Primary Mitochondrial Myopathy Research: Neurologists Understanding of Primary Mitochondrial Myopathies in Their Patients

Mann K[1], Stanley L[2], Wall T[3], DiMatteo M[3]

[1]MitoAction, Boston, MA 02109, [2]Foundation for Mitochondrial Medicine, Atlanta, GA 30327, [3]Stealth BioTherapeutics, Newton, MA 02466

INTRODUCTION

- The likelihood of developing significant primary mitochondrial disease (PMD) in the overall population is estimated to be 1 in 5,000[1]
  - Worldwide statistics may vary because some patients with primary mitochondrial myopathies (PMMs) develop mild, undetectable symptoms
- The overall awareness of PMD has increased over the past 25 years, although clinician knowledge remains suboptimal[2]
- Evidence-based clinical protocols are the preferred method for developing diagnostic and medical management recommendations; however, there are currently insufficient data in PMD[2-3]
- Patients with PMM are not diagnosed in a timely manner and have difficulty reaching the appropriate specialist to manage their neuromuscular symptoms[4]
- Patients with PMM often see multiple clinicians and initially consult a primary care physician; however, 55% of these patients receive their diagnosis from a neurologist[4]

OBJECTIVE

To understand how the lives of PMM patients with neuromuscular disease manifestations can be positively impacted by improvements in their management and journey through the healthcare system by increasing understanding of the neurologist's practice type/focus, knowledge base, and experience with PMMs

METHODS

- Respondents were recruited and screened via criteria designed to determine if the study was relevant to their clinical practice
- Qualitative Research included:
  - Up-front questionnaire completed prior to interviews (**Figure 1**)
  - One-on-one highly qualitative interviews were 1 hour in duration
  - Web-assisted telephone interviews were conducted

Figure 1. Up-front Questionnaire

Up-front Questionnaire

1. Overall, about how many patients do you see per month (existing and new) _____#
   a. Out of 100%, what % of your patients fall into the following age ranges:
      i. Under 16 _____%
      ii. 16-21 _____%
      iii. 22-50 _____%
      iv. 51+ _____%
      100%
2. Of the number in Q1, how many have some type of neuromuscular/neurodegenerative or movement disorder? _____#
   a. Over the past 2 years, has that number (circle one)
      i. Increased
      ii. Decreased
      iii. Stayed the same
3. Types of movement disorders managed (Place an 'x' in the appropriate box to show frequency of management):

Movement Disorders and Frequency of Management			
Disorder	**Routinely**	**Occasionally**	**Never**
Tremors			
Parkinsonism			
Dyskinesia			
Dystonia			
Ataxia			
Restless Leg Syndrome			
Other: Specify			

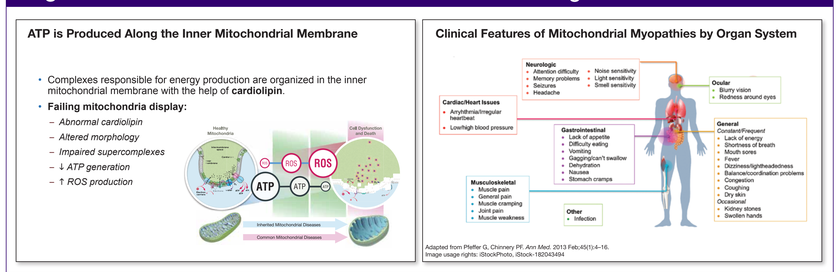
4. Types of Neuromuscular Disorders managed (Place an 'x' in the appropriate box to show frequency of management)

Disorders and Frequency of Management			
Disorder	**Routinely**	**Occasionally**	**Never**
Amyotrophic lateral sclerosis (ALS) or Lou Gehrig's Disease			
Charcot-Marie-Tooth (CMT) disease and other inherited neuropathies			
Muscular Dystrophies			
Myasthenia Gravis (MG)			
Myopathies			
Peripheral Neuropathies			
Neuromuscular – General			
Other – Specify			

THANK YOU

- Primary goals were to obtain an understanding about neurologists' practice type and focus, including areas of specialization and patient types, and to measure knowledge of PMM and experience with PMM patients
- Neurologists were asked about patient characteristics, areas of specialization, and diagnostic measures used to gain a better understanding of their practice type and focus (**Figure 1**)
- To measure the neurologists' knowledge of PMD and experience with PMM patients, neurologists answered questions such as:
  - Do you treat patients with PMD?
  - How is PMD diagnosed in your practice and by whom?
- Neurologists were asked to rate their knowledge of PMM based on a scale of 1 (no awareness at all) to 7 (high degree of awareness)
  - After initially rating their knowledge, the neurologists were shown a primer that detailed PMM symptoms and impact on organ systems, along with prevalence data (**Figure 2**)

