Mitochondrial Oxidative Phosphorylation (OXPHOS) Dysfunction:
A newly emerging category of Autistic Spectrum Disorder
Information for Primary Care Physicians

Compiled By: Dr. Susan Leib, M.D. and Alyssa Davi (parent/child advocate)
Presented at pediatric conference on December 2009, updated May 2010

Mitochondrial Awareness Week took place on September 20-26. Mitochondrial disease is currently greatly under-recognized. Disorders of energy metabolism are thought to affect roughly 1:4000 people and recent statistics suggest it might be as high as 1:1000 people.

Mitochondrial Oxidative Phosphorylation (known as OXPHOS) is emerging as a new category of autistic spectrum disorder (ASD) per Dr. Natowicz, a geneticist, at the Cleveland Clinic. Dr. John Shoffner, one of the leading diagnosticians in the field of mitochondrial medicine has said, “When you consider the frequency of autism in the general population, and you take 20% of that as a rough estimate of the proportion of children that may have these biochemical markers (of mitochondrial dysfunction), it begins to raise some interesting questions about how to approach diagnosis, mechanism of disease, and patient management in what could turn out to be significant numbers of individuals.” (from “Mitochondrial Dysfunction May Play a Role in Autism Spectrum Disorders Etiology”)

“Recently, Oliveira and colleagues published a population-based survey of school age children with ASD. They found that 7% of those who were fully tested met criteria for definite mitochondrial respiratory chain disorders and were also clinically indistinguishable from other children with ASD.” (from “Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis”)

For thousands of children that have been diagnosed ASD, this could mean new treatment options. Although OXPHOS is not thought to be curable at this time, children that have OXPHOS symptoms can be helped and/or managed by taking a “mito. cocktail”. If OXPHOS children can be identified sooner, medications and supplements would then be made available to a whole group of children (ASD and non-ASD children with atypical or unusual clinical presentations) that may currently be getting no biochemical treatment or metabolic support.

There is currently very little knowledge of these disorders in the general medical community as they were once thought to be rare. Knowing that this is no longer true, the top pediatric specialists in the field of mitochondrial medicine are now asking for early screening to occur by primary care physicians. The road to a diagnosis is often a long and difficult one for many families as the presentation of these disorders is often varied and complex. “It is hoped that greater familiarity among primary care physicians with the manifestations of mitochondrial disease will facilitate proper diagnosis and management of this growing cohort of pediatric
Mitochondrial disease should be considered in any patient with unexplained multi-system involvement and an unusual clinical presentation or regressive autism. Fatigue is a hallmark symptom.

Mitochondria are the “power plants” of the body. The organs in the body that require the most energy are the brain, muscle, “The parts of the body that need the most energy, such as the heart, brain, muscles and lungs are the most affected by mitochondrial disease. The affected individual may have strokes, seizures, gastro-intestinal problems (reflux, severe vomiting, constipation, diarrhea), swallowing difficulties, failure to thrive, blindness, deafness, heart and kidney problems, muscle failure, heat/cold intolerance, diabetes, lactic acidosis, immune system problems and liver disease. An undiagnosed child may exhibit feeding problems, be unable to fight typical childhood infections or have repeated infections and fevers without a known origin. A “red flag” for mitochondrial disease is when a child has more than 3 organ systems with problems or when a “typical” disease exhibits atypical qualities. (from www.UMDF.org)

The Mitochondrial Medicine Society lists the following as red flag symptoms (from www.mitosoc.org):

**Neurologic**
1. Cerebral stroke-like lesions in a nonvascular pattern
2. Basal ganglia disease
3. Encephalopathy, recurrent or with receiving valproate
4. Neurodegeneration
5. Epilepsy Partialis Continua
6. Myoclonus
7. Ataxia
8. MRI findings consistent with Leigh disease
9. Characteristic MRS peaks
   a. Lactate peak at 1.3 ppm TE at 35 and 135
   b. Succinate peak at 2.4 ppm

**Ophthalmologic**
1. Retinal degeneration
2. Ophthalmoplegia/paresis
3. Fluctuating/dysconjugate eye movements
4. Proptosis
5. Sudden- or insidious-onset optic neuropathy/atrophy

