SUMMARY – Mito-Austism: Information for Parents and Clinicians

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Introduction

Dr. Fran Kendall is a pediatrician and biochemical geneticist who has practiced medicine for more than 20 years. She has worked in private practice as well as academia and currently runs a private business, the Virtual Medical Practice, with her husband. She presented recently at a conference in Chicago on the link between mitochondrial disease and autism and discussed this issue during a teleconference with MitoAction in July 2011.

Autism Spectrum Disorders (ASD) are complex neurobiological disorders that affect a person's ability to communicate and relate to others. Its incidence is far greater than once thought, it affects all races and socioeconomic groups, and it is seen more often in males. Specific clinical symptoms can be used to describe autism, but the causes have been linked to a variety of genetic disorders.

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 its 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. (Oliveira G. et al., Dev Med Child Neurol. 2007 Oct;49(10):726-33.) Over the last 5-10 years, other studies have clearly shown a link between Mito and autism. The largest study to date comes out of UC Davis (JAMA, November 2010), which demonstrated that children with ASD are more likely to have deficiencies in Mito functioning and energy production than other children. This study shows there is a greater link than was previously believed between the two. However, it is not known whether the cause of the Mito dysfunction is from a genetic mutation or secondary Mito damage from toxicity.

Based on this research, it is important for children who are diagnosed with ASD to also be screened for mitochondrial disease. There is demonstrated evidence that treatment of the Mito improves the autism symptoms.

ASD kids with Mito have many of the typical Mito symptoms:

- GI issues
- Hypotonia/low tone
- Low carnitine levels
- Fatigue
- Autonomic dysfunction

But clinical presentation varies greatly from child to child, so if your child does not have these symptoms, it does not necessarily mean he does not have mitochondrial dysfunction.

When patients with ASD come to Dr. Kendall, she doesn't just look for Mito, but rather tries to uncover the underlying cause. Tier 1 diagnosis involves a basic workup, history, and lab tests (metabolic panel, ammonia level, etc.). Tier 2 involves more in-depth testing, which depends on the clinical symptoms revealed in the Tier 1 phase. This might involve Mito enzymes and/or DNA testing and brain MRIs, for example. Most general pediatricians may not know what to do with some of the results of these more complex metabolic tests, so they may need to consult specialists or geneticists.

Why is it important to know that Mito is the underlying cause of your child's autism? First, management of Mito often shows an improvement of autism symptoms. Second, children with mitochondrial disease often have many issues that need to be managed -- some that may appear to be unrelated to one another, but all may actually be related to the Mito. And lastly, you may want to know the risks for reoccurrence of the disease if you plan to have more children.

Children who get the Mito diagnosis and are put on a treatment plan have generally shown an improvement in autism symptoms and a much improved quality of life.

The Vaccine Controversy

Dr. Kendall does not believe that vaccines cause Mito or autism. She advises that parents have their children vaccinated. However, because the mechanism of a vaccine is to trigger the body to respond and build up antibodies (thus using energy), she does use caution at times. For example, she advises parents to give Advil before and after the vaccine. If a child is behind in her schedule and is due to have multiple vaccines, Dr. Kendall suggests spreading them out and not getting them all at once. The stress on the body could trigger other responses in a child with autism/Mito.

Background on Mitochondrial Disease

What are Mitochondria?
Cells make up all parts of the human body with the nucleus as the center of each cell. Mitochondria, located within the cell, are the "powerhouse" of the cell, providing energy. Respiratory chains exist within the mitochondria (there are 5 distinct chains or complexes); these essentially make up a group of chemicals that produces ATP, the body's energy source. The body takes in food and breaks it down, and ATP uses oxygen and phosphate to generate energy. This provides the body with an efficient way to turn on bodily functions, but because there is just this one "on switch," if there are problems (i.e., malfunctions/disease, etc.), the difficulties caused are multiple and difficult to pinpoint.

Incidence
Mitochondrial disease occurs in about 1 out of 400 individuals. A recent study in the UK looked at newborns for the presence or absence of Mito markers in the genes and found that the incidence was as high as 1 in 200 for "carriers" of Mito. (Cree LM, Samuels DC, Chinnery PF. Biochim Biophys Acta. 2009 Dec;1792(12):1097-102. Epub 2009 Mar 19. Review.) Click here for "The inheritance of pathogenic mitochondrial DNA

mutations": http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2785871/?tool=pubmed

Causes
Mito can be caused by genetic changes that are passed on to the next generation or by toxic effects to the mitochondria due to a variety of causes, all of which are not totally known. In either case, the results of mitochondrial damage/mutation cause a decrease in energy production and widespread symptoms. Other diseases, as well as some medications with known mitochondrial toxicity (such as HIV drugs and statin medications), may actually cause secondary mitochondrial abnormalities and decreased energy production. Heteroplasmy is responsible for the varying severity of mitochondrial impairment in each child (or adult).

Heteroplasmy refers to the varying number of mutated cells vs. healthy cells a person has. The greater the number of mutated cells, the more severe symptoms will be. Mitochondrial disease also affects each organ system differently in each child. Organs requiring a lot of energy to function optimally tend to be affected more significantly in mitochondrial disorders. The greater an organ is affected (the central nervous system, GI system, muscles, heart, etc.), the greater the symptoms will be. Therefore, no two children will have exactly the same clinical presentation.