Figure 2: Select Sections of the PMM Primer for Neurologists



- After the neurologists reviewed the primer, they were asked again to discuss their knowledge of PMM and discuss any gaps in knowledge based on the information

RESULTS

Neurologists' Practice Type and Focus

- Qualitative Research included interviews of neurologists (N=19) representing various areas of training and specification, practice settings, and number of patients seen per month (**Table 1**)

Table 1. Neurologist Practice Characteristics (N=19)

Type of Interview	Sample of Neurologists	Clinical Practice Setting	Number of Patients Seen per Month
One-on-one in-person interview	n=8 neurologists (various areas of training and specialization)	4 in university hospital setting 4 in private practice	~230 (range 150 to 400)
One-on-one web-assisted telephone interview	n=11 neurologists (8 neurologists specializing in neuromuscular disorders and 3 neurology generalists)	4 neuromuscular neurologists in hospital setting 4 neuromuscular neurologists in private practice 3 general neurologists in private practice	~250 (range 30 to 350)

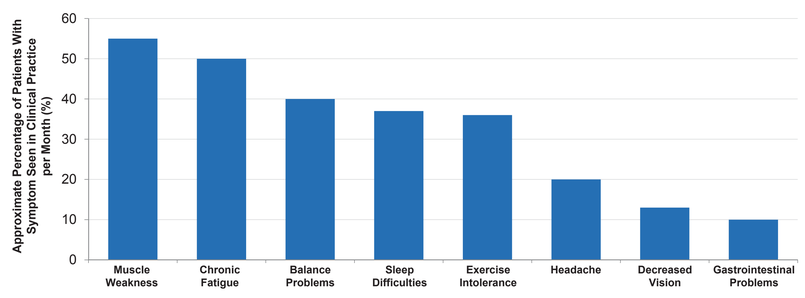
- Neuromuscular disorder neurologists reported seeing a greater number of neuromuscular patients per month, whether in a hospital or private practice setting
  - In the in-person interviews, neurologists reported an average of 30% of the patients in their practice had some type of neuromuscular disorder (range 15% to 80%)
  - In the telephone interviews, neurologists in both hospital and private practice reported seeing ~100 neuromuscular disorder patients per month (range 75 to 140)
- Neurologists identified the specific neurodegenerative and neuromuscular conditions they manage in clinical practice (**Table 2**)
  - Amyotrophic lateral sclerosis, myasthenia gravis, muscular dystrophy, neuropathies, and myopathies were reported as being the most common

Table 2. Neurodegenerative and Neuromuscular Conditions Treated by Neurologists in Clinical Practice

Neurodegenerative Conditions Managed in Clinical Practice	Neuromuscular Conditions Managed in Clinical Practice
Alzheimer's disease	Amyotrophic lateral sclerosis
Cognitive decline (for example, broader/dementia, vascular, cognitive, epilepsy)	Charcot-Marie-Tooth disease
Friedreich ataxia	Multiple sclerosis
Huntington's disease	Muscular dystrophy
Lewy Body disease	Myasthenia gravis
Nerve cell disease	Myopathy
Parkinson's disease	Myositis, including polymyositis and dermatomyositis
Spinal muscular atrophy	Peripheral neuropathy

- Neurologists reported the most commonly seen symptoms in clinical practice, which included muscle weakness, chronic fatigue, balance problems, and exercise intolerance (**Figure 3**)
  - Estimates of the percentage of common symptoms were similar for practice type and for general and neuromuscular neurologists

Figure 3: Symptoms Commonly Seen by Neuromuscular Neurologists in Clinical Practice Information



- Three of the 8 (37.5%) neurologists in the in-person interviews reported treating patients diagnosed with PMD
  - These patients with PMD are slow, rigid, had loss of balance, and other concomitant conditions, such as insomnia, constipation, gastrointestinal issues, ataxia, cardiac disease, and hearing difficulty
  - One patient was diagnosed through muscle biopsy
  - Two patients were diagnosed with both genetic testing and a muscle biopsy

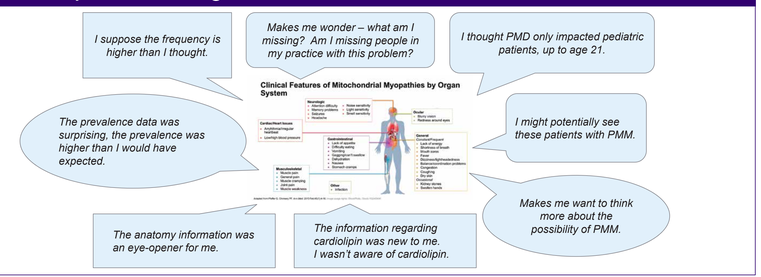
Diagnostic Measures

- Neurologists described a similar procedure in assessing a new patient
  - Patient history
  - Physical examination
  - Routine blood and enzyme panels
  - Other possible testing to including computed tomography scan, DaTscan, and electromyography
- Neurologists rarely order muscle biopsy and genetic testing
  - Genetic testing and muscle biopsies only ordered for patients with an unclear diagnosis (approximately 1% to 2% of patients)
  - Biopsy and genetic testing viewed as problematic

