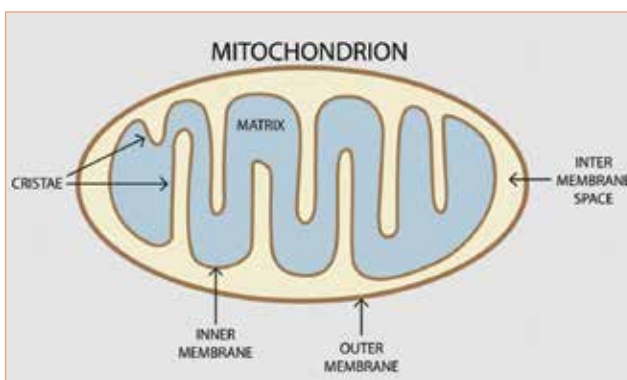

Figure. Morphology

The ATP translocator is then responsible for transferring ATP to the cytoplasm exchanging it for ADP.[5]

• *Causes of Mitochondrial Dysfunction.* Mitochondrial diseases are the result of DNA mutations of either nuclear or mitochondrial DNA. The respiratory chain is the essential final common pathway for aerobic metabolism, therefore tissues and organs that are dependent upon aerobic metabolism (central nervous system, heart) are preferentially affected in these disorders.

Mitochondrial DNA (mtDNA) lacks a significant DNA repair system and is in close proximity to the inner membrane and therefore to byproducts of oxidative phosphorylation system, reactive oxygen and nitrogen species, which are known to contribute to a high frequency mutation rate.[5] These mutations include: Point mutation which involves a single nucleotide (it may be the loss, substitution or insertion of it)[6]; rearrangement mutation where the DNA code is wrongly reshuffled or misplaced[6]; and deletion mutations in the mtDNA produced by the loss of nucleotides from a mtDNA sequence.[6]

In the random distribution of mtDNA molecules during cell division, a genetic drift, or random fluctuations in the appearance of a gene presumably owing to chance,[6] occurs in favor of normal or mutant mtDNA, which will lead to homoplasmy (the presence within a cell or organism of genetically identical mitochondria)[6] towards one of the two types of mtDNA. If the mutant mtDNA is in excess of 60% of the mitochondrias in tissues like the brain, heart and muscle, they are unable to meet their high energy demands and the symptomatology of the disease becomes apparent.[5] These are referred to as "primary mitochondrial diseases" because they are associated with defects in the oxidative phosphorylation system. They make up a heterogenous group of rare genetic diseases further classified as systemic or organ specific with onsets that go from childhood to late adulthood.

Of the 20% of the primary mitochondrial diseases (the other 80% are not considered of primary mitochondrial origin) whose causative gene have been identified, 80% are of nDNA origin and are due to mutations taking place in:

Origin of disorder	Oxidative phosphorylation complex affected	Function	Clinical phenotype
mtDNA (structural genes)	I		Dystonia
	III		Mitochondrial myopathy
	IV	Catalyses the electron transfer(most frequent cause of respiratory chain defects)	Encephalopathy
	IV		Encephalopathy, MELAS
	V		Leigh syndrome
nDNA (structural genes)	I	Iron-sulfur protein fraction	Leigh syndrome
	II		Leigh syndrome
	III	Flavoprotein fraction electron transfer	Hypoglycemia, lactic acidosis
nDNA (non-structural genes)	I	Complex assembly	Early onset progressive encephalopathy
	III	Complex assembly	Encephalopathy, hepatic failure and tubulopathy
	IV	Complex assembly	Leigh syndrome
	IV	Complex assembly/copper transport	Neonatal cardioencephalomyopathy due to COX deficiency

Table 1. Examples of Mitochondrial or Nuclear Origin Types of Genes Involved in Encoding Mitochondrial Proteins in Mitochondrial Diseases
(Based on Information from http://www.mitomapp.org/bin/view.pl/MITOMAP/ClinicalphenotypesPolypeptide, http://www.mitomap.org/bin/view.pl/MITOMAP/NuclearGenesStructural, and http://www.mitomap.org/bin/view.pl/MITOMAP/NuclearGenesNonStructural.)
Abbreviation: MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.

