

TOP 10 FACTS

Top Ten Facts you need to Know About the anesthetic management of Patients with mitochondrial disease

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Mitochondrial diseases are inherited metabolic disorders in which energy metabolism is impaired. They are one of the most prevalent genetic disorders affecting an estimated 1 in every 5000 adults. Impaired energy metabolism because of the mitochondrial or nuclear genome defects results in an increased risk for a wide range of complications affecting every system in the human body. Mitochondrial disorders substantially affect major organs with high metabolic requirements, such as the nervous system, muscles, heart, and gastrointestinal tract. Due to an increased susceptibility to metabolic stress during surgery, patients with mitochondrial diseases require increased consideration during anesthetic management. In this article we would like to discuss the top ten facts you need to know about perioperative management of patients with mitochondrial disease.

Introduction

Mitochondrial diseases are a group of inherited metabolic disorders in which energy metabolism is impaired. Together they form one of the most prevalent genetic disorders affecting an estimated 1 in every 5000 adults.¹ Impaired energy metabolism, because of the mitochondrial or nuclear genome defects, results in an increased risk for a wide range of complications affecting every system in the human body. ([Table 1](#)) Mitochondrial diseases are classified based on mitochondrial respiratory chain disorders, disorders associated with mitochondrial deletions and depletions, and disorders of the mitochondrial membrane. They are part of multiple clinical syndromes (CPEO = chronic progressive external ophthalmoplegia; KSS = Kearns-Sayre syndrome; LHON = Leber hereditary optic neuropathy; MELAS = mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MERRF = myoclonic epilepsy with ragged-red fibers; NARP = neurogenic weakness with ataxia and retinitis pigmentosa).¹ Substantially affecting major organs with high metabolic requirements, such as the nervous system, muscles, heart, and gastrointestinal tract,² mitochondrial diseases require increased consideration for patients during anesthetic management due to increased susceptibility to metabolic stress during surgery.^{2,3} This article discusses the top ten facts about the anesthetic management of patients with mitochondrial disease.

1. Patients scheduled for surgery require a multi-disciplinary approach involving patient-physician, cardiology, neurology, endocrinology, and genetics based on the severity of mitochondrial disease.^{1,2} It should begin with a focused patient history and physical assessment before a surgical procedure. The review includes complete medical

Table 1. Systemic effects of primary mitochondrial disease

Systems	Mitochondrial disease effects
Central nervous system & Peripheral nervous system	Developmental disability, Epilepsy, Spasticity & Tone abnormality, Movement disorders, Automimic & Brainstem dysfunction, Headache, Stroke (metabolic), Hearing loss (sensorineural), Eyes (cataracts, ophthalmoplegia, optic nerve atrophy, ptosis, retinopathy), Neuropathy
Heart	Conduction defects (heart block), Arrhythmias, Cardiomyopathy
Airway & Lungs	Difficult airway, Hypoventilation, Apnea, Aspiration, Pulmonary hypertension
Endocrinology	Growth hormone deficiency, Hypothyroidism, Hypoparathyroidism, Diabetes, Adrenal insufficiency, Osteopenia
Gastrointestinal	Dysphagia, Gastroparesis, Dysmotility, Constipation, Pseudo obstruction, Hepatic dysfunction, Pancreatic insufficiency, Failure to thrive.
Kidney	Glomerular dysfunction, Fanconi syndrome, Tubulopathy
Hematology & Immunology	Pancytopenia, Anemia (iron deficiency), Sideroblastic anemia, Recurrent infections
Musculoskeletal	Myopathy, Contractures, Fractures, Scoliosis, Fatigue, Exercise intolerance
Pregnancy	Preeclampsia, Gestational diabetes, Preterm labor

and family history of prior cardiopulmonary complications or myopathies. Patients with mitochondrial disease are at increased risk of respiratory depression secondary to the combination of anesthesia and preexisted muscle weakness.⁴ Based on the patient's functional capacity and planned surgical procedure, preoperative investigations such as complete blood count, chemistry, blood gas, electrocardiogram, echocardiogram, and spirometry are performed.^{3, 4}

2. Patients' fasting duration (NPO status) before surgery should be minimized to prevent hypoglycemia, and clear liquids with glucose continued until two hours before anesthesia. Cellular metabolism relies heavily on the mitochondria to produce energy and glucose. Since many anesthetics also suppress energy production, patients with mitochondrial diseases are particularly susceptible to hypoglycemia during anesthesia management.³ Patients should also be scheduled for early surgeries (preferably as the first case on the day) to minimize the risk of hypoglycemia.
3. Ringer Lactate (LR) as intravenous fluids should be avoided for patients with mitochondrial disease due to the increased risk of lactic acidosis. Lactate metabolism requires oxidative phosphorylation for the conversion of lactate to bicarbonate. This process is often disrupted in patients with mitochondrial disease, leading to increased susceptibility to lactic acidosis, as the body must rely increasingly on anaerobic metabolism. To prevent this acidosis from forming, a physiological electrolyte solution or dextrose-containing fluids should be used with glucose and electrolyte monitoring (unless the patients are on a ketogenic diet or demonstrated adverse reactions to dextrose-containing fluids).³⁻⁵

