MITOCHONDRIAL DISEASE:

OVERVIEW AND ASSOCIATED GI ISSUES

Fran D. Kendall, M.D.
VMP, LLC
Biochemical Genetics
Metabolic, Mitochondrial & Inherited Disorders

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OBJECTIVES

To provide basic background information on Mitochondrial Disease, its clinical features, diagnosis, treatment, prognosis, inheritance and to discuss its known GI complications

DISCLAIMER

Dr Kendall and VMP have no financial interest in any laboratory.
What are Mitochondria?

What is Mitochondrial Disease?

Unusual mitochondria in child with mitochondrial disease

Note many cristae on the right as if this organelle is trying to compensate for its lack of function.
Our Bodies Cells

- Smallest functioning unit of our bodies
- Many cells together make up tissues
- Many sheets of tissues make up our organs
The Powerplants

- Located inside our body cells
- Composed of an inner and outer membrane
- The energy producing pathway is the respiratory chain
- The respiratory chain consists of 5 complexes (groups of chemicals) that produce ATP
The Respiratory Chain

- Oxygen & phosphate used to make energy
- Composed of five complexes or groups of chemicals with a total of ~90 subunits
- Energy packets are known as ATP
Mitochondrial Energy Disorders

- Found in 1 in 4,000 individuals
- Carrier rate of common mtDNA mutations may be as high as 1 in 200
- Caused by an alteration in our inherited blueprint (gene mutation) or “toxic” affect of external factor such as medication including HIV drugs and some chemotherapeutic agents.
- Results in decreased energy production and localized or widespread problems
Organ systems most affected by Mito Disease

- CNS
- Muscles
- Cardiac
- GI system including Liver
- Kidneys

Comprehensive widespread symptoms list can be found at www.vmpgenetics.com
COMMON PROBLEMS IN MITOCHONDRIAL ENERGY DISORDERS

- Central Nervous system (Brain) problems such as developmental delays including autism, loss of function, seizures, hypotonia & weakness
- Failure to thrive
- Chronic fatigue
- Gastrointestinal issues such as chronic constipation
- Autonomic dysfunction such as irregular heart rate and blood pressure and temperature instability with heat intolerance.

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**THE MITO DISEASE GENES**

- There are 1,500 genes involved in coding for the various proteins and other compounds involved in OXIDATIVE PHOSPHORYLATION or mitochondrial energy production.

- These genes are contributed by two sets of inherited genetic material; the nuclear genes located inside the nucleus of our body cells and mitochondrial genes found inside the mitochondria of our cells.

- **Nuclear genes** are inherited from both parents and contribute the vast majority of the information needed for energy production.

- **Mitochondrial genes** are inherited EXCLUSIVELY through mom and contribute the remaining information.

- Inheritance patterns include autosomal recessive, autosomal dominant, maternal, X-linked and sporadic.
Approximately 850 proteins are encoded for by the nuclear mitochondrial genes

Many of these proteins are responsible for the control of electron transport chain structure and function and assembly

Autosomal recessive inheritance of nuclear gene defects is the most common etiology of pediatric patients with mitochondrial disorders.
Features of **Mitochondrial DNA (mtDNA)**

- Inherited exclusively through the maternal line
- Circular molecule, a number of copies in each mitochondrion (5-10 copies typical)
- 16,569 bases or pieces and 37 genes
- Mutated mtDNA may be present in varying amounts with wild type DNA (heteroplasmy)
Mitochondrial DNA

[Diagram showing mitochondrial DNA and its components, including subunits of NADH dehydrogenase, cytochrome c oxidase, ATP synthase, rRNA, and cytochrome b.]
Heteroplasmic of mtDNA
HOW IS MITOCHONDRIAL DISEASE DIAGNOSED?

- Several tiers of testing are utilized to diagnose mitochondrial disease
- Functional testing – examining the OXPHOS energy pathway.
- Gene testing – evaluation of mtDNA and nuclear mitochondrial genes
- Biomarker studies – lactate and pyruvate levels, CSF lactate, CPK, urine organic acids, carnitine levels.
- Radiographic studies – identification of mito related imagining abnormalities.
- Utilization of published Criteria such as the Bernier Criteria
Abnormalities in mitochondrial structure/size/shape/number on tissue biopsy

Enzymatic abnormalities on testing of the energy producing system (respiratory chain or electron transport chain)

Respirometry studies measures oxygen consumption in all of the complexes under conditions more reflective of in vivo functioning than isolated traditional enzyme assays

Blue and Clear native gels studies help assess protein complexes and supercomplexes and can identify assembly defects
Ragged Red Fibers
How often are ragged red fibers actually seen?

