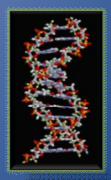


# Mitochondrial Disease and Autism

***Bridging the Gap***

Fran D. Kendall, M.D.
Virtual Medical Practice, LLC
Biochemical Genetics
Metabolic, Mitochondrial & Inherited Disorders

## Objectives

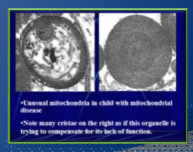
To provide basic background information on Mitochondrial Disease, its clinical features, diagnosis, treatment, prognosis, inheritance and to discuss its association with Autistic Spectrum Disorders (ASD).

**Disclaimer**
Dr Kendall and Virtual Medical Practice have no financial interest in any laboratory.

## The Big Questions

**What are Mitochondria?**

**What is Mitochondrial Disease?**

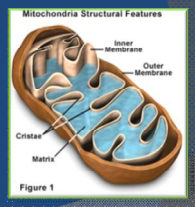



## Our Bodies Cells

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

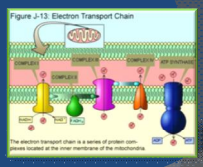

## The Powerplants

- 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

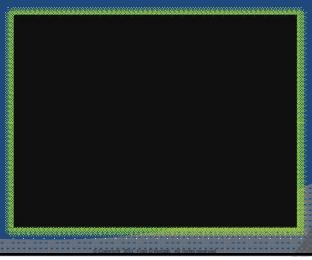



## The Respiratory Chain

- 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




## Electron Transport Chain



## 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
- Results in decreased energy production and localized or widespread problems

## The Genetics of Mito Disease

- There are hundreds of 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

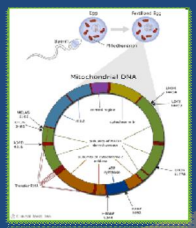
## Features of Mitochondrial Nuclear Genes

- 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 probably the most common etiology of pediatric patients with mitochondrial disorders.

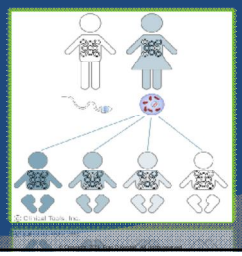
## Features of Mitochondrial DNA (mtDNA)

- Inherited exclusively through the maternal line
- Circular molecule, a number of copies in each mitochondrium (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




## Heteroplasmy of mtDNA



## Symptoms I – *listed on www.virtualmdpractice.com*

- **Brain**
  - Developmental Delays
  - Migraines
  - Seizures
  - Dementia
  - Autistic Features
  - Atypical Cerebral Palsy
  - Neuro-psychiatric Disturbances
  - Mental Retardation
  - Strokes

## Symptoms II – *listed on www.virtualmdpractice.com*

- **Nerves**
  - Absent reflexes
  - Fainting
  - Neuropathic pain
  - Weakness (may be intermittent)
  - Dysautonomia - temperature instability & other dysautonomic problems
- **Pancreas & Other Glands**
  - Diabetes and exocrine pancreatic failure (inability to make digestive enzymes)
  - Parathyroid failure (low calcium)

## Symptoms III – *listed on www.virtualmdpractice.com*

- **Muscles**
  - Weakness
  - Cramping
  - Hypotonia
  - Muscle pain
- **Gastrointestinal Problems**
  - Pseudo-obstruction
  - Dysmotility
  - Irritable bowel syndrome
  - Gastroesophogeal reflux
  - Diarrhea or constipation

## Symptoms IV – *listed on www.virtualmdpractice.com*

- **Kidneys**
  - Renal tubular acidosis or wasting
- **Heart**
  - Cardiomyopathy
  - Cardiac conduction defects (heart blocks)
- **Liver**
  - Liver failure
  - Hypoglycemia (low blood sugar)

## Symptoms V – *listed on www.virtualmdpractice.com*

- **Ears & Eyes**
  - Visual loss & blindness
  - Ptosis
  - Ophthalmoplegia
  - Optic atrophy
  - Hearing loss and deafness
  - Acquired strabismus
  - Retintis pigmentosa
- **Systemic**
  - Failure to gain weight
  - Chronic Fatigue
  - Unexplained vomiting
  - Short stature
  - Respiratory problems

## Common Problems in Mitochondrial Energy Disorders

- Central Nervous system (Brain) problems such as developmental delays including AUTISM AND AUTISTIC FEATURES, 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.

