Summary - Mitochondrial Myopathy

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This presentation is restricted to mitochondrial myopathy because mitochondrial disease discussions often evolve into an overwhelming discussion of 10 or more organ systems. Focusing on this single aspect of mitochondrial disease keeps the content focused, in-depth, and manageable. The pharmaceutical industry focuses on specific mitochondrial disease models to get their drugs to market and have targeted myopathy as one of those models. The FDA process to get these drugs approved as well as some of the current clinical trials will also be reviewed.

What is Myopathy?

Myopathy is any muscle disorder whereby muscle fibers do not function normally, resulting in weakness, cramps, or stiffness, due to a primary process in the muscle. Myopathy is not a problem with the brain, nerves, tendons, or other structures. For example, a stroke can damage nerves, causing muscle weakness, but is not a primary problem with the muscles, so not a true myopathy. Loose tendons, which can be an issue with EDS, can also mimic myopathy, but is truly a tendon problem. Upon testing, the muscle tissue is normal. True myopathy can be associated with many disease processes, not exclusively mitochondrial disease (slide 3). Myopathy involving skeletal muscles generally results in weakness. Any and/or all of the three types of muscle tissue found in the human body can have myopathy:

- Skeletal -- muscle around the bones and also around the eyes.
- Cardiac -- muscle of the heart.
- Smooth -- muscle lining the intestines, GI tract, bladder, and blood vessels.

Myopathies can be inherited or acquired. The World Health Organization (WHO) has recently re-coded diagnoses for the ICD-10 codes (slide 4). Acquired myopathies include drug-induced myopathies from glucocorticoids, alcohol, or other toxic agents and other disease processes such as the myositis group of diseases.

Main Causes of Myopathies in Adults

In practice, myopathies often have nothing to do with the mitochondrial, but are acquired or due to another cause (slide 5), including:

- **Inflammatory** (common cause) -- Polymyositis, inclusion body myositis, including cancer that causes inflammation within the body.
- **Endocrine** -- Thyroid, parathyroid, adrenal, pituitary. Hyper/hypothyroidism is the most common cause of myopathy. Therapeutic levels of thyroid hormones are needed for mitochondria to function normally. Thyroid disease looks just like a mitochondrial myopathy, but is easily cured by treating the thyroid disease. 1 percent to 2 percent of all women have hypothyroidism. The medication Synthroid restores normal thyroid hormone levels, causing the myopathy to disappear.

- **Toxicity** -- Alcohol, steroids, narcotics, colchicine, chloroquine. In the US, alcoholic myopathy is uncommon because even those who consume large amounts of alcohol tend to maintain proper nutrition. Steroids and other prescription medications, however, do cause myopathy.
- **Critical illness** -- Can be due to excessive bed rest and is treated effectively with physical therapy. Muscle atrophy from disuse does cause mitochondrial dysfunction in that tissue, but is not a primary mitochondrial disease.
- **Metabolic** -- Includes mitochondrial disease, but also specific cancers cause **paraneoplastic** syndrome whereby the cancer cells excrete antibodies that attack the muscles or the nerves, causing myopathy. The cancers can be tiny and even undetectable, but the myopathy, and then the antibody found in the blood, indicates that this patient will develop cancer in the lungs or breast in time.

Laboratory Evaluation
Testing can vary between physicians, but typically includes (slides 6-7):

- CBC -- common test for white and red blood cells.
- CMP -- common metabolic profile including glucose, electrolytes, kidney. and liver function.
- Free T4 & TSH -- thyroid levels.
- Fasting, early morning cortisol -- naturally occurring body steroid.
- ESR, C-reactive protein, ultra sensitive C-reactive protein -- inflammatory markers.
- Vitamin B12 level & methylmalonic acid -- deficiencies can affect brain and spinal cord issues that mimic myopathy.
- CK -- muscle enzyme.
- Fasting glucose, 2-hour glucose tolerance test and/or HbA1c -- new report finds that one-third of adult Europeans are diabetic or pre-diabetic. Diabetes is extremely common and can create symptoms that look like a myopathy.
- Paraneoplastic Panel, SPEP, urine monoclonal proteins/M-protein -- looking for pre-symptomatic cancers.
- Polysomnogram -- even without complaints of snoring or sleep apnea, which are often associated with symptoms that mimic a myopathy.
- Polysomnogram and multiple sleep latency test for excessive daytime sleepiness.