4. Propofol infusions for longer duration are avoided in patients with mitochondrial disorders due to its ability to disrupt mitochondrial function by inhibiting multiple metabolic pathways. Propofol inhibits the function of electron transport chain complexes and fatty acid transport.⁶ Propofol is also unique in that it can affect at least four different mechanisms of mitochondrial metabolism.⁶ While short-term use of propofol is typically well tolerated, several case reports have presented long-term propofol use in patients with mitochondrial disease, leading to propofol infusion syndrome.³ This connection is thought to be due to propofol leading to increased levels of acylcarnitine transferase. Propofol infusion syndrome can also lead to severe lactic acidosis, eventually leading to severe cardiac failure.⁴
5. Depolarizing muscle relaxants such as succinylcholine is avoided due to the increased risk of acute hyperkalemia and severe arrhythmias. There was also controversy over depolarizing neuromuscular blockers after a case report by Ohtani et al. showed the development of malignant hyperthermia in a 2-year-old with mitochondrial disease after using halothane and succinylcholine.^{7,8} However, there have been no additional reported cases of malignant hyperthermia in mitochondrial disease patients after using depolarizing muscle relaxants. Non-depolarizing muscle relaxants are preferable, although some studies have shown increased sensitivity.³
6. Although some patients may have hypersensitivity to volatile anesthetics, these anesthetics are safe to use. In-vitro, studies have also shown that volatile anesthetics suppress complex I and coenzyme Q functions.³ This disruption in oxidative phosphorylation makes patients with complex-I mitochondrial mutation more susceptible to volatile anesthetics. However, commonly used newer volatile anesthetics are typically not metabolized, which allows mitochondria to regain function quickly. Sevoflurane is preferred due to less respiratory function suppression than isoflurane and desflurane.⁴
7. Regional anesthesia (nerve blocks, neuraxial anesthesia) with local anesthetics are the preferred choice as they do not lead to central nervous system depression. There has been one case report of bradyarrhythmias after using bupivacaine, thought to be associated with the inhibition of acylcarnitine exchange.⁹ Lidocaine is the preferred local anesthetic due to its weaker effect on inhibiting carnitine-acylcarnitine translocase.^{6,9}

Table 2. Perioperative medications – Role in Mitochondrial disease

Drug Class	Mitochondrial effects & complications	Recommendations
Propofol (Dose > 4 mg/kg/hr for > 48 hours)	Acylcarnitine transferase, complexes I/II/IV inhibition- Metabolic acidosis, Propofol infusion syndrome, Cardiac failure	Avoid higher doses and infusions
Barbiturates/etomidate	Complex I inhibition, Mild inhibition of complex III (Etomidate)	Safe
Dexmedetomidine	Unknown, no complications	Safe
Opioids	Morphine (Mild complex I inhibition), Fentanyl/Remifentanyl (Minimal or no effects)	Safe
Benzodiazepines	Complex I/II/III inhibition- Electron transport chain inhibition.	Safe
Volatile anesthetics	Complex 1 and Coenzyme Q inhibition. Increased sensitivity may cause hepatotoxicity, neurotoxicity, and cardiac effects.	Safe
Ketamine	Complex 1 inhibition- Increase energy consumption	Safe
Local anesthetics (Bupivacaine, Ropivacaine, Lidocaine.)	Carnitine-acylcarnitine translocase inhibition - myopathy	Safe
Depolarizing muscle relaxants (Succinylcholine)	Hyperkalemia. Malignant hyperthermia.	Avoid
Non-depolarizing muscle relaxants	Increased sensitivity – weakness of respiratory muscles	Safe
Perioperative antibiotics (aminoglycosides, linezolid, tetracycline, azithromycin, and erythromycin)	Hearing loss	Avoid
Tylenol (High dose)	Deplete glutathione and cause liver damage.	Avoid higher doses
NSAIDS (Naproxen Ibuprofen, Diclofenac)	Mitochondrial DNA depletion – Lactic acidosis, encephalomyopathy, anemia, polyneuropathy, pancreatitis)	Avoid higher doses

8. No known side effects are reported with the perioperative use of dexmedetomidine in patients with mitochondrial disease. However, among opioids in mitochondrial disease patients, morphine shows mild complex-I inhibition, so it is preferable to use short-acting opioids (Fentanyl, remifentanyl).
9. Other than anesthetic medications used perioperatively (antibiotics, NSAIDS, Tylenol), we need to pay attention to each medication's risks, benefits, and alternatives to improve the outcome of patients with mitochondrial disease patients.^{1,10} ([Table 2](#))
10. Patients with mitochondrial disease were monitored closely in the post-operative period. The primary concern is respiratory depression due to muscle weakness. Postoperatively, these patients were observed in a high dependency unit based on pre-operative severity of mitochondrial disease and extent of surgery with appropriate post-operative investigations (electrolytes, lactate, and blood gas analysis).^{2,3}

Genomic diagnosis and mapping improved the early diagnosis of mitochondrial disease and management. Mitochondrial Medical Society (MMS) developed guidelines for diagnosis, standardized management, and preventive health care of patients diagnosed with primary mitochondrial

disease. As a result, patients with mitochondrial disease were optimized pre-operatively concerning the extent of the systemic disease, fasting times, intravenous fluid selection, type of anesthesia, perioperative medications, maintenance of normothermia, and appropriate postoperative care.

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