1. Genes encoding respiratory chain subunits:
   A. Respiratory chain assembly proteins
   B. Electron carrier CoQ_{10}
2. Genes affecting mtDNA integrity
3. Mitochondrial protein import
4. Lipid composition of the inner mitochondrial membrane
5. Intergenomic signaling
6. Mitochondrial dynamics, ie, motility, fusion, fission

As previously mentioned, disorders of the oxidative phosphorylation system can originate from mutations taking place in the mitochondrial or nuclear DNA, therefore they can follow all modalities of inheritance such as X-linked, autosomal recessive or dominant.[5]

• *Manifestations of Mitochondrial Diseases.* Mitochondrial diseases may affect a single organ (Ex. The eye in Lebors Optic Neuropathy), or may involve multiple organs (Ex. Friedrick Ataxia, Wilsons Disease) that present with neurological and myopathic clinical features.[7] Some of the most frequent manifestations of these diseases by system are listed in Table 2.

The primary mitochondrial diseases, associated with respiratory chain defects have varied clinical manifestations such as diabetes, endocrine dysfunction, hearing loss, hypertrophic cardiomyopathy, liver failure, ptosis of eyelids, obstructing vision, and seizures.[7]

Mitochondrial diseases can present at any age, but pediatric mitochondrial disease usually is more severe than adult onset and presents with progressive neurological, cardiac and liver dysfunction. In children the clinical presentation includes failure to thrive, hypotonia, blindness, deafness, a progressive cardiomyopathy, lactic acidosis, lethargy, and seizure activity.[8] The most recognizable syndromes of mitochondrial dysfunction are listed in Table 3.

System	Manifestation
Auditory	Sensorineural deafness related to cochlear and cranial nerve VIII dysfunction
Cardiovascular	Cardiac conduction blocks
	Predisposition to arrhythmias
	Wolff-Parkinson-White syndrome
	In severe forms: metabolic cardiomyopathy, hypertrophic or dilated
Nervous	A. Pediatric manifestations
	Developmental delay or regression
	Seizures
	Movement disorders
	B. Adult-onset manifestations
	Stroke like episodes
	Stroke
	Peripheral neuropathy
Endocrine	Type 2 diabetes
Gastrointestinal	A. Peristalsis disorders like: delayed gastric emptying with nausea and vomiting, constipation, diarrhea and intestinal pseudo-obstruction
	B. Exocrine pancreatic insufficiency causing fat malabsortion and poor growth.
Neuromuscular	Most common manifestations, they range from nonspecific exercise intolerance, exercise-induced myalgia to muscle wasting or weakness in a predominantly proximal distribution.
Visual	Progressive external ophthalmoplegia and ptosis.
	Pigmentary retinopathy
	When the nerve ganglion layer cells are affected, it results in painless sequential loss of visual acuity followed by optic atrophy.

Table 2. Clinical Manifestations by System
(Adapted from *BC Med J.* 2011;53(4); www.bcmj.org.)

In adult onset mitochondrial disease the presentation is usually more subtle, and usually a multisystem progressive disorder.[8]

• *Medical Management of Associated Disorders.* There is no cure for this group of diseases. Management is directed at the treatment of the clinical manifestations of the disease.[5]

Exercise training has been reported to alter the balance against mutated mtDNA and towards normal mtDNA. Aerobic exercise specifically has been reported to induce oxidative phosphorilation (OXPHOS) facilitating mitochondrial functions.

Ketogenic diet replacing glucose by precursors of ketones shifts the metabolism from glycolisis to β-oxidation of fatty acids in the mitochondria. They have also been found to decrease the mitochondrial reactive oxygen species (ROS) production, enhancing its biogenesis.