Mitochondrial Myopathy (MM) (G71.3 - ICD 10 code)
Mitochondrial myopathy is muscle dysfunction due to defects in the mitochondria (slide 8). One of the diagnostic problems with mitochondrial myopathy is the evolution of the testing leading to diagnosis. The diagnosis is only as good as the best testing available at the time. From the 1960s through the 1980s, the best test available was the muscle biopsy. Testing has become more refined and now utilizes genetic testing as the gold standard.

Many myopathies will result in:

- Ragged Red Fibers – This occurs with MMs, but also with many other muscle disorders such as Duchenne's Muscular Dystrophy, congenital myopathies, etc. Ragged red fibers simply indicate that there is a problem with the muscle but are not at all diagnostic for MM. Even in a healthy population, adults over age 50 have an average of 2 percent ragged red fibers within their tissues.

- Decrease Electron Transport Chain (ETC) function -- Early 1980s-developed technology to examine the ETC enzymology, which is uniquely mitochondrial in function. Until just a few years ago, defects in the ETC were thought to clearly indicate and were, therefore, diagnostic for mitochondrial disease. Research over the past 10 years has discovered that many factors affect the ETC, many of which have nothing to do with mitochondria. Although the muscle biopsy and ECT enzymology were the gold standard for diagnosis 10-15 years ago, these tests are no longer enough to accurately diagnosis primary mitochondrial disease.

- Exact same weakness found in mitochondrial myopathies. Very few findings on physical exam are unique to mitochondrial disease. Even ophthalmoplegia (droopy eyelids and eyes not moving up, down, left, and right properly) was once thought to be unique to mitochondrial disease, but now other disorders mimic the same finding, such as myotonic dystrophy, an oral-pharyngeal muscular dystrophy, as well as other disorders.

Mitochondrial proliferation and giant mitochondria on biopsy (slides 9-10) were thought to be diagnostic for mitochondrial disease in this patient in 1996. Testing today would have included genetic testing, which would not have indicated mitochondrial disease in this child.

Genetic Testing for Mitochondrial Disease (slide 11)

- Mitochondrial DNA select point mutation testing -- preferred sites: muscle, cheek, swab/salvia, urine sediment, but can be done on blood. Cost and turnaround time have improved greatly since testing began in 2000.
- Mitochondrial DNA whole genome testing -- preferred sites: muscle, cheek, swab/salvia, urine sediment, but can be done on blood. The number of genes tied to mitochondrial disease continues to rise.
- Long-range polymerase chain reaction or Southern blot -- preferred site: muscle, but can use cheek, swab/salvia, urine sediment. Blood is not reliable.
- Sequencing and deletion/duplication testing of specific nuclear genes or panel of genes. In 2006, single gene testing became available.
- Massive parallel sequencing (NextGen) of large numbers of nuclear genes, including all known mitochondrial-targeted genes, look-alike disease genes, or whole exome, along with high-density single nucleotide polymorphism micro-array. Labs now offer 1,100 gene sequencing for about $6,000 with a turnaround time of weeks instead of months.

Many patients who had a previous diagnosis of mitochondrial disease based on ETC enzymology, biopsies, etc., are not found to have a mutation supporting that mitochondrial disease diagnosis, frustrating both the treating physician and the patient.

Many physicians still do not know about Mito and patients remain undiagnosed. Most patients have muscle weakness AND something else -- seizures, GI issues, hearing or vision losses, stroke-like events, and so on. Even if the treating doctor knows the disease, trying to prove the diagnosis is cumbersome, expensive, and often without insurance company support to defray the costs. Some patients have the genetic testing, but a mutation is not found even though so strongly suspected. Therefore, patients remain in a suspected mitochondrial category rather than getting that genomic based diagnosis. Both clinically and genetically diagnosed patients can have mitochondrial myopathy.

Treatment for Myopathy
Some myopathies are treatable and even curable (slide 12)! With mitochondrial disease, the myopathy is not curable, but treatment does lend supportive care. Physical therapy and occupational therapy teach how to adapt to the disability to improve function. Assistive devices and bracing can be helpful. CoQ10 deficiencies, carnitine deficiencies, and creatine defects offer examples of rare, but truly responsive case.

Clinical Trial Work
Trials take a great deal of time and effort (slides 13-15). Many factors unique to mitochondrial disease render clinical trials problematic. For contrast, cystic fibrosis has mutation in one gene primarily affecting the lung and digestive enzymes in a predictable manner. Setting up a clinical trial would be straightforward. Conversely, mitochondrial disease has great variable on many fronts:

- Hundreds of distinct disorders, including 37 mtDNA genes and 1500+ nDNA genes, each with varied treatment needs.
- Age of onset -- birth to 60+ years, spanning the entire lifespan.
- Major organ systems affected -- brain, muscle, nerve, heart, liver pancreas, eye, ear, kidney. The FDA wants to know what is statically and specifically affected. With blood pressure studies, for example, blood pressure is the only parameter that need be studied to show therapeutic improvement. With mitochondrial disease, researchers want to know the affect on the heart, muscle, fatigue, cognition, and many other factors, rending reaching clinical significance nearly impossible with small sample sizes. One or two endpoints, therefore, can only be studied at a time.
- Therapies -- Symptomatic care, exercise, vitamins seldom improve function well enough to regain a normal life.