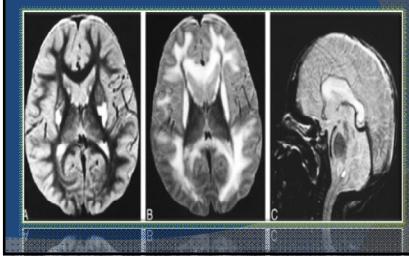
## Clinical Features Suggestive of Mitochondrial Energy Disorders

- Typical brain changes suggestive of Leigh disease or abnormalities in white matter
- Persistent, significant elevations in lactate (especially if in the brain) and other specific biochemical features
- Problems in many body systems suggestive of mitochondrial disease
- Strong family history of mitochondrial disease

## How is Mitochondrial Disease Diagnosed? *Traditional Evaluation*

- Clinical features, physical findings and minimal laboratory/radiographic studies, example specific brain lesions as seen in Leigh disease
- Clinical phenotype consistent with one of the well described subtypes of mitochondrial disease, such as MELAS and confirmed by gene test.
- Clinical features and findings suggestive of mitochondrial disease – tissue studies completed.

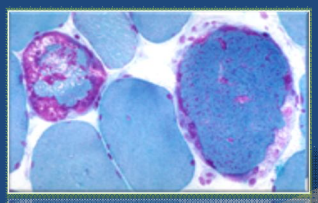
## Leigh Disease MRI Lesions



## Diagnosis of Mitochondrial Energy Disorders

- 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)
- Specific DNA changes that cause mitochondrial disease

## Ragged Red Fibers



## Examples of Nuclear Gene Mito Disease

- 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

## Examples of mtDNA Disease

- 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

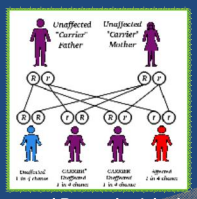
## Prognosis of Mitochondrial Energy Disorders

- 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

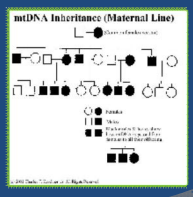
- Symptomatic – treat existing problems
- Preventative – early detection of associated problems
- Therapeutics very limited and include use of Coenzyme Q10

## Inheritance of Mitochondrial Energy Disorders




*Autosomal Recessive Inheritance*

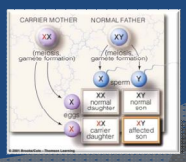
## Inheritance of Mitochondrial Energy Disorders




*Maternal Inheritance*

## Inheritance of Mitochondrial Energy Disorders

- Autosomal Dominant forms
- Sporadic
- X-linked




## Advancements And The Future

- Edison Pharma EPI 743 trial for Leigh Disease and MELAS patients
- Hemopoietic stem cell transplant for MNGIE
- Elimination of mtDNA mutation with nuclear transplant into healthy egg cells
- New less invasive testing including buccal swab enzyme testing and expanded gene panels to identify hundreds of the known mito genes

## Hot Topic in Mitochondrial Disease…

Autism and Mito

## What is Autism?

- A complex neurobiological disorder that typically lasts throughout a person's lifetime, is a part of a group of disorders known as autism spectrum disorders (ASD) and affects the ability to communicate and relate to others
- Also associated with rigid routines and repetitive behaviors
- 1 in 90 individuals is diagnosed with autism making it more common that pediatric cancer, diabetes and AIDS combined
- Occurs in all racial, ethnic and social groups and is 4 times more likely to affect boys than girls.
- An underlying diagnosis is established in only 2% - 36% of cases

## Mito Disorders and Autism

- One 2005 population based study in Portugal suggested that 7.2 out of 100 patients with ASD have an underlying mito disorder.
- A 2007 study by the same group revised their population figures and noted 4.1 out of 100 patients with autism had underlying mitochondrial disease.
- Although mito appears to be a rare cause of autism, it is one of the more common definable causes of ASD.