**Gastroenterologic**
1. Unexplained or valproate induced liver failure
2. Severe dysmotility
3. Pseudo-obstructive episodes

**Cardiovascular**
1. Hypertrophic cardiomyopathy with rhythm disturbance
2. Unexplained heart block in a child
3. Cardiomyopathy with lactic acidosis (> 5 mM)
4. Dilated cardiomyopathy with muscle weakness
5. Wolff-Parkinson-White arrhythmia

**Other**
1. Exercise intolerance out-of-proportion to weakness
2. Delayed waking from general anesthesia
3. Episodes of acute rhabdomyolysis
4. Unexplained hypotonia, failure-to-thrive, and acidosis

Additional possible symptoms can be found at:

http://www.umdf.org/site/c.otJV7MMLqE/b.5692883/k.C0C7/Possible_Symptoms.htm
The Mitochondrial Medicine Society lists the following as initial tests (from www.mitosoc.org):

- Basic Chemistries
- Liver enzymes & Ammonia
- Complete Blood Count
- Creatine Kinase
- Blood Lactate & Pyruvate
- Quantitative Plasma Amino Acids
- Quantitative Urine Organic Acids
- Plasma Acylcarnitine Profile

- Lactate & Pyruvate
- Quantitative Amino Acids
- Neurotransmitter studies
- Routine Studies including glucose, protein, & cell count

- Echocardiogram
- Electrocardiogram
- Ophthalmic exam
- Auditory exam
- Brain MRI

- Karyotype
- Fragile X testing
- Neurology Consult
- Genetics Consult

Negative results have a high false negative rate; If mitochondrial disease is suspected, refer the patient to a mitochondrial disease center.

Laboratory evaluation of patients with possible mitochondrial disease from the United Mitochondrial Disease Foundation

The Mitochondrial Medicine Society lists the following as Findings Suggestive of Mitochondrial Dysfunction (from www.mitosoc.org):

- Amino Acids (plasma/CSF)
  a. Elevated alanine
  b. Alanine/Lysine ratio > 3
  c. Elevated glycine, proline, tyrosine or sarcosine

- Organic Acids (urine)
  a. TCA intermediates
  b. Ethylmalonate
  c. 3-methylglutaconate
  d. Dicarboxylic Acids

- Acylcarnitines (plasma)
  a. Low free carnitine
  b. Elevated acyl/free carnitine ratio
  c. Elevations suggesting disrupted fatty acid oxidation
The following links are for Primary Care Physicians to help with initial testing, referrals, diagnosis and management of a patient with suspected Mitochondrial Disease.

A Modern Approach to the Treatment of Mitochondrial Disease
http://www.springerlink.com/content/d872354q672090mq/?p=fd9ba0ec0d2a4789b9d74c7daf763fa0&pi=2
Mitochondrial Disease: A Practical Approach for Primary Care Physicians
http://pediatrics.aappublications.org/cgi/content/full/120/6/1326

Clinicians Guide to the management of Mitochondrial Disease: A Manual for Primary Care Providers
http://www.mitoaction.org/guide/table-contents

Mitochondrial and Metabolic Disorders- A Primary Care Physician’s Guide
http://biochemgen.ucsd.edu/mmec/ep-toct.htm

Dr. Mark Korson, Chief of the Metabolic Program at Tufts New England Medical Center, speaks about Mitochondrial Disease and Patient Challenges (5 minute video)
http://www.youtube.com/mitoaction#play/all/F38FD8F6D9124E1B-all/1/-zf3eYRGpk0

Related OXPHOS research articles:

Mitochondrial Dysfunction May Play a Role in Autistic Spectrum Disorders Etiology

Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis

Oxidative Phosphorylation (OXPHOS) Defects in Children with Autistic Spectrum Disorders

Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression

Mitochondrial Dysfunction in Autism Spectrum Disorders: A Population Based Study

Relative Carnitine Deficiency in Autism

Websites for further information:
www.mitosoc.org
www.mitoaction.org
www.umdf.org

List of Mitochondrial Disease Doctors/Specialists (with hospital affiliation) can be found at:
http://www.mitosoc.org/blogs/diagnosis/providers