Genetics

The genetics of mitochondrial disease are complex because there are more than 1,500 genes involved that make proteins. There are two kinds of mitochondrial genes. Most are called nuclear mitochondrial genes, located inside the nucleus of the body's cells, and are inherited from both sets of parents. The others, called mitochondrial genes (37 in number), are located in the mitochondria outside the nucleus, and are inherited exclusively from the maternal side. Dr. Kendall said it is currently believed that the vast number of pediatric mitochondrial disease cases are due to nuclear gene mutations, in which the mom and dad each contribute nuclear genes to the (symptomatic) child.

Symptoms

The symptoms of Mito can mimic almost any clinical symptom, making diagnosis difficult. Symptoms range from:

- Developmental delays
- Seizures
- Dysautonomia
- Hearing and vision loss
- Muscle weakness
- Various GI symptoms such as dysmotility
- Enlarged heart
- Kidney or liver failure
- Chronic fatigue
- Failure to thrive

Many of these symptoms are often seen in children with autism and indicate that additional testing may be required to get a complete diagnosis.

Specific clinical features that are red flags of Mito include:

- Changes in the brain
- Elevated lactate levels
- Problems in multiple body systems that don't appear to be connected
- Family history of Mito

Diagnosing Mito

Clinicians can further identify clinical features associated with mitochondrial disease by conducting a thorough family history in conjunction with specific diagnostic testing, including some basic blood tests. (http://virtualmdpractice.com/documents/GeneticTestingforASD.pdf) For example, some types of Mito, particularly those with mtDNA mutation such as MELAS, can be confirmed through genetic testing. In addition, newer blood tests can detect nuclear DNA mutations (nDNA) in which case both parents are carriers of the mutation. However, there are more than 1,000 nDNA mutations potentially associated with mitochondrial disorders. And not all are able to be detected at this time. When clinical features are suggestive of Mito yet testing is not definitive, then tissue studies can be done, such as muscle biopsy, skin fibroblast, buccal swabs (inside the cheek), and cerebral spinal fluid (CSF). Most clinicians prefer the least invasive studies as a primary approach. For years, muscle biopsy has been considered the gold standard of definitive testing; however, muscle biopsy does carry the risk of both false negative and false positive. In addition, muscle biopsy is the most invasive and expensive approach to diagnosis.

Recommended evaluation for ASD patients (taken from www.virtualmdpractice.com)

TIER 1 - Basic workup 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 ACID
- URINE ORGANIC ACIDS
- PLASMA ACYLCARNITINES
- THYROID FUNCTION TESTS

TIER 2 - Depending on clinical features and 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

Developments in genetic testing are promising, as now both mtDNA and nDNA mutations can be identified.

Until recently, approximately 10 percent of the nuclear DNA genes were able to be identified via diagnostic blood tests. Today, far more of the nDNA have been identified, broadening the scope of diagnosis by blood test for patients who have nDNA mutations.

Currently, several clinical diagnostic labs, including Baylor, Medomics, and Transgenomic, are now offering an array of nuclear gene sequencing tests. In the Fall 2009 edition of Dr. Kendall's newsletter, VirtualNews, she shared that Center for Molecular and Mitochondrial Medicine and Genetics at UC Irvine, among others, is involved in identifying nuclear gene mutations. Identifying the gene cause for a Complex I or other mitochondrial disorder is important to provide the possibility of prenatal diagnosis for carrier couples and to better understand why one Complex I defect can present with Leigh disease, a typically more aggressive form of Mito disease, and another with a more static course of low-tone and developmental delays. Each gene involved in energy production makes a unique protein that subsequently provides a specific function in the energy producing pathway. Identifying and understanding each gene and its function will ultimately lead to treatments for the broad spectrum of Mito disease.

Three laboratories currently provide expanded nuclear gene testing:

- Baylor College of Medicine: http://www.bcm.edu/geneticlabs/?PMID=9246
- Transgenomic Next-Generation Sequencing: http://labs.transgenomic.com/library/602182-00.pdf
- Medomics nuclear gene testing: http://www.medomics.com/MitoNucleomeDx

Prognosis & Treatment

Prognosis is variable although Mito is typically considered a progressive disease. However, mitochondrial disease patients respond well to symptom management; prevention and stabilization are important cornerstones of treatment. Symptom progression is more likely with increased physiologic stressors, such as illness and surgery, therefore treatment modalities are aimed at reducing and minimizing stress. For example, giving IV fluids early and at home can help stabilize the disease in some patients. Treatment also involves preventing problems and addressing those that do appear early. Early detection of symptoms is especially important. Therapeutic

remedies are still limited, but the use of the "Mito cocktail" and Coenzyme Q10 have proved very helpful for many patients.

Additional resources
The following resources are available to families seeking information and advocacy tools discussing the link between Mito and autism. They can be found at Dr. Kendall's website, www.virtualmdpractice.com

For a handout discussing Autism and Mito Disorders: http://virtualmdpractice.com/documents/MitoAutism3panel2011.pdf

For a list of possible Mito symptoms with a list of genetic testing for ASD patients: http://virtualmdpractice.com/documents/GeneticTestingforASD.pdf