Mitochondrial Disease & its Anesthetic Considerations

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Objectives

- Discuss the structure of the Mitochondrion
- Discuss the main function of the Mitochondrion
- Detecting and Diagnosing mitochondrial diseases
- Treatment of mitochondrial diseases
- Anesthetic considerations for patients with mitochondrial diseases
- Case Review
Endosymbiotic theory

The ENDOSYMBIOTIC THEORY

1. Infoldings in the plasma membrane of an ancestral prokaryote gave rise to endomembrane components, including a nucleus and endoplasmic reticulum.

2. In a first endosymbiotic event, the ancestral eukaryote consumed aerobic bacteria that evolved into mitochondria.

3. In a second endosymbiotic event, the early eukaryote consumed photosynthetic bacteria that evolved into chloroplasts.

Figure 2: The first eukaryote may have originated from an ancestral prokaryote that had undergone membrane proliferation, compartmentalization of cellular function (into a nucleus, lysosomes, and an endoplasmic reticulum), and the establishment of endosymbiotic relationships with an aerobic prokaryote and, in some cases, a photosynthetic prokaryote to form mitochondria and chloroplasts, respectively.

The mitochondrial genome is circular, whereas the nuclear genome is linear.

The mitochondrial genome is built of 16,569 DNA base pairs, whereas the nuclear genome is made of 3.3 billion DNA base pairs.

The mitochondrial genome contains 37 genes that encode 13 proteins, 22 tRNAs, and 2 rRNAs.

The small mitochondrial genome are unable to produce all of the proteins needed for functionality; thus, mitochondria rely heavily on imported nuclear gene products.
Mitochondrial import pathways for precursor proteins.
Mitochondrial Gene Inheritance

- Unaffected father
- Affected mother
- Affected father
- Unaffected mother

- Affected children
- Unaffected children

Degree depends on the amount of affected mitochondria.
Fission vs. Fussion
Function

- Energy production in the form of ATP
- Thermogenesis
- Storage and Regulation of Calcium Ions
- Apoptosis
- Cholesterol and Neurotransmitter Metabolism
- Detoxification of Ammonia
Cellular Respiration

Respiration is NOT breathing!

All organisms respire - it is the production of ATP from organic molecules.

Aerobic respiration requires oxygen - this is where ventilation and gas exchange come in.
ATP Production

Ref: http://www.tritec-inc.org/science-units/energy2013-KeyToLife/images/pelosi/Picture1_krebs.jpg
Oxidative phosphorylation

Ref: https://sites.google.com/site/accessrevision/biology/cell-form-and-function/cellular-respiration
Mitochondrial diseases

- Clinical and biochemical disorders resulting from dysfunction of the mitochondria. First clinically described in 1960.

- This results in a lack of cellular energy to perform various functions and in the accumulation of byproducts that impair or destroy the cell itself.

- They can be caused by mutation of genes encoded by either nuclear DNA or mitochondrial DNA (mtDNA).

- Mitochondrial disorders may present at any age.

- There is an estimated incidence of 1 in 4000 live births suffering from mitochondrial disease in the United States.

- These diseases have varying etiologies and are often very difficult to classify.
Clinical Manifestation

- Heart
  - Conduction disorder
  - Wolff-Parkinson-White syndrome
  - Cardiomyopathy
- Eye
  - Optic neuropathy
  - Ophthalmoplegia
  - Retinopathy
- Liver
  - Hepatopathy
- Kidney
  - Fanconi's syndrome
  - Glomerulopathy
- Pancreas
  - Diabetes mellitus
- Blood
  - Pearson's syndrome
- Skeletal muscle
  - Weakness
  - Fatigue
  - Myopathy
  - Neuropathy
- Brain
  - Seizures
  - Myoclonus
  - Ataxia
  - Stroke
  - Dementia
  - Migraine
- Colon
  - Pseudo-obstruction
- Nuclear DNA
  - Subunits
  - Oxidative phosphorylation
- Mitochondrial DNA
- Nuclear DNA


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Signs and Symptoms

- loss of motor control
- muscle weakness and pain
- gastro-intestinal disorders and swallowing difficulties
- poor growth
- cardiac disease
- liver disease
- diabetes
- respiratory complications
- seizures
- visual/hearing problems
- lactic acidosis
- developmental delays
- susceptibility to infection.
Scientists have discovered over 40 different mitochondrial diseases.

