## Mitochondrial Disease

Basics

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## Primary Mitochondrial Disease is Genetic

Pathogenic Variant in Mitochondrial or Nuclear DNA Imbalance between number of healthy and unhealthy mitochondria in an organ Abundance of Unhealthy Mitochondria

- Decreased ATP Generation
- Increased Reactive Oxygen Species (ROS)
- Increased Apoptosis
- Organ Dysfunction and Physiologic Symptoms

# Some Organs Are More Affected

Common Symptoms Are Termed "Red Flag" Symptoms

# Neurologic Symptoms Are Common

The Brain Uses 20% of the ATP Created by All Mitochondria

### Neurologic Red Flags



Strokes in a Nonvascular Distribution



#### **Myoclonic Epilepsy**



Epilepsia Partialis Continua

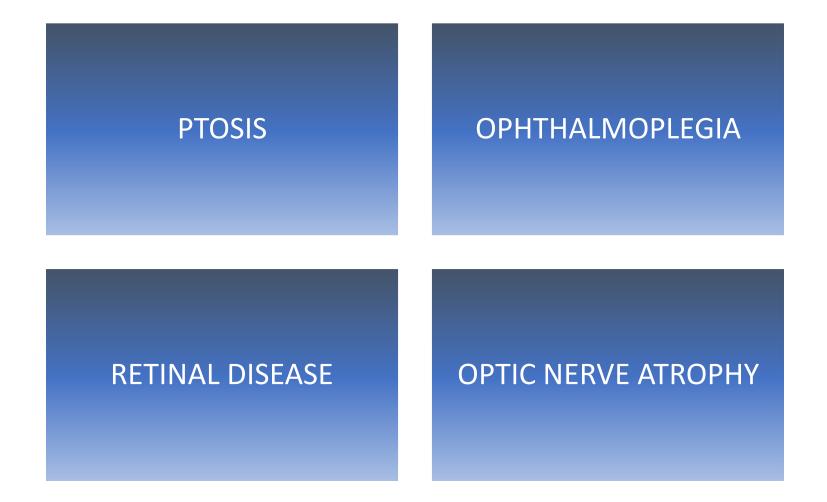


Disease of the Basal Ganglia, Thalami or other Deep Gray Matter Nuclei



**Cerebellar Disease** 

#### Ophthalmologic Red Flags



#### Other Red Flags



#### Sensorineural Hearing Loss



Cardiomyopathy or Cardiac Conduction Defects



Renal Tubular Acidosis or a Tubulopathy



Dysmotility and Pseudo-obstruction

# Associated but Less Specific Endocrine Symptoms



- Maternally Inherited Diabetes & Deafness
- Mitochondrial Encephalomyopathy, Lactic Acidosis & Stroke
- Leigh Syndrome
- Chronic Progressive External Ophthalmoplegia
- Kearns-Sayre Syndrome

The Most Common Mitochondrial Syndromes Maternally Inherited Diabetes and Deafness (MIDD) Due to a common 3243 A>G pathogenic mtDNA variant



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Mildest form of this specific genetic disease



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Maternally inherited

Hearing loss

Diabetes with onset in childhood or young adulthood

Cardiomyopathy

Other Endocrinopathies

#### Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke (MELAS)

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Also due to the common 3243 A>G pathogenic mtDNA variant

Most severe form of this genetic disease

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Includes the symptoms of MIDD with progression to include strokes



Strokes are not typical ischemic or embolic/thrombotic events and due to a combination of regional/focal ATP deficit, epileptiform activity and focal vessel collapse

#### Leigh Syndrome



#### Most common pediatric mitochondrial disease



Not a singular disease and can be due to one of hundreds of pathogenic variants (mutations) in the nuclear DNA or mtDNA



Injury to the deep gray matter nuclei of the brain and brainstem



Associated symptoms include developmental regression, abnormalities of tone, refractory movement disorders, eye movement problems, irregular respiratory drive and cerebellar dysfunction Chronic Progressive External Ophthalmoplegia (CPEO)

- Due to a large deletion of the mtDNA
- Ophthalmoplegia with frozen eyes and ptosis develop over time

#### Kearns-Sayre Syndrome



Also due to a deletion of the mitochondrial DNA that is often de novo



Multisystem disease in addition to the symptoms seen with CPEO



High risk of endocrinopathies



High risk of sudden onset heart block which can be fatal



Associated neuropathy and myopathy