... less than 2.5% of cases. And in pediatric patients histological studies are often normal. They are most often abnormal in adult patients with mtDNA gene defects.
Less invasive skin biopsy for skin fibroblast culture and OXPHOS enzyme assays

Buccal swab OXPHOS enzyme assays
- Approximately 80%-85% correlation between swab testing results and muscle biopsy enzyme assays
- Good screening tool
- Still under development
There are approximately 1,500 genes involved in mitochondrial energy production.

mtDNA sequencing screens 37 maternally inherited genes

Nuclear gene panels vary from lab to lab and range from screening 100+ to 1,100 nuclear mito genes

- Baylor
- Courtagen
- GeneDx
- Transgenomics

Of note, some gene testing can now be completed on saliva & urine samples.
EXAMPLES OF SPECIFIC GENE MUTATIONS

- MELAS (Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke Like Episodes) due to tRNA 3243 mtDNA mutation
- MERRF (Myoclonic Epilepsy and Ragged Red Fibers) due to tRNA 8344 mutation
- Complex I nuclear gene mutations - example NDUFV1 patients with leukodystrophy and myoclonic epilepsy
- Complex IV assembly gene mutations - example SURF1 mutations associated with Leigh disease
MEtabolic Abnormalities Supportive of Mitochondrial Disease

- Increased blood and/or CSF lactate and pyruvate and/or ratio
- Decreased plasma carnitine
- Increased blood alanine
- Generalized aminoaciduria
- Increase lactate, pyruvate, Kreb cycle intermediates, tiglylglycine, and 2-oxoadipic acid on organic acid analysis
Leigh Disease MRI Lesions

A

B

C

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PROGNOSIS OF MITOCHONDRIAL ENERGY DISORDERS

- Quite variable but typically progressive over time
- Patients can face severe disabilities and early death
- Many patients stabilize or show improvements with institution of care
- Problems typically worsen with stressors such as illness and surgery
Current Treatment of Mitochondrial Energy Disorders

- Symptomatic – treat existing problems
- Preventative – early detection of associated problems using every 6-12 month multisystem screening studies
- Therapeutics very limited and often include the use of Coenzyme Q10, L-carnitine, Riboflavin, Alpha lipoic acid and Creatine

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AND NOW...

GI ISSUES AND MITO
Common GI Issues in Mitochondrial Disease

- **Gastrointestinal Problems**
  - Gastroesophageal reflux
  - Dysphagia
  - Pseudo-obstruction
  - Gastroparesis and dysmotility
  - Irritable bowel syndrome
  - Diarrhea or constipation
  - Exocrine pancreatic failure
  - Pancreatitis

- **Liver**
  - Liver dysfunction/failure
  - Hypoglycemia

- **Systemic**
  - Failure to thrive
  - Neurovisceral pain
  - Abdominal migraines
  - Cyclic Vomiting
Treatment of GERD

- Small, frequent meals
- H2 receptor antagonists – example Zantac
- Proton Pump Inhibitors (PPIs) – example Prevacid
- Antireflux surgery – for patients with documented chronic reflux with recalcitrant symptoms. However, surgery has complication rate (10-20%). Resumption of pre-operative medication treatment (>50%) is common and will likely increase over time.
**APPROACHES TO CYCLIC VOMITING**

- To control the signs and symptoms often used are:
  - Anti-nausea drugs (Zofran)
  - Sedatives
  - Acid-suppressing medications

- Hospitalization for intravenous fluids to prevent dehydration

- In many cases, the same types of medications used for migraines often help stop or even prevent episodes of cyclic vomiting. These medications include:
  - Tricyclic antidepressants, such as amitriptyline and nortriptyline (Pamelor)
  - Triptans, such as sumatriptan (Imitrex) and zolmitriptan (Zomig)
  - Analgesics, such as ibuprofen (Advil, Motrin, others)
GASTROPARESIS THERAPIES

- Dietary modifications:
  - Eat smaller meals more frequently.
  - Eat low-fiber forms of high-fiber foods, such as well-cooked fruits and vegetables rather than raw fruits and vegetables.
  - Choose mostly low-fat foods, but if you can tolerate them, add small servings of fatty foods to your diet.
  - Avoid fibrous fruits and vegetables, such as oranges and broccoli, that may cause bezoars.
  - If liquids are easier for you to ingest, try soups and pureed foods.
  - Drink water throughout each meal.
  - Try gentle exercise after you eat, such as going for a walk.

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For complete intolerance of food or liquids, placement of jejunostomy tube to by-pass the stomach.

