Anesthetic Management of a Pediatric Patient with a Complex III Mitochondrial Disorder

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Learning Objectives:
1. List characteristics of mitochondrial diseases and how they relate to anesthesia
2. Formulate an appropriate anesthetic plan for a patient with mitochondrial disease
3. Identify common anesthetic problems seen in mitochondrial disease patients

Stem Case and Key Questions:

L.W. is a 4 year old boy known to have a mitochondrial disorder, specifically complex III deficiency. He has had recurrent bouts of fungemia, bacterial sepsis, and central line infections due to immune dysfunction and a history of pancytopenia. He remains TPN dependent due to poor gut motility. L.W. has a jejunostomy tube in place but attempts at increasing his tube feeds have been unsuccessful due to intestinal pseudo-obstruction. The patient has diffuse hypotonia and readily becomes tired and short of breath with minimal exertion or when holding a conversation. He requires continuous oxygen via a nasal cannula. L.W. also has a hearing deficit for which he uses bilateral hearing aids. The patient has an infected PICC line (peripherally inserted central catheter) but his blood cultures have remained negative. Currently, the infected PICC line is being used because of L.W.’s difficult intravenous access.

1. What are mitochondrial diseases?
2. What are common symptoms associated with mitochondrial diseases?
3. What is the incidence of mitochondrial disease?

L.W. presents today for an endoscopic gastroduodenoscopy (EGD), laparascopic liver biopsy and ileostomy placement. ENT also added bilateral ear exams with pressure equalizing tube removal and an auditory brainstem response (ABR) test. A new PICC line is to be placed while the patient is anesthetized.

4. Considering the patient’s complex history, what are your primary concerns when formulating your anesthetic plan?
5. Are there additional tests and/or labs which you would want preoperatively?

6. What would you tell the parents in terms of risks of anesthesia and possible postoperative anesthetic complications?

   The patient’s lab results include Na 137, K 4.5, Cr 0.4, glucose 94, Hgb 14.4, Hct 41.1, platelets 145. The patient’s ALT is high at 404. A chest radiograph from four days prior shows evidence of atelectasis but no consolidations. The most recent echocardiogram shows a tiny patent foramen ovale with otherwise normal structure and cardiac function. No vegetations are seen on echo.

   On physical exam, you see a small frail boy in his large bed. He weighs 11.8 kg. He has a Mallampati class I airway without loose teeth. L.W. is on continuous nasal oxygen and has clear breath sounds bilaterally. His cardiac exam was unremarkable.

   Upon review of prior anesthetic records, you see that all of the patient’s prior anesthetics have thus far been administered without volatile anesthetics or propofol.

7. Are there specific intravenous anesthetics that should be avoided in mitochondrial patients?

8. If the infected PICC line was not accessed, how would you proceed with induction of anesthesia?

9. Are inhaled anesthetics safe to use?

10. Why should lactated ringer’s solution be avoided?

11. Knowing the extent of the planned surgical procedure, is an arterial line warranted?

   After premedication with IV Midazolam, the patient is taken to the O.R. Once ASA monitors are placed, a bolus dose of Precedex (dexmedetomidine) of 1mcg/kg was administered over 10 minutes. The patient was intubated easily after IV doses of ketamine, fentanyl, additional midazolam, and rocuronium. Maintenance infusions of dexmedetomidine and remifentanil were used during the case and titrated throughout. Intermittent ketamine and fentanyl bolus doses were also used for anesthesia maintenance. An additional dose of rocuronium was given 2.5 hours prior to the end of surgery. Total anesthetic time was approximately 4.5 hours.

12. In addition to anesthesia and analgesia, are there additional goals for anesthetic management?

13. Given when the last dose of rocuronium was given, does the patient need neuromuscular reversal?

   At the end of the procedure, the patient was spontaneously ventilating via the endotracheal tube.

14. Having just undergone intra-abdominal surgery and given the patient’s medical history, is it safe to extubate? If so, what are your criteria for extubation?

15. What are options for postoperative pain control? Is regional anesthesia safe for patients with mitochondrial disease?
Prior to emergence, a lumbar epidural catheter was inserted via sterile technique for postoperative pain control. The catheter was loaded with 1 ml/kg of 0.2% ropivacaine. The patient was extubated in the operating room once he was awake and met extubation criteria.

