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Highlights of the 2010 UMDF Symposium

As a 20-year veteran of mitochondrial medicine, Dr. Kendall was excited to see some of the fabulous research and collaborative efforts underway to improve mitochondrial medicine. She was honored to participate in an expert panel and provide answers to patients in the "MITO DOC IS IN" sessions.

While there was more information than we can possibly provide in this newsletter, we will highlight the developments that seem to be of most interest & importance now and list additional info in upcoming editions:

Dr Kendall was interviewed by the UMDF on Mito medicine, where it is headed and our unique practice model.

The Mayo Biobank – *Please help us help you!!* Finally, the mitochondrial professional and family communities can work together to gather samples and data to allow expeditious research! A major impediment to research for rare disorders is having enough information or DNA to conduct a statistically significant study or trial. Easy access to patient samples and data will help expedite this process. We are encouraging all of our patients and families to participate. Participation will require signing of a consent form acknowledging your participation in the Biobank, completion of a short questionnaire, possible blood sample and transfer of leftover skin, muscle or other tissue samples you are comfortable with relinquishing (this last step is NOT required). For more information call 1-877-594-2149, go to http://mayoresearch.mayo.edu/mitochondrial-disease-biobank or email mitochondrialdb@mayo.edu.

Specific Gene Diagnoses Grows in Importance – It is becoming increasingly apparent that having a specific gene diagnosis will be needed in the future for better understanding of pathophysiology and ultimately treatment of various types of mito disease since therapies will likely be sub-type specific. Information on several disease specific treatments was presented and discussed including the use of Idebenone therapy for LHON (Leber's Hereditary Optic Neuropathy) and L-arginine for MELAS (Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like Episodes). The latter treatment trial is ongoing. Please contact us if you are interested in participating!

Biopsy Talk - MitoAction

You may listen to a MitoAction.org podcast of Dr Kendall lecturing on the ins/outs of biopsies and taking questions from monthly listeners at:

- MitoAction.org website
- ITUNES/Podcasts
- Resource Tab on www.virtualmdpractice.com

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Links

http://mayoresearch.mayo.edu/mitochondrial-disease-biobank

www.mitoaction.org

www.umdf.org

If you received this newsletter secondhand, please email us at info@virtualmdpractice.com to be added to future mailings.

New Diagnostic Tools – the race is on! – Currently there is a non-invasive clinical test to screen mitochondrial enzyme functioning utilizing buccal (cheek) swabs. Using a large Q-tip, cheek cells are gently scraped from the inside of the mouth and sent for analysis. While still in the development stages, the data looks promising. Buccal swab enzyme testing completed on 26 patients previously diagnosed with mitochondrial disorders based on muscle enzymology noted a direct correlation of results in 23 of the 26 patients. The three samples that did not correlate were from the same lab originally collected on young patients suggesting that either that specific laboratory or the age of the patients may have influenced the original results. The development of a less expensive, less invasive screening test piggybacks nicely with the development of expansive nuclear gene panels by several biotech labs including Baylor and Medomics. While the labs are keeping their progress under wraps for now, expansive gene testing will likely be available in the next year. The ability to determine the molecular basis of most mitochondrial disorders is coming soon!

Expansion of Basic Mito Knowledge – A number of lectures focused on the mitochondrial dysfunction found in several disorders including Parkinson's disease, Alzheimer's and ALS. Although this research has no immediate implications for the care of those with classic mitochondrial disease (MELAS, complex I defects), the expanded knowledge will lead to a better understanding of mito processes and ultimately to viable treatments.

PINK1 – not just for girls! – To help curb the accumulation of mtDNA mutations with age, our body cells utilize a number of quality control pathways to "clean up" cellular damage. Recent studies suggest that PINK1 and Parkin, two proteins defective in autosomal recessive (inherited) forms of Parkinson's disease, are part of this "clean up" crew. Researchers postulated that the loss of these quality control pathways led to parkinsonism by allowing damaged mitochondrial to accumulate in the brain. When this PINK1/Parkin pathway was upregulated (turned on faster) the scientists found that over 90% of the mutated DNA was removed from mouse cells resulting in return to normal mitochondrial functioning. Ultimately upregulation of these "clean up" crews may be beneficial for a variety of diseases caused by mito damage.

Do You or Your Child Really Have Mito?

When patients are suspected of having mitochondrial disease, muscle biopsies are often obtained for respiratory chain enzymology, histology studies and some gene testing. Abnormal results often come in the form of certain complex deficiencies such as a complex I defect or a combination of complex deficiencies.

However, most people do not recognize that MUSCLE ENZYMOLOGY FROM BIOPSIES IS NOT ABSOLUTE! There are known false positives and false negatives with mitochondrial enzymology. In addition, abnormalities in mitochondrial enzyme complex assays can be due to a true disease process in the mitochondria (due to a mitochondrial or nuclear gene mutation) or a secondary process that essentially makes

the mitochondria sick when they were initially programmed to function normally (examples include Parkinson's disease, Alzheimer's disease and other disorders that "poison" the cell environment and make the mitochondria sick). Because of these false positives, false negatives and "secondary affects" many practitioners will no longer rely just on enzymology for a mito diagnosis. They seek confirmation with a mito gene diagnosis.

Case in point - a number of our patients previously diagnosed with a mitochondrial disorder by muscle biopsy have been re-diagnosed with other diseases including chromosome deletions. Obviously, this radically alters the impact to patients and their families and underscores the need for the molecular confirmation of any biochemical mito diagnoses. Please refer to my biopsy podcast for MitoAction.org in ITunes, or go to our website for an MP3 file and to download a 15 page Patient Handout on biopsies for more information.

Leigh Disease Clinical Treatment Trials

A drug trial for Leigh disease patients with known molecular defects is in its early stages but looks promising. We recently enrolled one of our patients into this clinical trial, being run exclusively out of Stanford University for the time being.

Leigh disease is typically a very aggressive form of mitochondrial disease caused by both nuclear and mtDNA gene mutations. The disorder results in specific brain lesions and severe neurological problems for affected individuals. To date, treatment for this and other mito disorders has been primarily symptomatic and preventative.

For additional information or for consideration of being enrolled in the trial please contact us for more information.

PDH Deficiency and Dichloroacetate Therapy

Dr. Kendall has been invited to be a clinical collaborator and to sit on a NIH funded study group to develop a study design for a phase 3 trial of DCA treatment of PDH deficiency. Phase 3 trials are designed to determine how effective a given drug is in treating a specific disease when compared to standard or other therapies.

Pyruvate dehydrogenase deficiency (PDH) alters the body's ability to metabolism pyruvate, a compound generated primarily from glucose (sugar) breakdown, resulting in its conversion to lactate. Lactate or Lactic acid can then accumulate and overwhelm the body's ability to buffer it causing metabolic acidosis along with other clinical problems. PDH deficiency, a type of energy disorder, is one of the most common causes of congenital lactic acidosis with over 90% of cases being due to an alternation in the E1 alpha subunit of the enzyme. Dichloroacetate stimulates PDH enzyme activity theoretically causing a drop in lactate accumulation and resolution of associated acidosis. Too few patients with PDH deficiency have participated in controlled trials of DCA to fully understand the drug's impact. However, a review of 46 patients with PDH treated subacutely or chronically with oral DCA found that the drug

exerted a lactate-lowering effect, was generally well tolerated despite some of the reported side effects (reversible liver and nerve toxicity) and improved clinical measures in most patients.

VMP will be recruiting patients for this University of Florida based trial once it is commenced. For more information please contact us.