Mitochondrial Disorders and Anesthetic Implications

University of Michigan

Ying Eva Lu-Boettcher, MD
Disclosures

• No conflict of interest or financial disclosures.
Objectives

• Review of mitochondrial disorders, hereditary myopathies, and anesthetic implications.

• Recommendations from literature review for anesthetic management.

• Case discussion and anesthetic complexity.
Case Presentation

16 year-old ASA 3 female.

Presents for a bronchoscopy through a pre-existing tracheostomy for excision of granulation tissue.

De novo mutation in CTBP1 gene (chromosome 4), associated with mitochondrial myopathy and dysfunction.

Mutation in GPD1L, associated with Brugada Syndrome type 2, undergoing workup due to sudden cardiac arrest with resultant anoxic brain injury in 2016.
Comorbidities:

- **Neurological:**
  - Microcephaly, cleft lip s/p repair, globally hypotonic, progressive developmental delay, wheelchair bound.
  - Severe neuromuscular scoliosis s/p 2 corrective surgeries.

- **Respiratory:**
  - Tracheostomy in 2012. 24-hr dependence upon Trilogy vent: RR 18, TV 180’s, PS at 18 cmH2O, PEEP of 5 cm H2O.
  - 5.0 pediatric Bivona uncuffed tracheostomy tube.
  - ENT: granulation tissue.
Comorbidities Cont’d:

- **Cardiovascular:**
  - Anatomically normal on echocardiogram.
  - GPD1L mutation found on genetic testing, associated with Brugada Syndrome type 2, currently under investigation.
  - EKG: NSR

- **GI:**
  - Dysphagia s/p G-tube placement.
Outpatient Medications

- Albuterol
- Miralax
- Artificial Tears
- Multivitamins
- Erythromycin
- Nystatin cream
BirthHx/PMHx

• Uncomplicated prenatal hx. Born at 37 weeks.

• Microcephaly noted at birth with a cleft lip.

• 6 mo: noted at that time to have low tone, had poor growth and was late to meet developmental milestones. Progressive decline.

• Diagnosed with "degenerative mitochondrial disease" through muscle biopsy.

• Whole-exome sequencing (WES) demonstrated a de novo mutation C terminal Binding protein 1 (CTBP1), associated with mitochondrial myopathy and dysfunction (1).

• Mutation in GPD1L gene was also detected.
Anesthetic History

• One previously documented anesthetic here at University of Michigan. Uneventful anesthetic history.

• Records demonstrate one previous 45 min direct laryngoscopy and bronchoscopy in 2017:
  – 1mg/kg propofol bolus
  – 30 minutes worth of propofol infusion
  – Dexamethasone
  – Phenylephrine.
Anesthetic Considerations

Mitochondrial Myopathy

Brugada
Preoperative Course

• Baseline labs.

• Preoperatively, defibrillator pads were placed on patient.

• Patient did not require preoperative anxiolytics.
Intraoperative Course

- Transported to the operating room on home ventilator.

- Ventilated via pre-existing tracheostomy.

- IV Induction: 1mg of midazolam, 25mcg of fentanyl, and 0.6mg/kg of ketamine.

- Hypotension and bradycardia was treated with epinephrine, phenylephrine, and glycopyrrolate.
Postoperative Course

• Maintained on home ventilator at preoperative settings.

• Recovered in the PACU and admitted to the PICU postoperatively without complications.
Overview of Neuromuscular Diseases

**Hereditary Disorders**
- **Pre-junctional**
  - Peripheral Neuropathies:
    - Charcot-Marie-Tooth
    - Friedrichs Ataxia
- **Junctional**
  - Myasthenic Syndromes
- **Post-junctional**
  - Mitochondrial Disorders
  - Dystrophies
    - Duchene
    - Becker’s
    - Facioscapulohumeral
    - Emery-Dreifuss
    - Limb-girdle
  - Myotonias
    - Dystrophic:
      - Myotonic Dystrophy
    - Non-dystrophic:
      - Myotonia Congenita
      - Hyper/Hypokalemic Periodic Paralysis
  - Central Core Disease, Multiminicore Disease

**Acquired Disorders**
- **Pre-junctional**
  - Motor neuron disease
  - Multiple Sclerosis
  - Guillain-Barre Syndrome
  - Peripheral Neuropathies – Diabetes Mellitus
- **Junctional**
  - Myasthenia Gravis
  - Eaton-Lambert Syndrome
- **Post-junctional**
  - Inflammatory Myopathies
  - Critical Illness Myopathy
Hereditary Myopathies