Goals of therapy and how to measure treatment success (slides 16-17) are also specific to the many body systems affected by mitochondrial disease. For example, decreasing seizures, documented by a seizure count, would be a clinical trial outcome that the FDA would embrace in terms of a successful therapeutic endpoint. Keep in mind, that if an endpoint is seizure count, but the study finds any significant improvement in muscle strength, even though the seizure count remains the same, the study is considered a

failure as the predicted outcome was not met. The drug company would have to then sponsor another study to look at muscle strength as the outcome for the FDA to approve the drug. Knowing what a study drug may be capable of impacting can be helpful prior to study design. Drugs under FDA investigation are listed on slide 21.

Rationale for Vitamin and Co-factor Therapy (slides 18-20)

- Stimulate poorly functioning enzymes
- Antioxidant activity to reduce oxidative stress
- Alternate energy sources
- Improved muscle bulk
- Scavenge free-fatty acids and poisonous organic acids
- Bypass blocked components of the electron transport chain

Therapies for mitochondrial disease have evolved over time with the list actually growing smaller over time. For example, Dr. Cohen has recently dropped his use of Levocarnitine due to potential toxicity to the heart and in light of recent studies documenting no significant improvement with use. Long lists of supplements are expensive, difficult to consume, especially for a child, and physicians were viewed as vitamin pushers. Dr. Cohen favors the use of Alpha Lipoic Acid, Arginine/Citrulline, CoQ10, Riboflavin, Creatine Monohydrate, and Folinic Acid with his typical treatment plan outlined on slide 22.

Clinical Trials

Randomized clinical trials include placebo controlled, crossover design, double-blind trials (slides 23- 29). The FDA is looking for functional improvement using verified tools and scales so that improvement is measurable and not subjective. The FDA also seeks fewer adverse events (fewer hospitalizations, for example) and/or an altered natural history of a disease. The FDA is not looking for lower lactic acid levels, improved brain MRIs, reduced ragged red fiber counts, improved ETC enzymology, nor normalization of abnormal organic acids. With help of the NIH, a list of common data elements for mitochondrial disease has been created and verified as proven endpoints, which can be used in mitochondrial trials (https://commondataelements.ninds.nih.gov/MITO.aspx#tab=Data_Standards).

Dr. Cohen and his team put together a large toolbox of proven measuring tools for the neurological assessment of drug efficacy, citing the Berry-Albright Dystonia Scale as an example that might be used to evaluate a therapy for Leigh's Syndrome. Cognitive development, vision, language development, muscle strength and endurance, lab values, and other tools are now available for use in trials. The FDA prefers simple endpoints such as adverse events counts, quality of life scales, 6-minute walk tests, and so on.

Phase 3 Clinical Trials have to excite patients and investigators, be financially viable, and carry the perception that getting better will be worth the travel for the patient (slide 30). Phase 3 trials must have a placebo-receiving control group, be randomized (flip of the coin as to who is in which arm), and be doubled-blinded (neither the patient nor

treating staff knows which therapy or if placebo has been given). Ultimately, the study should have crossover at a designated time (patients who received placebo switch arms to then receive study drug and vice versa).

EPI-743 (Edison Pharma) (slides 31-33)

- First drug to trial for mitochondrial disease (2012), specifically Leigh Syndrome.
- Four study sites: Akron, Baylor, Stanford, and Seattle.
- 36 patients, randomized to drug at 5 mb/kg/day or 15 mg/kg/day vs. Placebo (1:1) for 6 months
- All patients on placebo get drug at 6 months at 15 mg/kg/day and others on drug continue at their current dose.
- Primary outcome measures were Newcastle Pediatric Mitochondrial Disease Scale (NPMDS) Sections 1-3, adverse event count.
- Secondary outcomes were measured in a number of ways, including neuromuscular function, respiratory function, morbidity, mortality, and others.

RP-103 (Raptor Pharma) (slide 34)

- Study children with inherited mitochondrial disease.
- Open label, meaning all study participants receive the drug.
- Dose escalation to see how much drug would be tolerated.
- Similar endpoint to the EPI-743 study.
- Purpose was not for FDA approval, but rather to assess dose, safety, efficacy, and tolerability.