Pharmacologic therapy includes administration of sodium bicarbonate or dichloroacetate to remove toxic metabolites, such as lactic acid, which leads to lactic acidosis and imbalance of cellular pH and also administration of electron acceptors such as: menadiol and vitamin C.

Pharmacologic therapy also includes administration of metabolites and cofactors such as: CoQ_{10}, vitamins B1 and B2, L-carnitine, creatine, folic acid and copper, ROS scavengers: vitamin E, CoQ_{10}, idebenone and dihydrolipoate. Calcium channel blockers are used to rebalance calcium homeostasis.

Symptomatic therapy includes drug therapy with anticonvulsants, antipsychotics and insulin to name a few. Surgical treatments include heart transplantation, upper blepharoplasties, and insertion of cochlear implants. Hemodialysis is performed to get rid of excessive hazardous metabolites.

Some treatment modalities under development include:[5]

Enhancement of mitochondrial biogenenesis by upregulating mitochondrial soluble adenylyl cyclase, which activates mitochondrial protein kinase A and improves COX activity in cases where the residual COX activity is not too diminished.

Another modality includes gene therapy, one approach being gene shifting, which reduces the mutant mtDNA in favor of healthy DNA and, inhibition of mutant mtDNA replication by peptide-nucleic acids.

Somatic stem cell therapy: allogeneic hematopoietic stem cell transplantation in patients with mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE) was accomplished to reduce thymidine and deoxyuridine levels in the blood.

Germline therapy: use of nuclear transfer technology aims to remove mitochondria carrying mutant mtDNA from maternal oocytes replacing them with healthy mitochondria from a donor's ooplasm.

Protein transduction domain (PTD) technology offers a mechanism for the delivery of human recombinant proteins inside organelles, like the mitochondria. These human mitochondrial proteins would be engineered using recombinant DNA and PTD technologies at specific mitochondrial sites where their function is needed.

Families with a history of mitochondrial diseases should be offered genetic counseling with prenatal or preimplantation diagnosis by analyzing amniocytes or chorionic villi for mutations so they can prevent transmission to their descendants.[5]

Implications for the Anesthetist

• *Relationship Between Mitochondrial Dysfunction and Malignant Hyperthermia.* Recent evidence has shown that only King syndrome and central core disease are the two neuromuscular disorders linked to malignant hyperthermia susceptibility.[4,5] Duchenne muscular dystrophy and mitochondrial disease association to malignant hyperthermia have mostly been dismissed.[4-8]

Syndrome	Features	Genetics
Alpers	Encephalopathy, seizures, and hepatic dysfunction	Autosomal recessive Autosomal dominant
Kearns-Sayre	External opthalmoplegia, pigmentary retinopathy, elevated CSF protein, cerebellar ataxia and cardiac conduction defects	Mitochondrial DNA, often sporadic
Leigh	Neonatal subacute encephalopathy with bilateral symmetric midbrain and basal ganglia necrosis on MRI	Autosomal recessive, mitochondrial DNA, X-linked
MELAS	Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes	Mitochondrial DNA
MERRF	Myoclonic epilepsy with ragged-red fibers on muscle biopsy	Mitochondrial DNA
MIDD	Maternally inherited diabetes and deafness	Mitochondrial DNA
MNGIE	Mitochondrial neurogastrointestinal encephalopathy	Autosomal recessive
NARP	Neurogenic weakness, ataxia, and retinitis pigmentosa	Mitochondrial DNA
Pearson	Sideroblastic anemia, pancytopenia, exocrine pancreatic insufficiency and renal tubulopathy	Mitochondrial DNA
SANDO	Sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia	Autosomal dominant

Table 3. Syndromes of Mitochondrial Dysfunction[7]
(Adapted from *BC Med J.* 2011;53(4); www.bcmj.org.)

