Mitochondrial Disease

Basics

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

PTOSIS

OPHTHALMOPLEGIA

RETINAL DISEASE

OPTIC NERVE ATROPHY

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

ADRENAL INSUFFICIENCY

DIABETES

GROWTH HORMONE DEFICIENCY

HYPOPARATHYROIDISM

HYPOTHYROIDISM

SHORT STATURE

The Most Common Mitochondrial Syndromes

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

Maternally Inherited Diabetes and Deafness (MIDD)

- Due to a common 3243 A>G pathogenic mtDNA variant
- Mildest form of this specific genetic disease
- Maternally inherited
- Hearing loss
- Diabetes with onset in childhood or young adulthood
- Cardiomyopathy
- Other Endocrinopathies

Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke (MELAS)

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

Most severe form of this genetic disease

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