- Post-junctional
  - Mitochondrial Disorders
  - Dystrophies
    - Duchene
    - Becker’s
    - Facioscapulohumeral
    - Emery-Dreifuss
    - Limb-girdle
  - Myotonias
    - Dystrophic:
      - Myotonic Dystrophy
    - Non-dystrophic:
      - Myotonia Congenita
      - Hyper/Hypokalemic Periodic Paralysis
  - Central Core Disease, Multiminicore Disease
Mitochondria and ECT

- Oxidative phosphorylation and ATP synthesis.
- Complexes I-IV:
  - Complex I: NADH Dehydrogenase
  - Complex II: Succinate Dehydrogenase
  - Complex III: Cytochrome bc1 Complex
  - Complex IV: Cytochrome C Oxidase
  - Complex V: ATP synthase
Mitochondrial Myopathies Overview

- Mitochondrial myopathy: early fatigue and/or fixed muscle weakness.

- Can result from mitochondrial DNA mutations and/or nuclear DNA mutations.
  - mitochondrial genome separate nuclear DNA: maternal inheritance, exhibits heteroplasy.

- The most commonly seen mitochondrial syndromes all of which involve respiratory chain defects/systemic manifestations:
  - Leigh syndrome
  - Kearns–Sayre syndrome

- Other rarer mitochondrial disorders include MERRF and MELAS.
Kearns-Sayre Syndrome

Rare multisystem mitochondrial encephalomyopathy.

- Triad of external opthalmoplegia, pigmentary retinopathy, and cardiac conduction defects.
- Bilateral ptosis is seen.
- Frequent features: bilateral sensorineural deafness, central nervous system involvement (cerebellar ataxia, dysarthria, bilateral facial weakness, intellectual delay), and skeletal muscle myopathy.
Leigh Syndrome:

- Severe neurodegenerative disorder that manifests within months of life (5).
- Degeneration of the central nervous system (i.e., brain, spinal cord, and optic nerve)
- Poor sucking ability, dysphagia, loss of head control and motor skills, failure to thrive, seizures, hypotonia, cerebellar ataxia, peripheral neuropathy, hypertrophic cardiomyopathy, and lactic acid accumulation.
General Anesthetic Recommendations for Mitochondrial Myopathies

• Preop:
  – Baseline comorbidities and the degree of organ system involvement.
  – Avoid prolonged fasting and hypovolemia.

• Intraop:
  – Avoid hypoglycemia.
  – Maintain normothermia.
  – Adequate treatment of pain.
  – Avoid using orthopedic tourniquets.
  – Select patients do not metabolize lactate normally, avoid LR (i.e.: in MELAS, Leigh syndrome)
  – Most anesthetics have a depressant effect on mitochondria.
General Anesthetic Recommendations for Mitochondrial Myopathies

• Post op:
  – Respiratory failure can occur postoperatively
  – Impaired swallowing can lead to aspiration.

• Anesthetics:
  • Mitochondrial patients often require smaller doses of general anesthetics, local anesthetics, sedatives, analgesics, and neuromuscular blockers.
<table>
<thead>
<tr>
<th>Anesthetics</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Morphine inhibits complex I.</td>
</tr>
<tr>
<td>Depolarizing muscle relaxant</td>
<td>Should not be administered in any patient with mitochondrial myopathy</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td></td>
</tr>
<tr>
<td>Nondepolarizing neuromuscular blocking drugs</td>
<td>Exaggerated sensitivity.</td>
</tr>
<tr>
<td>Isoflurane, sevoflurane, and desflurane</td>
<td>Suppress oxidative phosphorylation, particularly at complex I, coenzyme Q. Low dose volatiles appear well tolerated.</td>
</tr>
<tr>
<td>Etomidate, barbiturates, midazolam</td>
<td>Inhibits complex I, but well tolerated in case reports</td>
</tr>
<tr>
<td>Nitrous Oxide</td>
<td>No evidence of mitochondrial depression</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Inconclusive evidence of complex I inhibition.</td>
</tr>
<tr>
<td><strong>Local anesthetics for regional techniques</strong></td>
<td>Ropivacaine and lidocaine inhibit carnitine–acylcarnitine translocase to a lesser degree than does bupivacaine. Chloroprocaine, tetracaine is unstudied.</td>
</tr>
<tr>
<td>Remifentanil, fentanyl, sufentanil, alfentanil</td>
<td>No evidence of mitochondrial suppression</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>No evidence of mitochondrial suppression</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>No evidence of mitochondrial suppression</td>
</tr>
</tbody>
</table>
Summary of Anesthetic Recommendations

- Small intravenous boluses of benzodiazepines or ketamine; possibly low dose bolus of propofol.