Bendavia - (Stealth Biotherapeutics) (slide 36-43)

- Mitochondrial Myopathy Trial.
- 4 amino acid composition.
- Targets cardiolipin, a critical part of the inner mitochondrial membrane, which becomes misshapen and dysfunctional with mitochondrial disease.
- Forms a net over cardiolipin, helping to stabilize and retain cardiolipin's shape, promoting bioenergetic efficiency.
- Kidneys were purposely damaged by tying off blood flow to the point of near death. Blood flow was reestablished and Bendavia also administered, and normal kidney function was established.
- Bendavia for Diabetic Retinopathy (called **Ocuvia**) restored visual function in mouse model of mitochondrial dysfunction.
- Phase I/II Clinical trial -- Phase I (looking for the best dose) and Phase II (efficacy).
    - Boston, San Diego, Pittsburg, and Akron study sites.
    - Ages 16-65 years.
    - Three cohorts of 12 patient with genetically confirmed mitochondrial myopathy receive either placebo (3/12) or drug (9/12) at 0.01, 0.1, or 0.25 mg/kg/hour x 2 hours for 5 doses.
    - Primary endpoints -- safety and tolerability of ascending doses.
    - Secondary endpoints – 6-minute walk test, cardiopulmonary exercise testing, pharmacokinetic and pharmacodynamic data.

- Exploratory endpoints -- plasma, blood, and urine biomarkers and other functional measurements.

RTA-408 (Reata) (slides 44-50)

- Mitochondrial Myopathy Trials.
- Synthetic triterpenoid -- broad anticancer and anti-inflammatory action by increasing Nrf2 in the body and inhibiting NF kB (nuclear factor Kappa-light-chain enhancer of activated B cells).
- Thought to improve mitochondrial function by increasing mitochondrial respiration and biogenesis (produce more, healthy mitochondria), and has potent antioxidant capacity.
- MOTOR Study-- Phase 2 study of safety, efficacy, and pharmacodynamics of RTA 408 in the treatment of Mitochondrial Myopathy.
    - Sites -- Copenhagen (Denmark), UCLA, Mass General Hospital, Akron Children's, Children's Hospital of Philadelphia, University of Pittsburg, Baylor (Houston), University of Texas, Institute for Exercise and Environmental Medicine (Dallas).
    - Inclusion Criterion -- Mitochondrial myopathy, ages 18-75, No changes in exercise, have the ability to complete maximal exercise testing, but a peak workload of <1.5 Watt/k.
    - Exclusion Criterion -- Uncontrolled diabetes, significant heart disease, abnormal basic labs and not be on list of several dozen drugs that activate the P450 2C8 or 3A4 systems.
    - 12-week study.
    - Primary outcome measures -- measure change of peak workload in watts/kg during exercise testing.
    - Secondary outcome measure -- measure the change in the distance walked in during the 6-minute walk test.

Once approved by the FDA, study drugs would become available to a greater audience, both those with genetically confirmed and clinical diagnoses. The mitochondrial myopathy focused drugs would also be opened up for other diseases, such as diabetes.

The process of FDA approval has been slowed because it has taken much longer than expected to enroll just 36 patients. The Mito community is encouraged to help make these drugs available to the wider population by enrolling in the studies. Patients have an opportunity to change further generations' options for treatment.

Additional Reading

National Institute of Health - NINDS Mitochondrial Myopathy Information Page.

MDA - Mitochondrial Myopathies.

Clinical Trials:

Clinical Trials, Studies, and Registries for Mitochondrial Disease.

Bendavia

Bendavia
Stealth BT mitochondrial myopathy trial
A Study Investigating the Safety, Tolerability, and Efficacy of MTP-131 **(Bendavia)**for the Treatment of Mitochondrial Myopathy (MMPOWER).

RTA 408
RTA 408 Capsules in Patients With Mitochondrial Myopathy - MOTOR.

RP103
Open-Label, Dose-Escalating Study to Assess Safety, Tolerability, Efficacy, PK and PD of **RP103** in Children With Inherited Mitochondrial Disease (RP103-MITO-001).

A Long-Term Extension Study of RP103-MITO-001 to Assess RP103 in Children With Inherited Mitochondrial Disease.

EPI-743
Leighs Syndrome Trial.
Long-Term Safety and Efficacy Evaluation of EPI-743 in Children With Leigh Syndrome.

EPI-743 for Metabolism or Mitochondrial Disorders.