Early on diseases would be classed by clinical syndrome e.g

- **CPEO**: chronic progressive external ophthalmoplegia
- **MELAS**: mitochondrial encephalopathy with lactid acidosis and stroke like episodes
- **MERRF**: myoclonic epilepsy with ragged red fibers
- **LHON**: Leber hereditary optic neuropathy
Classifying the diseases

Genocopies
- diseases that are caused by the same mutation but which may not look the same clinically

Phenocopies
- different mutations in mtDNA and nDNA can lead to the same diseases.

**primary mitochondrial disease**: a mutation in the mitochondria causes the organelle to malfunction and produce symptoms.

**secondary mitochondrial disease**: genetic alteration is present, but does not produce any symptoms of disease until an external environmental force triggers mitochondrial dysfunction.
Causes of Mitochondrial diseases

- The major cause of the disease is gene inheritance. Either nucleic or mitochondrial genes

- The other cause is mitochondrial toxins. Various agents including commonly used drugs have been found to be toxic to the mitochondria.
# Mitochondrial toxins

## Table of Reported Drugs with Mitochondrial Toxicity

<table>
<thead>
<tr>
<th>Pharmacologic Category</th>
<th>Toxin</th>
<th>Action</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anticonvulsants</td>
<td>Valproate (Depakote)</td>
<td>Sequesters carnitine; decreases fatty acid oxidation, Krebs, ETC activity and oxidative-phosphorylation; complex IV inhibition</td>
<td>Hepatopathy</td>
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<td>2. Psychotropic</td>
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<tr>
<td>a. Antidepressants</td>
<td>Amitriptyline (Elavil)</td>
<td>Causes autonomic dysfunction</td>
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<td></td>
<td>Amoxapine</td>
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<td></td>
<td>Fluoxetine (Prozac)</td>
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<td></td>
<td>Citalopram (Cipramil)</td>
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<td>b. Antipsychotics</td>
<td>Chlorpromazine (Thorazine)</td>
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<td></td>
<td>Fluphenazine (Prolixin)</td>
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<td></td>
<td>Haloperidol (Haldol)</td>
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<td></td>
<td>Resperidone (Risperidol)</td>
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<td>c. Barbituates</td>
<td>Phenobarbit al</td>
<td>Reduces mito protein synthesis; dec # and size of mitochondria</td>
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<td></td>
<td>Secobarbital (Seconal)</td>
<td>inhibits NADH dehydrogenase (complex I)</td>
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<td></td>
<td>Butalbital (Florinal)</td>
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<td>Amobarbital (Amytal)</td>
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<td></td>
<td>Pentobarbital (Nembutal)</td>
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<tr>
<td>d. Anxiety meds</td>
<td>Alprazolam (Xanax)</td>
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<td>Diazepam (Vallium, Diastat)</td>
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<td>4. Cholesterol meds</td>
<td>Statins</td>
<td>Reduce endogenous coenzyme Q10</td>
<td>Myopathy</td>
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<td></td>
<td>Bile acids-cholestyramine</td>
<td>Inhibits ETC</td>
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<td></td>
<td>Ciprofibrate</td>
<td>Inhibits complex I</td>
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# Mitochondrial toxins

