

## Summary - Mito Medical Society Publications 2014-2015 Dr. Sumit Parikh

*Director of the Cleveland Clinic Neurogenetics, Metabolic, and Mitochondrial Disease Program*

*Past President of the Mitochondrial Medicine Society*

The Mitochondrial Medical Society (MMS) is a professional organization composed of physicians, residents, nurse practitioners, nurses, and other medical professionals who all share an interest in mitochondrial medicine. MMS is a relatively young organization - about 15 years old, and a fairly small organization, but in the past 5 years has been quite active. Each MMS president is tasked with coming up with an interest focus for the group, exploring a new topic in the world of mitochondrial medicine. Dr. Parikh's focus of interest during his MMS presidency (2012-2015) centered around the fact that patients could go to five different centers for care and receive two or three different diagnoses. Clinicians did not always agree on whether a patient had a primary mitochondrial disease. Questions raised were: Do discrepancies exist in mitochondrial disease diagnosis and treatment, and, if so, what can be done to eliminate these discrepancies?

These questions brought about the **The North American Mitochondrial Disease Survey (2012) and the Consensus Project (2013)** to both survey and find consensus on the practice of mitochondrial medicine (slide 1).

**The North American Mitochondrial Disease Survey & Consensus Project** asked if a consensus exists in mitochondrial medicine practice in North America and questioned if a need for consensus criteria exists (slide 2). Invitations were sent to a variety of neurologic and metabolic societies known to practice mitochondrial medicine. Of the 37 initial volunteers, 32 physicians and nurse practitioners completed all the surveys to give complete data (slide 3), capturing 80-90% of mitochondrial centers across North America, including two individuals in Canada (slide 4). A variety of specialists who run mitochondrial clinics were represented: biochemical geneticists, neurometabolism specialists, neurologists, clinical geneticists, and neurogeneticists, (slide 5). A variety of questions were posed and the responses elicited interesting information.

### **Results Part One - Diagnostic process:**

- 81% of the physicians surveyed, while trained in pediatrics, saw both children and adults who had mitochondrial disease (slide 6).
- Half (50%) of new patient consults take 60-90 minutes. Although 40-60 minutes are allotted per patient visit, Mito patients tended to require significantly more time, typically 60-120 minutes. Mito patients also require long pre-appointment preparation time, presenting with large volumes of medical records that need review. Most doctors are given 10-20 minutes to see a followup patient, but Mito patients require 30-50 minutes. The survey demonstrated that patients with mitochondrial disorders required much more of a physician's time than administrations currently allot for patient care (slides 7-9).

- Nearly all clinicians (95%) prescreen patients by way of medical records and 50% cancel the appointment if no records are provided. Medical records contain valuable information, such as previous test results, changes over time, treatments that have helped and it's just not fair for the physician to not have access to that information prior to the appointment.
- Because the medical record system can be cumbersome and it may be difficult to get needed records after the visits, patients should keep records (data, test results, blood urine, scans, etc.) in a physical binder or a virtual binder (pdf or thumb drive), bringing the binder to all appointments. Physician notes are not essential to obtain.
- How clinicians order, interpret, and perceive lab tests, genetic tests, and other tests is not consistent (slides 10-11). Some lab results are much better than others and give true positive results, while others may not be so definitive. Important data versus non-essential data is often not separated out. Laboratories were then queried, and a supplemental report was written: Perception of various laboratories that perform mitochondrial testing (slide 12). Patients can read this report to see how well the various companies perform.
- Diagnostic criteria for Mito, including muscle biopsies, is also variable among those surveyed (slides 13-14). About 60% use specific diagnostic criteria for Mito, while 40% use "gut" feelings to make a final determination, thus noting the variability of how strictly criteria are used to come up with a diagnosis. In the 1980s-early 2000s, patients with lab findings and/or muscle biopsies indicating that mitochondria were not working properly often received a Mito diagnosis. Recent scientific advances and gene mapping, however, proved that mitochondrial dysfunction was actually caused by other disease conditions. As genetics improved, about half the patients shown to have been mislabeled with primary mitochondrial disease. Many patients were thrown for a loop when the Mito diagnosis was removed, but in fact, with a more accurate diagnosis, better care options become available. Despite recent genetic advances, however, the survey reported that only about 37% of clinicians reported requiring a genetic diagnosis to diagnosis primary mitochondrial disease (slide 15).
- All clinicians (100%) believe in secondary mitochondrial dysfunction (slide 16). Mitochondrial dysfunction means that a patient does not have mitochondrial disease, a progressive and degenerative disorder, but rather has a different disease process, toxin, or other mitochondria stressor that hampers mitochondrial function. Most clinicians (66%) were unsure of how to treat mitochondrial dysfunction (slide 16).
- Primary mitochondrial disease means that there is a genetic mutation or defect causing mitochondria to be made or work improperly. The mutation may have pathogenic (harmful) results and cause disease or may be benign, causing no problems. All the diagnostic tests, like lactate levels or enzyme studies in blood, urine, and muscle biopsies, are tests of function, targeting if the mitochondria are working. These tests do not tell us why the mitochondria are not working. Is the structure of the factory blueprint faulty (primary disease), or is a hurricane preventing the factory from working properly (secondary dysfunction)? The lab results for primary and secondary Mito will look identical.
- Both Alzheimer's and diabetes have mitochondrial dysfunction but we are not sure yet how to treat the mitochondrial aspects of these diseases.