## Case Study: One

One study evaluated five patients with ASD and family histories of mitochondrial DNA diseases.

- Three patients had isolated autistic features and two had additional neurological findings.
- Two patients had the common MELAS A3243G mutation.
- One patient had mtDNA depletion.

## Case Study: Two

Weissman et al reported the association of ASD with the mtDNA A4295G mutation in a 15 year old with a number of other neurological findings including hearing loss.

## UC Davis Study – Giulivi et.al. JAMA, November 2010

- Children with ASD are far more likely to have a defect in their ability to produce energy than typically developing children
- Discovered widespread reduced mitochondrial enzyme function among autistic children, affecting complex I in 60% of the patients
- Association established utilizing WBC (lymphocyte) testing

## Rossignol & Frye – Molecular Psychiatry, January 2011

- Children on the autism spectrum also reside along a spectrum of mitochondrial dysfunction of varying severity
- Emphasized the need for ASD children to be screened for possible mitochondrial dysfunction citing improvements in children with ASD & mito dysfunction after initiation of mito disease management

## Conclusion of Studies

- The link between mitochondrial dysfunction and autism is greater than suspected
- It remains uncertain if this association is due to a primary defect in mitochondrial functioning due to gene mutations or dysfunction caused by other factor(s).
- Mitochondrial disease should be considered when associated with other neurological and body system complications and/or a family history of mitochondrial disease.

## Recommended Evaluation for ASD Patients

- **TIER 1** – *basic work up recommended for all patients*
  - CHROMOSOME MICROARRAY STUDIES
  - COMPLETE METABOLIC PANEL, CBC, CPK
  - AMMONIA LEVEL
  - LACTATE AND PYRUVATE LEVELS
  - CARNITINE, PLASMA TOTAL AND FREE
  - COENZYME Q10 LEVEL
  - PLASMA AND URINE AMINO ACIDS
  - URINE ORGANIC ACIDS
  - PLASMA ACYLCARNITINES
  - THYROID FUNCTION TESTS

*list is located on our website, www.virtualmdpractice.com*

## Recommended Evaluation for ASD Patients

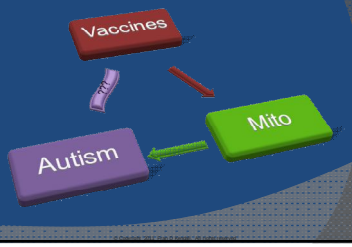
- **TIER 2** – *depends on clinical features & results of Tier 1 testing*
  - MITOCHONDRIAL ENZYME AND/OR DNA TESTING
  - RETT SYNDROME DNA TESTING
  - PTEN MUTATIONAL ANALYSIS
  - NLGN3, NLGN4X, SHANK3, SNRPN GENE TESTING
  - LYSOSOMAL ENZYME TESTING
  - PEROXISOME DISEASE TESTING (VLCFAS)
  - CSF STUDIES FOR LACTATE AND PYRUVATE, AMINO ACIDS AND NEUROTRANSMITTERS
  - BRAIN MRI

*list is located on our website, www.virtualmdpractice.com*

## Why is it important to know if an ASD patient has mito?

- For implementation of treatment & protocols
- Monitoring in affected individuals
- To determine recurrence risks for future children
- To determine risk for other family members

## Mito, Autism, and Vaccines

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and

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Virtual Medical Practice, LLC

*expanding genetic horizons…*

www.virtualmdpractice.com

info@virtualmdpractice.com

404.720.0820 Voice | 404.601.9931 fax