Summary - Mitochondrial Medicine Society Update - 2016

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Dr. Goldstein is very active in the mitochondrial disease community: clinically, with research, and as a leader in the field. She is involved in both North America Mitochondrial Disease Consortium (NAMDC) and UMDF's registries and encourages all patients to register. For more information on the NAMDC patient registry click: http://www.rarediseasesnetwork.org/cms/namdc/Get-Involved/Contact-Registry.

UMDF is actively recruiting participants for their registry as well. Research is also important to the Mito community. MitoAction is doing a great job at keeping the community updated about all ongoing clinical trials targeting the mitochondrial disease population. Pittsburgh is a site for the Reata Pharmaceuticals trial as well as the Stealth BioTherapeutics trial, which both target adults with mitochondrial myopathy. Both companies are beginning to look at trials for the pediatric population, and there are several other companies who are doing trials, such as Raptor. Even more companies are developing protocols and designing future trials for mitochondrial disease patients.

The Mitochondrial Medicine Society (MMS) was founded in 2000 with the purpose of advancing education, research, and global collaboration in clinical mitochondrial medicine. Founded by Dr. Bob Naviaux and Dr. Richard Haas at the University of California at San Diego, the society represents an international group of physicians, researchers, and clinicians working toward better diagnosis, management, and treatment of mitochondrial disease

(http://www.mitosoc.org). The MMS website is an excellent repository of published papers and information, and is a wonderful resource to pass on to primary and other treating physicians. The website features a worldwide map with symbols denoting physicians who have identified themselves as specializing in mitochondrial disease (yellow squares), mitochondrial support groups (red balloons), mitochondrial medicine networks (black dots), NAMDC sites (purple stars), and patient registries around the globe (green diamonds) (http://www.mitosoc.org/clinics/). MMS clinicians develop and implement projects that are extremely important to the mitochondrial disease patient community. Under Dr. Goldstein's leadership, MMS is tackling organ transplantation, stroke protocol for MELAS, standards of care, and centers for excellence for mitochondrial disease patients (slide 2).

MMS's Current Projects

A) Solid Organ Transplantation -- spearheaded by Dr. Parikh in Cleveland (slide 3). Dr. Parikh will present the poster to the Society for Inherited Metabolic Disorders (SIMD) this week in Florida and then will submit for journal publication. As clinicians, transplantation of organs in a Mito patient is a question often asked. The poster is titled "Solid Organ Transplantation in Mitochondrial Disease: Proceed with Caution" specifically to counter the thought held by many transplant physicians to not proceed at all when a Mito patient needs an organ. Proceed with caution is geared toward liver transplantation in the POLG population (Alpers-Huttnelocher syndrome), a well-known issue for the past decade.

Current literature is filled with documentation that Mito patients have poor outcomes after transplants but only in limited case reports and case series. Many doctors believe that Mito is a contraindication to organ transplantation. Whether or not the underlying disease impacts transplantation morbidity and mortality was unclear. Solid organ transplant cases of the heart, kidney, and liver in patients with a confirmed genetic mitochondrial diagnosis were collected and analyzed. 35 patients from 17 Mito centers including North America, UK, and Australia were studied. As expected, the POLG patients had the poorest outcomes post-transplant. For the rest of the results of this project, please stayed tuned for the upcoming publication which will be posted on the MMS website.

B) Stroke Protocol for MELAS Publication -- spearheaded by Dr. Koenig (slide 4). Many papers, especially from the Japanese group (Dr Koga), have published the use of arginine for stroke-like events, but literature to support the use was difficult to find. A stronger published document was needed in the United States for ERs and other clinicians. A stroke protocol is now published online in *JAMA Neurology* for stroke-like episodes in patients with mitochondrial disease (see also: http://www.ncbi.nlm.nih.gov/pubmed/26954033).

- MELAS patients have stroke-like episodes and recent advances in understanding the pathophysiology of these episodes have lead to improved treatment options.
- Evidence supports using a nitric oxide precursor, arginine, to both prevent and reduce the severity of strokes in patients with MELAS.
- Although more study is needed regarding the dosing and timing of arginine therapy, urgent administration of nitric oxide precursors in the ER for patients with MELAS is recommended.