## Table of Reported Drugs with Mitochondrial Toxicity

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<tbody>
<tr>
<td><strong>5. Analgesic/anti-inflammatory</strong></td>
<td>ASA (Aspirin)</td>
<td>Inhibits ETC and uncouples oxidative-phosphorylation</td>
<td>Reye syndrome (hepatic failure)</td>
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<td></td>
<td>Acetaminophen (Tylenol)</td>
<td>Increases oxidative stress</td>
<td>Hepatopathy</td>
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<td></td>
<td>Indomethacin (Indocin)</td>
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<td></td>
<td>Naproxen (Aleve)</td>
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<td></td>
<td>Diclofenac</td>
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<tr>
<td><strong>6. Antibiotics</strong></td>
<td>Tetracycline, minocycline</td>
<td>Inhibit beta-oxidation; inhibit mito protein synthesis</td>
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<tr>
<td></td>
<td>Chloramphenical</td>
<td>Inhibits mito protein synthesis</td>
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<td></td>
<td>Aminoglycosides</td>
<td>Impair mtDNA translation</td>
<td>Hearing loss; cardiac toxicity; renal toxicity</td>
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<tr>
<td></td>
<td>Linezolid (Zyvox)</td>
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<td>Lactic acidosis, optic and peripheral neuropathy</td>
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<td><strong>7. Anti-arrhythmic</strong></td>
<td>Amiodarone</td>
<td>Inhibits beta-oxidation</td>
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<tr>
<td><strong>8. Steroids</strong></td>
<td></td>
<td>Reduce transmembrane mito potential</td>
<td>Reports of deterioration in Kearns-Sayre syndrome</td>
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<tr>
<td><strong>9. Anti-viral</strong></td>
<td>Interferon</td>
<td>Impairs mtDNA transcription</td>
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<tr>
<td><strong>10. Anti-retroviral</strong></td>
<td>Zidovudine</td>
<td>Impairs mtDNA replication which causes mtDNA depletion; decreases complex I and IV activity</td>
<td>Carnitine deficiency; lactic acidosis; lipodystrophy; neuropathy; myopathy; hypatic dysfunction</td>
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<td><strong>11. Cancer meds</strong></td>
<td>Doxorubicine (Adriamycin)</td>
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<tr>
<td></td>
<td>Cis-platinum</td>
<td>Impairs mtDNA transcription</td>
<td>Hearing loss; cardiac toxicity; renal toxicity</td>
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</table>
# Mitochondrial Toxins

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<tbody>
<tr>
<td>12.</td>
<td>Diabetes meds</td>
<td>Metformin</td>
<td>Inhibits oxidative-phosphorylation; enhanced glycolysis</td>
</tr>
<tr>
<td>13.</td>
<td>Beta-blockers</td>
<td></td>
<td>Causes oxidative stress</td>
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<tr>
<td>14.</td>
<td>Immunizations</td>
<td></td>
<td>No scientific data on oxidative-phosphorylation adverse effects</td>
</tr>
</tbody>
</table>
Mitochondrial diseases are difficult to diagnose. Referral to an appropriate research center is critical.

Combination of clinical observations, laboratory evaluation, cerebral imaging, and muscle biopsies are used to aid diagnosis.

A single blood or urine lab test with normal results does not rule out or confirm a 100% diagnosis of mitochondrial disease.

Genetic testing can be done to assess for known mutations
Who knew.....
Muscle Biopsy

- When treated with a dye that stains mitochondria red, muscles affected by mitochondrial disease often show ragged red fibers — muscle cells (fibers) that have excessive abnormal mitochondria.

- Other stains can detect the absence of essential mitochondrial enzymes in the muscle.

- It is also possible to extract mitochondrial proteins from the muscle and measure their activity.
Ragged Red Fibers

Red Ragged Fibers
Diseases of the mitochondria can be caused by defects in nuclear or mitochondrial DNA and result in decreased energy availability for cell processes. When muscle is stained with Gomori Trichrome, characteristic ragged-red fibers are visible under the microscope. This appearance is due to the accumulation of abnormal mitochondria below the plasma membrane of the muscle fiber. These may extend throughout the muscle fiber as the disease severity increases. The mitochondrial aggregates cause the contour of the muscle fiber to become irregular, causing the "ragged" appearance. Besides muscle, what other tissues would you expect to suffer the most damage from a mitochondrial defect?
There is no definitive cure for mitochondrial diseases

Therapy is aimed at alleviating symptoms, maintaining optimal health, using preventive measures to mitigate symptom worsening during times of physiologic stress, and avoiding mitochondrial toxins.