- Continuous infusion of dexmedetomidine.

- Low dose inhalation of volatiles such as sevoflurane.

- Bolus dosing or continuous infusion of short- or ultrashort-acting opioids such as fentanyl, sufentanil, alfentanil, or remifentanil.

- In general, regional anesthesia is well tolerated by patients with mitochondrial myopathies. Most neural blockade uses doses of local are well below the doses necessary for mitochondrial effects.
### Other Hereditary Myopathies

- **Post-junctional**
  - Mitochondrial Disorders
  - Dystrophies
    - Duchene
    - Becker’s
    - Facioscapulohumeral
    - Emery-Dreifuss
    - Limb-girdle
  - Myotonias
    - Dystrophic:
      - Myotonic Dystrophy
    - Non-dystrophic:
      - Myotonia Congenita
      - Hyper/Hypokalemic Periodic Paralysis
  - Central Core Disease, Multiminicore Disease
Muscular Dystrophies

- At least 5 forms of muscular dystrophy are relevant to anesthesia management:
  1. Duchenne Muscular Dystrophy*
  2. Becker Muscular Dystrophy*
  3. Fascioscapulohumeral Dystrophy (FSHD)
  4. Emery Dreifuss Dystrophy
  5. Limb girdle Dystrophy
• Most common and severe muscular dystrophy (1 in 3000 male newborns)
• X-linked disorder, mutation in the dystrophin gene located on chromosome Xp21.
• Typical surgeries: Muscle biopsies, orthopedics, tendon releases, tendon transfers, correction of scoliosis
Duchenne Muscular Dystrophy

**Short Term**
- Muscle regeneration
- Muscle fibers of different sizes

**Long Term**
- Muscle atrophy
- Very weak

**Cell Death**
- Fat
- Fibrotic tissue
Duchenne and Becker Muscular Dystrophy

• Anesthetic considerations:
  – Anesthesia induced rhabdomyolysis: avoid volatiles and succinylcholine
  – More sensitive to nondepolarizing NMBD’s
  – Increased risk for bleeding due to platelet dysfunction and smooth muscle dysfunction.
  – Ventricular noncompliance due to myocardial fibrosis.
Post-junctional

- Mitochondrial Disorders
- Dystrophies
  - Duchene
  - Becker’s
  - Facioscapulohumeral
  - Emery-Dreifuss
  - Limb-girdle
- Myotonias
  - Dystrophic:
    - Myotonic Dystrophy
  - Non-dystrophic:
    - Myotonia Congenita
    - Hyper/Hypokalemic Periodic Paralysis
- Central Core Disease, Multiminicore Disease
Myotonic Syndromes

- Family of channelopathies mostly affecting muscle. The abnormalities in the channels lead to prolonged depolarization in the membrane once an AP is generated.

- Prolonged stimulation of the actin-myosin contractile apparatus of the muscle cell.

- Dystrophic and non-dystrophic.
Hyperkalemic and Hypokalemic Periodic Paralysis

Hyperkalemic Periodic Paralysis:
- Autosomal dominant disorder of a sodium channel, resulting in hyperexcitability followed by inactive/flaccid paralysis.
- Triggered by increased serum potassium, cold, hunger, stress.

Anesthetic consideration:
- Preop potassium depletion with loop diuretics may be employed, avoid potassium containing fluids.
- Avoid acidosis, treatments for hyperkalemia.
- Keep fasting to minimal preoperatively.
Hyperkalemic and hypokalemic Periodic Paralysis

**Hypokalemic Periodic Paralysis:**

- Autosomal dominant disorder of calcium channel.
- Presents as asymmetrical muscle paralysis/weakness in the setting of decreased serum potassium.
- The mutation: dihydropyridine receptor, linked to MH.

- Anesthetic considerations:
  - Do NOT use depolarizing NMBD, volatiles.
  - Use short acting NDNMBD.
  - Avoid K shifting drugs, avoid excess glucose, salt solutions, and alkalosis.
Myotonic Dystrophy

- Dystrophic autosomal dominant disease that manifest in early adulthood.