16. What are your immediate concerns once the patient is in the recovery room?

Discussion:

Mitochondria are intracellular organelles which house the electron transfer chain and oxidative phosphorylation pathways responsible for ATP production. Enzymes for other metabolic processes, such as the Krebs cycle, beta fatty oxidation, the tricarboxylic acid cycle, and the urea cycle, are also located within mitochondria (1). Errors in synthesis of mitochondrial proteins can result from defects in nuclear DNA, mitochondrial DNA, or mitochondrial transfer RNA (2). The term “mitochondrial disease” describes a host of different syndromes caused by various mitochondrial defects. Inheritance is multifactorial, this causing multiple phenotypes and variable clinical presentations. Currently treatment is mainly supportive and dependent on the organ systems involved. Supplementation of various vitamins and cofactors, such a coenzyme Q, biotin, and L-carnitine can help to slow disease progression (2). Every year 1000-4000 children in the U.S. are born with a mitochondrial disorder (3).

Mitochondrial defects have profound systemic effects since all cells of the body, except erythrocytes, could be affected. Muscle weakness and lactic acidosis are common to most mitochondrial diseases. Neurologic symptoms may include ataxia, seizures, peripheral neuropathy, ophthalmoplegia, ptosis, hearing and vision defects, hypotonia, and developmental delays. Cardiac manifestations such as conduction delays or cardiomyopathy can occur. Disorders of gut motility, including swallowing disorders, GERD, and pseudo-obstruction may occur. Liver and kidney function could be severely impaired. Metabolic problems such as diabetes, hypothyroidism, and hypoglycemia can occur. Due to muscle weakness, many patients are prone to respiratory issues such as hypoventilation, obstructive sleep apnea, and/or aspiration. Immunologic impairment makes some patients very prone to infections. Hematologic problems such as anemia, thrombocytopenia, and other coagulation disorders are possible (2). Patients can also exhibit failure to thrive, mental retardation, autism, neuropsychiatric disturbances, fatigue, and problems with temperature regulation (3).

Caring for mitochondrial disease patients can be understandably quite challenging. However, there are some general principles to keep in mind. Metabolic derangements make these patients vulnerable to hypoglycemia and lactic acidosis from prolonged fasting, especially when stressed. Normoglycemia should be maintained so as to decrease glucose oxidation and a resultant increase in lactic acidosis. Lactate-free intravenous solutions (preferably normal saline or dextrose containing water or saline) should be administered (1). Prolonged preoperative fasting should be avoided. Inevitably some patients require preoperative administration of dextrose containing IV fluids (3). Normothermia, normocarbia, and maintenance of normal acid-base balance are very important. Neuromuscular blockers must be used judiciously with the knowledge that these patients can be more sensitive to nondepolarizing agents (2). Potential postoperative issues include respiratory depression due to muscle weakness, possible prolonged intubation, increased lactic acid levels, temperature derangements, and difficult pain control.
Anesthetic techniques for mitochondrial disease patients are numerous and greatly varied. There are conflicting reports in the medical literature on this topic. Much research is still needed to elucidate which are the safest and most effective anesthetic techniques to use. Anesthetic agents that seemingly should be avoided, such as propofol, have been used successfully in these patients. Despite more questions than answers, there are data on some anesthetic agents and their effects on the mitochondria. Anesthesia providers must weigh this data against possible theoretical risks to their patients. Spinal and epidural anesthesia have been used successfully in mitochondrial patients. Neuroaxial techniques should be avoided in patients exhibiting spinal cord disease or peripheral neuropathy (4). It is still unknown as to whether mitochondrial disease patients are more prone to malignant hyperthermia as there are conflicting case reports in medical journals.

### Anesthetic Agents and their Effects on the Mitochondria

<table>
<thead>
<tr>
<th>Anesthetic Agent</th>
<th>Mitochondrial Effects</th>
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<tbody>
<tr>
<td>Local anesthetics</td>
<td>Inhibit mitochondrial enzymes and disrupt oxidative phosphorylation (OxPhos)</td>
</tr>
<tr>
<td>Propofol</td>
<td>Uncouples OxPhos, inhibits electron transport chain (ETC), acts on calcium channel proteins thus decreasing contractility</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Inhibits complex I of ETC</td>
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<tr>
<td>Volatile anesthetics</td>
<td>Inhibit complex I of ETC</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Inhibit complex I of ETC</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Inhibit adenosine nucleotide translocase</td>
</tr>
<tr>
<td>Opiods</td>
<td>No data on their effect on mitochondria</td>
</tr>
<tr>
<td>Etomidate</td>
<td>Inhibits complex I and III of ETC</td>
</tr>
</tbody>
</table>

Table information summarized from “Mito 101-Anesthesia”; [www.umdf.org](http://www.umdf.org), Sirrs S and O’Riley M authors (3) and Devin A et al (5)

### References:

3. United Mitochondrial Disease Fund: [www.umdf.org](http://www.umdf.org)