The use of antioxidant supplements aimed at reducing reactive oxygen species that are produced in increased amounts in this disease.
Exercise Training

EXERCISE TRAINING

BIOPENESIS → FUSION ↔ FISSON → MITOPHAGY

ADDITION OF HEALTHY MITOCHONDRIA

REMOVAL OF DAMAGED MITOCHONDRIA

ENHANCED METABOLIC FUNCTION/PERFORMANCE
The heterogeneity of the diseases makes it very difficult to have the one perfect anesthetic.

The lack of clinical trials investigating the effects of anesthetic agents in patients with mitochondrial disease has limited the anesthetists ability to deliver the perfect anesthetic.

Adverse effects on mitochondrial function of many agents used in anesthesia have been documented in vitro, but there are few reports of adverse events in vivo.

The theoretical effects of any agent need to be considered in the general context of any one patient’s medical history.
Anesthetic Effects in Mitochondrial Disease

This study has been terminated.
(However, no intervention reduced the risk of major morbidity or 1 yr mortality)

Sponsor:
• d sessler

Information provided by (Responsible Party):
• d sessler, Cleveland Clinic Foundation

ClinicalTrials.gov Identifier:
NCT01001585
First received: October 21, 2009
Last updated: March 5, 2015
Last verified: March 2015

Purpose

Summary. At the present, the investigators do not have the perfect anesthetic for mitochondrial patients. When possible, consideration should be given to the use of local anesthetics in small amounts. When a general anesthetic is necessary, they each carry significant risks and have been associated with poor outcomes. At present it is not possible to eliminate one group as less safe than others. What is clear is that these patients must be monitored more closely than other patients. The advent of the bispectral index (BIS) monitor may allow us to monitor their depth of anesthesia more closely and thus expose these patients only to the minimum amount of drug necessary to carry out the surgical procedure.

Purpose. The investigators hypothesize that specific mitochondrial diseases, in particular those that decrease complex I function, make certain children hypersensitive to volatile anesthetics. These same patients may be at increased risk for adverse outcomes following general anesthesia. The specific aims of this application are:

1. Determine which molecular defects in mitochondrial function lead to altered sensitivity to the VA sevoflurane.
Purpose

This pilot study is a prospective, randomized clinical trial to evaluate the effect of anesthesia in the mitochondrial dysfunction patient.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>Mitochondrial Diseases</td>
<td>Drug: Sevoflurane</td>
</tr>
<tr>
<td></td>
<td>Drug: Dexmedetomidine</td>
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<tr>
<td></td>
<td>Drug: Propofol</td>
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Study Type: Interventional
Pre-op Evaluation

- Multi-system involvement in these disorders necessitates a thorough pre-op evaluation including family history.

- Determine degree of neurological and musculoskeletal compromise.

- Careful cardiac assessment including EKG and echocardiography.

- Renal and Hepatic function

- All clinical manifestations of MD, including seizures, arrhythmias, cardiac dysfunction, myopathy, and endocrinopathies, can be worsened by trauma, illness, or surgical stress.

- Duration of NPO status
Local, regional or general?

Deterioration of Kearns-Sayre syndrome following articaine administration for local anesthesia.

Finsterer J¹, Haberler C, Schmiedel J.

Anesthesia for corrective spinal surgery in a patient with Leigh's disease.

Cooper MA¹, Fox R.

Effect of a Single Dose of Propofol and Lack of Dextrose Administration in a Child With Mitochondrial Disease: A Case Report

Haifa Mtaweh, MD¹,⁴, Hülya Bayır, MD¹,²,⁴, Patrick M. Kochanek, MD¹,⁴, and Michael J. Bell, MD¹,³,⁴
Pre Medication

- Avoid lactated ringers solution which could increase lactate load.