- Autism - unsure whether a primary or secondary mitochondrial disorder (slide 17). 78% question what "traditional autism" looks like in comparison to Mito-autism.
- Muscle biopsies can yield both false positive and false negative results, with differences of opinions among doctors as to how to interpret results (slide 18-19).
- Skin biopsies also have false negative and false positive results (slide 20) with a good deal of skew with the perception of these results among clinicians.

### **Results Part Two - Treating Mitochondrial Disease** (slides 20-31)

- Although similarities are reported, little consensus exists among clinicians about how to treat mitochondrial disease. There are overall similarities but there was a general lack of consensus with too many clinicians "doing their own thing." Although agreement is reported regarding needing more time with Mito patients, how clinics are structured, which labs are better, and the need for both more time with patients and for more adult Mito specialists, great variability about how to interpret tests, when to diagnosis mitochondrial disease, and how to treat patients persist (slide 33).
- Almost every clinician has their own version of the what to include in the Mito cocktail, and at what dose. The only consensus is the use of CoQ10. About 50% of clinicians start patients off with a full cocktail while the other 50% start with just one individual supplement (slide 22-23). Treatments recommended by those surveyed as well as the recommended preventative screenings also vary (slides 24-31). This disparity proves to be confusing to families who may seek a second opinion or need to change providers, but then have to face very different approaches, never quite knowing which treatment plan is most effective.
- Most clinicians are involved in increasing awareness and knowledge of mitochondrial disease (slide 31).

### **Methods to Develop Consensus** (slides 33-35)

A search for scientific backing so that consensus can be reached by practitioners is a vital role of medicine. Methods to find **consensus criteria** include (slide 36):

- Evidenced-based or science-backed practice, and keep in mind that science changes! Utilizing the Oxford Basis of Evidence (slide 37) may not work for mitochondrial disease because a high level of science does not exist yet.
- Eminence-based practice - relying on intelligent and experienced clinicians.
- Committee-based - may rely on who has the strongest voice or personality, which is not true consensus.
- NIH style consensus - allowing non-experts to decide.
- Individual approach - the current state of mitochondrial disease practice, relying on individual clinician decisions.
- The **Delphi Method** (Slides 38-41) - useful when some science is available, but not enough to use the Oxford method and is often used with rare diseases. This method pools the resources of intelligent experienced people to find consensus, but does not use the voices of a few clinicians to control the decisions. The Delphi method was used to try to find consensus among Mito clinicians. Clinician subgroups were given topics and data to review and then they were to submit summaries. Larger groups read the summary, looked at surveys and looked to see if there was consensus (85% or more agreement). If there was no consensus, then the process was to show

everyone the data and go back and resurvey to see if the extended reading and discussions with other clinicians brought care closer to a consensus. In some cases, there may not be enough knowledge about the issue at hand, so more research is needed. This method is not completely based in science and there may be some bias involved as the Mito community is relatively small, but is less personality driven and is quantifiable.

**The consensus statement from the Mitochondrial Medical Society is available (slide 45)**

at <http://www.nature.com/gim/journal/vaop/ncurrent/abs/gim2014177a.html>. The consensus groups included different specialties, such as anesthesia, genetics, biochemical genetics, neurology, and nurse practitioners (slide 42-43).

**Consensus criteria (Slide 46):**

- Biochemical testing in blood, urine & spinal fluid
- Genetic testing
- Pathology & biochemical testing of tissue
- Neuroimaging
- Treatment of acute stroke
- Exercise
- Anesthesia
- Treatment during illness
- Treatment with vitamins and xenobiotics
- Specific recommendations for diagnosis, DNA, tissue collection and pathology, stroke-like episodes, exercise, anesthesia, illness, vitamin and xenobiotic use can be found in the article referenced above and are also cut and paste into the slides (47-54).

Certainly, clinicians who find that certain treatments work for their patients should not stop such treatments. Formal scientific evidence is not strong enough yet to recommend certain treatments for all patients, which does not mean that current treatment is not effective. Preventative Care Guidelines have not been addressed by the MMS (how often EKGs, Echos, blood work, hearing screens, etc.), but fortunately the United Kingdom Newcastle Group is working on this area of science in mitochondrial disease.

**Summary** - consensus building regarding both diagnosis and treatment of mitochondrial disease will continue and will benefit all patients. This study has generated criteria for generalists to begin the process of learning about mitochondrial disease. Insurance companies also need to know the standards of care for mitochondrial disease to have cause to cover testing and treatment. More can be found at [mitosoc.org](http://mitosoc.org) - the website for the Mitochondrial Medicine Society.

**Additional Readings:**

[mitosoc.org](http://mitosoc.org)

<http://www.nature.com/gim/journal/vaop/ncurrent/abs/gim2014177a.html>

<http://www.ncbi.nlm.nih.gov/pubmed/25503498>