Medications to treat gastroparesis may include:
- **Medications to control nausea and vomiting.** Anti-emetic medications include prochlorperazine (Compro), diphenhydramine (Benadryl, Unisom) and lorazepam (Ativan).
- **Medications to stimulate the stomach muscles.** These medications include metoclopramide (Reglan) and erythromycin.

Experimental treatments:
- Botox – relaxes the pyloric muscle in some patients
- Implantation of electrical pacemaker.
**Constipation**

- **Dietary & lifestyle changes**
  - Good hydration
  - Ingestion of fruits and vegetables, especially uncooked
  - Use of whole grain breads and cereals

- **Laxatives**
  - Osmotic laxatives - work by drawing water into the colon. They are safe and perhaps are the preferred all-purpose laxatives. Examples include Milk of Magnesia and citrate of Magnesia. We also use Fiber Gummies and Sugar Free Jelly Beans which contain Sorbitol.
  - Stimulant laxatives - work by signaling the muscles and nerves of the intestine to contract. These laxatives work relatively quickly, but tend to produce more cramping. Examples include Dulcolax and Senecott.
  - Enemas

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**New Medications**

- **Amitiza** - an oral treatment (capsule) approved by the FDA in 2006. It works by increasing fluid secretion in the small intestine. It helps to ease the passage of the stool. It improves symptoms associated with chronic idiopathic (of unknown cause) constipation.

**Surgical Interventions**

- Placement of C-tube for fluid infusion
- Removal of portions of the GI tract
- Placement of central line for administration of TPN in cases of complete gut dysmotility and failure.
Abdominal migraine is a migraine attack without the headache. These most commonly occur in children from five to nine years of age. A child with an abdominal migraine will complain of stomach pain; he may also complain of nausea and might have to vomit. He will develop photophobia (sensitivity to light), be irritable, lose his appetite and have diarrhea. He may have a flushed or pale face with dark circles under his eyes. In rare instances, he may also complain of head pain. His symptoms could last anywhere from 1 to 72 hours.
ABDOMINAL MIGRAINE THERAPEUTICS

- Propranolol - a beta blocker is prescribed to treat or prevent migraine in children.
- Cyproheptadine (Periactin) - an anti-histamine that affects the level of serotonin.
- Amitriptyline (Elavil) precise action of tricyclic antidepressants is not fully understood, but it is believed that the most important effect is the decreased reuptake of norepinephrine and serotonin.
- Triptans - *not licensed for pediatric use.*
NEUROVISCERAL PAIN

- Neurontin
- Amitriptyline
Examples of Mitochondrial Disorders with Prominent GI Issues

- MNGIE
- MELAS
- Pearson marrow-pancreas syndrome
- Mitochondrial Hepatopathies
**MNGIE**

(MITOCHONDRIAL NEUROGASTROINTESTINAL ENCEPHALOPATHY)

- Onset typically by age 20
- Characterized by leukodystrophy, peripheral neuropathy, ptosis, ophthalmoplegia, progressive dysphagia and severe dysmotility with extreme cachexia
- Caused by autosomal recessive mutations in the TYMP gene which encodes for thymidine phosphorylase, a gene involved in thymidine metabolism which results in disruption of maintenance and repair of mtDNA causing it to become unstable.
- Multi-center hemopoietic stem cell trial promising
MELAS (Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke Like Episodes)

- Onset typically in childhood but adult onset known
- Neurodegenerative course with stroke like episodes, seizures and dementia, elevated lactate
- Pancreatitis can occur frequently in this disorder
- Associated with mtDNA 3243 tRNA mutation
- Symptomatic treatment with use of L-arginine for strokes.
PEARSON MARROW-PANCREAS SYNDROME

- Onset in infancy
- Characterized by sideroblastic anemia and exocrine pancreatic dysfunction
- Other clinical features include FTT, pancreatic fibrosis with IDDM, muscle involvement, hepatomegaly, cholestasis, progressive liver failure
- Most patients die in infancy or by several years of age but the few who survive into adulthood develop symptoms of Kearns-Sayre syndrome
- Caused by a deletion in mitochondrial DNA.
Clinical features range from hepatic steatosis, cholestasis and chronic liver disease with insidious onset to neonatal liver failure, the latter frequently associated with neuromuscular symptoms.

Most mitochondrial diseases with primary involvement of the liver are caused by nuclear, rather than mtDNA mutation.

NO consensus on the role of liver transplantation in mitochondrial hepatopathies, largely because of the multisystem nature of the disorders. Literature review notes a survival rate in these patients of less than 50%.