- Avoid respiratory depressants, patients have inadequate response to hypoxia or hypercapnia.
Induction

- Sensitivity to induction agents
- Ketamine and barbiturates inhibit complex I
- Etomidate inhibits complex I and complex II
- Propofol has been shown to be most problematic as it inhibits complex I and IV as well as disrupting fatty acid transport. Conflicting opinions however persist on single dose use.
Propofol-related infusion syndrome (PRIS) is a rare yet often fatal syndrome that has been observed in critically ill patients receiving propofol for sedation.

Doses greater than 4mg/kg/hr for durations longer than 48 hours place a patient at risk for PRIS.

PRIS is characterized by severe unexplained metabolic acidosis, arrhythmias, acute renal failure, rhabdomyolysis, hyperkalemia, and cardiovascular collapse.

The exact pathophysiology of PRIS remains to be determined, but is thought to be related to impaired tissue metabolism.

Risk factors for developing PRIS include sepsis, severe cerebral injury, and high propofol doses.

Early recognition of the manifestations is the key to managing PRIS. If is suspected, propofol should be discontinued and an alternative sedative agent initiated. General measures to support cardiac and renal function should be initiated promptly in patients with suspected PRIS.
Muscle Relaxation

- There is conflicting evidence on the use of muscle relaxants.
- It is generally thought that there could be an increased sensitivity to non depolarizing muscle relaxants.
- Succinylcholine has been used successfully but is often avoided as these patients are thought to have a susceptibility to MH and could be subject to hyperkalemia if they are inactive.
Analgesia

- Beneficial in minimizing oxygen demand

- However impaired respiratory control necessitates that opioids are used with caution.

- Remifentanil is thought to have less effect on mitochondrial energetics than fentanyl which is preferred over morphine.

- L.A’s have been shown to inhibit complex I & acylcarnitine transferase. Lidocaine<ropivicaine<bupivacaine
Intra-op

- Monitor blood glucose especially in long cases.
- Less tolerance to hypoxia
- Maintain normothermia. Hypothermia further depresses mitochondrial activity.
- Keep patient hydrated
Emergence

- May not be a good candidate for deep extubation
- Consider leaving on ventilator or going to PACU on ventilator if far from baseline.
Post-Op

- Crucial period for these patients
- Exacerbation of mitochondrial disease may not be immediate.
- Warrants patients to be monitored longer
- Do not transfer from OR to stage 2 recovery.
46 year old male pt. 6’2” 80kg BMI 22.6 scheduled for vascular access port.

PMH: recent diagnosis of genetically associated mitochondrial disease, industrial injury that required transplantation of toes to right hand.

PSH: appendectomy, tonsillectomy, depression, chronic pain, GERD, left heart catheterization

Allergies: Penicillin
Patient states he has been feeling progressively weak and fatigued since July 2013. Work up done for lymes dz, adrenal insufficiency and myasthenia gravis all negative.

Pt muscle biopsy in 2009 which showed no pathology.

Meds: L-carnitine, L-arginine, vit c, vit d3, riboflavin, duloxetine, ubiquinone, dextrose 30mg po q morning,
What did we do?

- Switched patient’s IV fluids from LR to 0.9% NSS which was already running in the pre operative area.
- Checked patients blood glucose in pre op.
- Made anesthesiologist and surgeon aware of concerns with patient’s disease process.
Upon deliberation, consensus was reached to perform a MAC anesthetic

Anesthesia start time at **17:15** due to delay in surgeons other cases

- Midazolam 2mg, ketamine 20mg, precedex infusion 1mcg/kg bolus then started infusion (total 98mcg), fentanyl 35mcg.

Anesthesia stop time 18:13. SBP 90-130’s, HR 70’s NSR

- No untoward events. Intra op. Pt. was discharged home later that evening.
Any Questions?
References


UMDF. (n.d.) *understanding mitochondrial disease*. Retrieved February 17, 2016, from United Mitochondrial Disease Foundation: umdf.org