- Mutation is in the human dystrophica myotonica-protein kinase gene (DMPK), prolonged channel activation causes prolonged muscle contraction.

- Muscle wasting and incomplete muscle relaxation after a stimulus.
Anesthetic considerations:

- Restrictive lung disease, OSA, intellectual impairment may be seen.
- Avoid triggers: hypothermia, shivering, mechanical and electrical stimulation (including twitch monitors).
- Respiratory depression, severe cardiac conduction abnormalities, cardiomyopathy, developmental delay, dysphagia and decreased gastric motility.
- Nondepolarizing muscle relaxants: avoid or use sparingly.
- Avoid depolarizing NMBD: contractures and hyperkalemia.
- Bulbar weakness: increased aspiration risk.
○ Post-junctional
  ▪ Mitochondrial Disorders
  ▪ Dystrophies
    • Duchene
    • Becker’s
    • Facioscapulohumeral
    • Emery-Dreifuss
    • Limb-girdle
  ▪ Myotonias
    • Dystrophic:
      ○ Myotonic Dystrophy
    • Non-dystrophic:
      ○ Myotonia Congenita
      ○ Hyper/Hypokalemic Periodic Paralysis
  ▪ Central Core Disease, Multiminicore Disease
Central Core Disease

- Autosomal Dominant, mutations in the RYR1 gene on chromosome 19q13.1.
- Persistent, non progressive muscle weakness of (proximal muscles), particularly muscles in the upper legs and hips.
- Muscle weakness causes affected infants to appear "floppy" and can delay the development of motor skills.
- Associated with scoliosis, hip dislocation, and contractures that restrict the movement of certain joints.
Central Core Disease:

- Patients are particularly predisposed to malignant hyperthermia (MH) in response to standard triggering agents.

- Prolonged neuromuscular block in response to non-depolarizing neuromuscular blockers.
# Malignant Hyperthermia

<table>
<thead>
<tr>
<th>Associated with Malignant Hyperthermia</th>
<th>Associated with Anesthesia Induced Rhabdomyolysis (not MH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Central Core Disease.</td>
<td>1. Duchene Muscular Dystrophy</td>
</tr>
<tr>
<td>2. King Denborough Syndrome.</td>
<td>2. Becker Muscular Dystrophy</td>
</tr>
<tr>
<td>4. Nenaline rod myopathy with \textit{RyR1} mutation.</td>
<td></td>
</tr>
<tr>
<td>5. Hypokalemic periodic paralysis*.</td>
<td></td>
</tr>
<tr>
<td>6. Exertional Rhabdomyolysis (ER) and Exertional Heat Illness (EHI)*. (6)</td>
<td></td>
</tr>
</tbody>
</table>
# Muscle Relaxants

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Depolarizing muscle relaxants (succinylcholine)</th>
<th>Non-depolarizing muscle relaxants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne and Becker Muscular Dystrophy</td>
<td>Avoid</td>
<td>Increased sensitivity</td>
</tr>
<tr>
<td>Myotonic Dystrophy</td>
<td>Avoid</td>
<td>Increased sensitivity</td>
</tr>
<tr>
<td>Central Core Disease</td>
<td>Avoid</td>
<td>Increased sensitivity</td>
</tr>
<tr>
<td>Inflammatory myopathies</td>
<td>Avoid</td>
<td>Variable sensitivity</td>
</tr>
<tr>
<td>Mitochondrial Myopathies</td>
<td>Avoid</td>
<td>Variable sensitivity</td>
</tr>
</tbody>
</table>
NMBD’s and Myotonias

• A subset of myotonias: myotonia congenita, Becker’s, myotonic dystrophy, twitch monitors can trigger myotonic episodes.

• If non depolarizing NMBD has to be used, use minimal doses and reverse with 4mg/kg dose of Sugammadex.

• Most myotonic contractions can be precipitated by anticholinergic reversal agents, thus do not use.
Conclusions

• Anesthetic planning for patients with multiple mutations require clear understanding of the contraindications as well as the planned surgical intervention.

• Mitochondrial myopathies require a non-mitochondrial depressant anesthetic. Review recommendations.

• In myopathies in general, avoid succinylcholine and use non-depolarizing NMBD very sparingly, if at all.
References

• Sommerville, E.W. et al. “De novo CTBP1 variant is associated with decreased mitochondrial respiratory chain activities.” *Neurol Genet* 2017;3; DOI 10.1212


Questions?

Thank you!