Otherwise symptomatic treatment
CLASSIFICATION OF MITOCHONDRIAL HEPATOPATHIES

- Neonatal liver failure:
  - Complex I deficiency (NADH: ubiquinone oxidoreductase)
  - Complex IV deficiency (cytochrome c oxidase) (SCO1 mutations)
  - Complex III deficiency (ubiquinol: cytochrome c oxidoreductase) (BCS1L mutations)
  - Multiple Complex deficiencies

- Mitochondrial DNA depletion syndrome (DGUOK, MPV17, and POLG mutations)

- Delayed-onset liver failure: Alpers' disease (complex I deficiency, POLG mutations)

- Chronic diarrhea (villous atrophy) with hepatic involvement (complex III deficiency)

- Navajo neurohepatopathy (mtDNA depletion; MPV17 mutations)
Present with acute liver failure at several weeks to months of life with death within weeks to months after onset of symptoms.

Associated symptoms include lethargy, hypotonia, vomiting, poor suck and weak cry, recurrent apnea and seizures (myoclonic epilepsy).

Markedly elevated plasma lactate concentration.

Respiratory chain complex analysis of liver or muscle generally shows low activity of complex I, III, or IV (COX) with COX deficiency being the most common.

Molecular causes include mutations in the SCO1 gene (copper chaperone of COX) and BCS1L gene (assembly protein of complex III). Of note, patients with BCS1L mutations usually have renal tubulopathy as well.
Patients who present with the hepatocerebral form of MDS developed hepatomegaly and progressive liver failure during the first several weeks of life with onset of death a few months later.

Associated symptoms include vomiting, GERD, FTT, DD, hypotonia, nystagmus, and on occasion pyramidal signs, cardiomegaly, tubulopathy and amyotrophia (wasting of muscle tissue)

Increased lactate, hypoglycemia, elevated AST/ALT, coagulopathy and elevated total and conjugated bilirubin.

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Considerable overlap with neonatal liver failure form of respiratory chain disease with major difference in the demonstration in MDS of a low ratio (<10%) of the normal amount of ntDNA to nuclear DNA in affected tissues with normal mtDNA sequencing.

Enzymology may show complex I, III and IV defects in liver.

Several nuclear genes including DGUOK (maintains supply of dNTPs for mtDNA synthesis), POLG (essential for mtDNA replication)and MPR17 (essential for mtDNA maintenance) are associated with MDS
Onset of symptoms typically between 2 months and 8 years of life but can be seen in young adults.

Diagnostic triad includes 1) refractory, mixed-type seizures with a focal component; 2) episodic psychomotor regression associated with intercurrent illnesses; 3) hepatopathy with or without acute liver failure.

Liver failure is preceded by the development of hypotonia, feeding difficulties, GERD, FTT, ataxia and onset of refractory partial motor epilepsy or multifocal myoclonus.

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Liver symptoms include hepatomegaly, jaundice, and progressive coagulopathy and hypoglycemia.

CSF and blood lactate and pyruvate can be elevated.

VEP may show asymmetric abnormalities.

In some patients complex I enzyme abnormalities are shown in liver or muscle.

POLG mutations have been identified in these patients.
Villous Atrophy Syndrome

- First described in two unrelated children with severe anorexia, vomiting, chronic diarrhea and villus atrophy in the first year of life
- Liver involvement included increased AST/ALT, hepatomegaly, and steatosis
- Diarrhea, vomiting and lactic acidosis worsen with high dextrose IVF or enteral nutrition.
- Resolution of diarrhea by 5 years with onset of RP, ataxia, deafness and proximal muscle weakness with death in first decade of life.
- Complex III defect in skeletal muscle
- Heteroplastic mtDNA rearrangements that involved deletion and deletion duplication.
Navajo Neurohepatopathy (NNH)

- Sensorimotor neuropathy with progressive liver disease confined to Navajo children.
- Three forms with variable age of onset and prominence of liver dysfunction.
- Typically associated with weakness, hypotonia, mutiliation. Corneal ulceration, FTT, recurrent infections, Reye-like syndrome episodes, cholestasis, cirrhosis, and liver failure.
- Brain MRI notable for progressive white matter lesions, +/- Lactate and pyruvate elevations.
- Complex I, III, IV deficiencies on enzymology.
- Associated with MPV17 mutations and mtDNA depletion.
THANK YOU!

www.vmpgenetics.com
info@vmpgenetics.com
404.720.0820 voice | 404.793.0775 fax

and

you can follow us on Facebook!
www.facebook.com/DrKendallVMP

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