Stroke Protocol:

- IV arginine 0.5 grams/kg/day x 3-5 days while patient has symptoms
- Maintenance -- PO arginine 0.3 grams/kg/day

C) Standards of Care for Mitochondrial Disease Patients (slide 5)

No standard of care for mitochondrial disease exists, meaning that each center may treat patients somewhat differently. Standards of care are being developed and eventually will be published so care becomes more consistent. This uniformity of care improves morbidity and mortality rates, and will better define what should be included in

the Centers of Excellence. Over 30 doctors are participating in this project, working in small groups to review known literature for a specific organ or system to create a summary. The Newcastle-upon-Tyne Group in England has agreed to help with this project, having already developed online guidelines.

* Recommendations on lab work and testing needed and how often.

* Separate recommendations for high-risk disease groups. For example, KSS patients are at risk for arrhythmia and may need stepped-up guidelines in that area.

* Timeline -- distribute completed reviews to each other by late summer and then review and prepare manuscript by early 2017.

* 20 areas of study have been created, and small groups of clinicians will research each area (slides 6-9), including:

- Anesthesia -- Guidelines already have been reviewed with recommendations published in the consensus statement (*Genetics in Medicine*, Dec. 2015) http://www.ncbi.nlm.nih.gov/pubmed/25503498.
- Audiology -- Sensorineural hearing loss and cochlear implants with guidelines on how often patients need to be screened and followed by audiology testing.
- Cardiac -- Cardiomyopathy, dysrhythmias, pacemaker placement, hypertension, and chest pain.
- Critical illness -- Endocrine worsening, especially adrenal insufficiency, acid-base status, worsening acid-base status, dysrhythmias in this setting, respiratory issues related to weakness, and more.
- Endocrine -- Thyroid and parathyroid issues, including calcium and vitamin D, adrenal issues, diabetes, short stature and growth hormone deficiency and short stature, and bone density issues, especially as it relates to non-ambulatory patients and osteoporosis.
- GI --- Liver disease, constipation, motility, nutrition, failure to thrive.
- Hematology -- Anemia and bone marrow failure.
- Immunologic
- Neurology -- Divided into 4 sections: epilepsy, migraine, and movement disorders.
- Myopathy, neuropathy, tone and movement disorders, including spasticity and dystonia.
- Developmental delay and learning disabilities.
- Stroke -- Already published.
- Orthopedic -- Focus on scoliosis.
- Ophthalmologic -- Retinal and optic nerve disease, ptosis, and ophthalmoplegia.
- Pregnancy -- Mitochondrial transfer therapy, metabolic stress of pregnancy on Mito patients, and other topics.
- Psychiatric -- Depression, anxiety, personality disorders, autism, and behavior issues.
- Pulmonology -- Central and obstructive apnea, respiratory insufficiency, and sleep-related issues.
- Renal/Acid Base -- Acidosis, renal tubular acidosis, glomerulonephritis.
- Surgical precautions -- Guidelines already published in consensus statement.

- Constitutional (fatigue, pain) -- fatigue, pain, weight management, and high-altitude travel.

D) Centers of Excellence (COE) (slide 10)
Feedback from the community is essential for this project. Today no COE, nor national guidelines for a COE, for mitochondrial disease exists.

- Create focus groups of patients, families, caregivers -- A “wish list” of what services, physicians are expected to be in a center. Focus groups will be live -- phone calls or family meetings.
- Input from Support Groups -- LHON, MitoAction, UMDF, etc. What do these groups who work so closely with the Mito community feel should be included in COE.
- Creation of Surveys -- Via email in order to reach even more people.
- Distribution of Surveys and Data Collection.
- Checklist of COE requirements -- To best serve the Mito community.
- Questionnaires collected from potential COE -- Many examples already in place with other organizations.
- Governing Board to check COE is following published standards of care and fulfilling requirements –Via questionnaires, site visits, and other methods.

Using cystic fibrosis as a model of the success of COEs, CF survival has increased 10-fold (slides 11-12) over past decades. Patient registries and the development of CF COEs have dramatically impacted the disease. Standards of care, homogeneity of care, and advances in medicine are a product of COEs. MMS would like to see survival rates patterns mimic those of CF over the past 50 years.