• *Local Anesthetics Effects on Mitochondrial Function.* Bupivacaine has been found to induce sarcomer disruption and structural alteration of mitochondria in studies conducted in rats and human cells.[9,10] It directly affects the mitochondrial function by concentration dependent depolarization of its external membrane and oxidation of pyridine nucleotides. It opens the permeability transition pore in the inner mitochondrial membrane which plays a key role in apoptosis. It also affects the resting respiration of mitochondria and decreases the transmembrane electrical potential and the ATP synthesis rate.[11,12]

Ropivacaine and bupivacaine block the electron transfer, inhibiting complex I of the respiratory chain. Ropivacaine interferes with mitochondrial energy transduction by dissipating the electrochemical protein gradient.[11,12]

Cocaine, proparacaine and tetracaine interfere with mitochondrial function by dissipating its membrane potential.

These findings suggests that local anesthetics should be used with caution in this patient population using the minimum effective anesthetic concentration, titrated to the patient's requirements.[1]

• *Selection of Anesthetic Agents.* Given the depressant effects that propofol has on mitochondria, propofol is contraindicated in these patients. It is well known to inhibit mitochondrial function at complex I and also is involved in uncoupling oxidative phosphorylation. In addition to these effects propofol has been demonstrated to affect mitochondrial function by at least four different mechanisms involving complex I, complex II, complex IV, and complex V. It has also been demonstrated to inhibit β-oxidation and carnitine palmitoyl transferase I, which is responsible for inhibition of the transport of long-chain fatty acids.[1] These depressant effects on

the mitochondria are thought to explain the propofol infusion syndrome (PRIS), which consists of metabolic acidosis, refractory cardiac failure, fever, and muscle cell damage. It has been proposed that children who develop metabolic acidosis and myocardial failure after a propofol infusion may have a subclinical form of mitochondrial disease.[13]

The use of halogenated agents in children with suspected neuromuscular diseases was studied by Flick et al. They reviewed 274 charts of children who had undergone muscle biopsy for instances of malignant hyperthermia and/or rhabdomyolysis. They all received halogenated agents with or without succinylcholine and no child developed malignant hyperthermia or rhabdomyolysis.[4] At this time the decision to use halogenated agents for these patients seems the most appropriate.[13]

The use of succinylcholine is contraindicated because of the possibility of triggering a myotonic crisis with the subsequent difficulty in ventilation and intubation.[14]

It is recommended that nondepolarizing neuromuscular agents be used with caution, since the response to this drug group cannot be predicted with certainty in this patient population.[14,15,16] The duration of paralysis will likely be prolonged, when this occurs aniticholinesterases should be avoided because their use can trigger a myotonic crisis.[14]

In 1992 the US Food and Drug administration warned against the use of succinylcholine in young children and adolescents due to being a common cause of pediatric cardiac arrest during anesthesia. It is for this reason that it should be reserved for emergency intubations or when immediate securing of the airway is critical.[18]

In the case of a patient who presents for a diagnostic muscle biopsy for suspected mitochondrial disease, ket-