Knowledge of Primary Mitochondrial Disease

- Neurologists are generally aware of PMD and reported it may be more common in their practice than originally thought
- When asked to rate their knowledge on a 7-point scale (1=no awareness, 7=high degree of awareness), neurologists self-rated at 4 or above regarding their awareness and knowledge of PMD
  - Two (2) neurologists of various specialization in the one-on-one interviews rated knowledge as a 4
  - Three (3) general neurologists in telephone interviews rated knowledge as an average of 4
  - Six (6) neurologists of various specialization in the one-on-one interviews rated knowledge as 5 or higher
  - Eight (8) neuromuscular neurologists in web-based interviews rated knowledge as an average of 6
- Neurologists reported that overall knowledge of PMD was not very detailed or specific
  - In the telephone interviews, while all indicated they had some awareness of PMD, most stated that they only knew general information
  - Typically, the source of information was medical training or exposure via the patients that were ultimately diagnosed with PMD in clinical practice
- After reviewing the PMM primer information, the neurologists identified key points and potential gaps in their knowledge (**Figure 4**)

Figure 4: Sample of Neurologists' Reactions to PMM Primer Information



- PMM itself was not a term commonly recognized
  - More familiar with specific types of PMD
- Several neurologists indicated that they had seen a case of PMD as a resident; some thought it was only a pediatric condition
- Some neurologists indicated that they occasionally had diagnosed a patient specifically with some type of PMD in their practice
  - Leber's hereditary optic neuropathy (LHON)
  - Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
  - Kearns-Sayre syndrome (KSS)
- As a result of reviewing the primer information, neurologists felt that there were probably undiagnosed patients exhibiting symptoms of PMM in their practice since they do not immediately consider PMM as a diagnosis
  - Patients with "milder" symptoms may have a PMM diagnosis that could potentially be missed
- PMM viewed as a serious condition that presented more rarely than epidemiology suggests
  - Neurologists focused more on one specific type of PMD rather than commonality of the presentation
- General neurologists and subspecialists indicated that neuromuscular subspecialists would be the primary specialty to manage adult patients with PMM

CONCLUSIONS

- This small qualitative research study was highly iterative and serves as a preliminary step to a more focused, larger study with neurologists, and the findings are qualitative in nature and should be considered directional rather than conclusive
- Neurologists see an average of ~230 to 250 patients per month with numerous neurodegenerative and neuromuscular conditions
- The symptoms most commonly seen in clinical practice by neurologists include the 5 most common symptoms reported by patients with PMM, which are muscle weakness, fatigue, exercise intolerance, gastrointestinal problems, and balance problems
- Muscle biopsy and genetic testing is rarely ordered
- Neuromuscular neurologists are clearly the best poised medical professionals to provide a diagnosis in adults who present with signs and symptoms of PMM
- Neurologists require additional educational materials to directly support the identification of symptoms possibly indicative of PMM in adults
- The results indicate a call to action to provide additional education for adult neurologists on the epidemiology, clinical presentation, and diagnostic approach for adults with PMM
- These survey findings highlight the need for continued research and educational efforts aimed at improving access to timely diagnosis and appropriate supportive care and management for patients with PMD

REFERENCES

1. Ahuja AS. Understanding mitochondrial myopathies: a review. *Peer J.* 2018;6:e4790.
2. Parikh S, Goldstein A, Koening MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med.* 2015;17:689-701.
3. Parikh S, Goldstein A, Koenig MK, et al. Practice patterns of mitochondrial disease physicians in North America. Part 1: diagnostic and clinical challenges. *Mitochondrion.* 2014;14(1):26-33.
4. Grier J, Hirano M, Karaa A, et al. Diagnostic odyssey of patients with mitochondrial disease: results of a survey. *Neurol Genet.* 2018;4(2):e230.
5. Zolkipli-Cunningham Z, Xiao R, Stoddart A, et al. Mitochondrial disease patient motivations and barriers to participate in clinical trials. *PLoS One.* 2018;13(5):e0197513.

Acknowledgements:

This study was sponsored by Stealth BioTherapeutics. Medical writing assistance was provided by James A. Shiffer, RPh, Write On Time Medical Communications, LLC.

Poster presented at UMDF Mitochondrial Medicine 2018, June 27-30, 2018, Nashville, Tennessee, USA