Authors	Journal and year published	Title	Recommendations
Schwartz D and Raghunathan K	*Paediatric Anaesthesia* 2009	Anesthesia and mitochondrial disorders	"..propofol might not be a good choice in these children."[20]
Ferrari F	*Paediatric Anaesthesia* 2009	Anesthesia care for muscle biopsy in children with myopathies	"Intravenous anesthesia, followed by local anesthesia by plastic surgeon..."[21]
Driessen J and Smeitink J	*Paediatric Anaesthesia* 2009	Author's reply to: anesthesia care for muscle biopsy in children with myopathies	.. "when there is a suspected mitochondrial disorder, local anesthetic agents given prior to the muscle biopsy, may interfere with the diagnostic value of the biopsy. Because of their mitochondrial depressant effect, administration of local anesthetic should be better postponed until the biopsy is harvested."[22]
Maurtua et al	*International Journal of Obstetric Anesthesia* 2009	Anesthetic management of an obstetric patient with MELAS syndrome: case report and literature review	"Regional analgesia and anesthesia may be beneficial in reducing metabolic demands associated with the stress and pain of labor and delivery. If general anesthesia is required, propofol infusions should be avoided to prevent further decreasing ATP production."[23]
Schnabel et al	*Paediatric Anaesthesia* 2008	Anesthetic management for a child with mitochondrial complex II deficiency	"a total intravenous technique and under avoidance of muscle relaxants..."[24]
Flick et al	*Paediatric Anaesthesia* 2007	The risk of malignant hyperthermia in children undergoing muscle biopsy for suspected neuromuscular disorder	"…it has been recommended that those caring for children that have or may have mitochondrial disorders consider avoiding the use of propofol because of concerns that this group may be at particular risk for the propofol infusion syndrome. ...reassurance with regard to the use of volatile anesthetics in those undergoing diagnostic muscle biopsy."[4]
Driessen et al	*Paediatric Anaesthesia* 2007	Anesthesia-related morbidity and mortality after surgery for muscle biopsy in children with mitochondrial defects	"Propofol may probably no longer be considered the anesthetic of choice for children with a suspected or proven mitochondrial disorder given its depressant effects on mitochondrial function".[9]
Sasano et al	*Journal of Anesthesia* 2007	Anesthetic management of a patient with mitochondrial myopathy (MELAS) during laparotomy	1."..we avoided the use of succinylcholine and volatile anesthetics. 2.…Neuromuscular blockade should be administered carefully. 3..Bicarbonated Ringer's solution may help prevent exacerbation of lactic acidosis… 4. It is very important to maintain normothermia.."[19]
Weinberg and Baughman	*Anesthesiology* 2006	Carnitine deficiency, mitochondrial metabolism, and abnormal response to anesthetics	"..development of mitochondrial β-oxidation defects when propofol is used for sedation."[25]
Finsterer et al	*Clinical Neuropharmacology* 2005	Deterioration of Kearns-Sayre syndrome following articaine administration for local anesthesia	"Articaine should be used with caution in Kearns-Sayre syndrome because of its presumed direct mitochondrial toxic effect."[13]
Aouad et al	*Paediatric Anaesthesia* 2005	Resistance to cisatracurium in a patient with MELAS syndrome	"We conclude that the response to muscle relaxants in patients with MELAS syndrome is not predictable, requiring careful titration of NDMR and adequate monitoring of the neuromuscular blockade."[17]
Hara et al	*Journal of Clinical Anesthesia* 2004	Anesthetic management for cardioverter-defibrillator implantation in a patient with Kearns-Sayre syndrome	"Neuromuscular blocking drugs and anesthetics, including opioids and sedatives that may have muscle relaxing properties and affect cardiac conduction, should not be used or used only in smaller doses.."[26]

Table 4. Anesthesia-Related Articles Reviewed (2009-2004)

amine and low-dose halogenated agents are the best anesthetic choice.[1] Furthermore, local anesthetic administration should be postponed until after the muscle biopsy is harvested because due to their mitochondrial depressant effect its use beforehand can interfere with the diagnostic value of the biopsy.[1]

• *Intravenous Fluid Selection.* Lactate metabolism is impaired in patients with mitochondrial diseases, therefore lactated Ringer's solution should be avoided and 9% normal saline should be the intravenous fluid of choice. If there is a metabolic disturbance bicarbonated Ringer's solution has been reported to be more effective in maintaining pH than acetated Ringer's, since the bicarbonate is physiological and therefore does not require a metabolic process to alkalinize.[15]

Maintaining normothermia is crucial for these patients since hypothermia depresses mitochondrial function and increases metabolic stress to regain it.[15]

In Table 4, you will find the articles reviewed, organized in reverse chronological order, with a summary of their most important anesthetic recommendations for this unusual group of diseases. Much is still unknown in the study of these diseases and the anesthetic implications these patients present. This literature narrative aims to summarize the current views and recommendations.

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