Primary Mitochondrial Myopathy Research: Patient Perspectives on Their Journey Through the Healthcare System

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INTRODUCTION

- Primary mitochondrial myopathies (PMM) are genetic disorders that impair normal mitochondrial function, ultimately affecting neurologic (central and peripheral), musculoskeletal, gastrointestinal, and cardiovascular function[1-4]
- We conducted a survey of patients and caregivers to determine the unmet needs of this patient population and the disease burden associated with PMM throughout the patient's lifespan

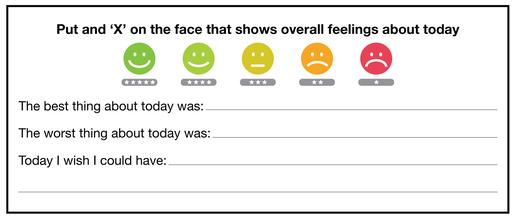
OBJECTIVE

To better understand how to positively impact the lives of patients with PMM by improving their access to timely and appropriate care and management

METHODS

- Respondents included patients with a diagnosis of PMM, with or without genetic confirmation, and/or their caregivers
- Perspectives from PMM patients and/or their caregivers were gained through a 3-part study:
  - Symptom-form completion
  - One-on-one interviews
  - Completion of a 7-day journal (**Figure 1**)

Figure 1. Respondent Overall Feelings Journal



- Questions developed to assess the impact of PMM on patients and caregivers included those surrounding patient characteristics, burden of disease, satisfaction with care, and treatment options
- In an effort to understand day-to-day symptoms associated with PMM, an abbreviated symptom list was completed for 7 days by all respondents

RESULTS

Respondent Characteristics

- Nineteen symptom forms were returned to investigators and identified as complete for inclusion
  - Eight (8) in-person interviews and completed mail-in journals
  - Eleven (11) remaining forms, interviews, and journals
- Respondents included pediatric and adult patients with a diagnosis of PMM (N=19) (**Table 1**):
  - Age birth to 3 years (n=2)
  - Age 4 to 15 years (n=5)
  - Age 16 to 21 years (n=3)
  - Age ≥22 years (n=9)

Table 1. Respondent Demographics

Respondent	Demographic Information
Caregiver	Female (without PMM) caregiver of 2-year-old child with PMM
Caregiver	Female (without PMM) caregiver of a 3-year-old with PMM
Caregiver	Female (without PMM) caregiver of a 10-year-old male with PMM (no speech)
Patient	13-year-old female with PMM
Caregiver	Female (without PMM) caregiver of a 13-year-old with PMM
Patient	15-year-old female with PMM
Caregiver	Female (with PMM) caregiver of a 15-year-old with PMM
Patient	16-year-old male with PMM
Caregiver	Female (without PMM) caregiver of a 18-year-old male with PMM
Caregiver	Male (without PMM) caregiver of a 21-year-old female with PMM
Patient	26-year-old female with PMM
Caregiver	Female (without PMM) caregiver of a 26-year-old female with PMM
Patient	28-year-old female with PMM
Caregiver	Female (without PMM) caregiver of a 28-year-old female with PMM
Caregiver	Female (without PMM) caregiver of a 32-year-old male with PMM
Patient	44-year-old female with PMM
Patient	48-year-old female with PMM
Patient	63-year-old male with PMM
Patient	63-year-old male with PMM

Time to Initial Diagnosis

- PMM patients ≥22 years of age (n=9) experienced the longest time from initial symptom presentation to diagnosis (**Figure 2**)
- Typically, younger children had a shorter time to diagnosis
  - Children with more overt symptoms (ie, failure to thrive or reach expected milestones) were diagnosed even more rapidly
  - Female patients reported a longer average time from symptom demonstration to initial diagnosis of PMM throughout the lifespan

Figure 2. Average Time from Symptom Demonstration to Initial Diagnosis of PMM across the Lifespan

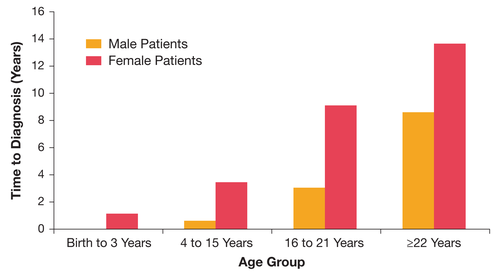


Table 2. Diagnoses Received and Medical/Cognitive Tests Conducted Prior to Diagnosis of PMM

Age Group	Diagnoses Prior to PMM Diagnosis		Testing Conducted/Services Provided Prior to PMM Diagnosis	
Birth to 3 years of age	Developmental delay seizures		MRI EEG Physical Therapy Occupational Therapy	Speech Therapy Early Childhood Developmental Services
4 to 15 years of age	Reflux Munchausen Syndrome by Proxy Delayed milestones	GERD Behavioral issues Seizures Autism	School Case Manager Speech Therapy Physical Therapy School Co-Op	
16 to 21 years of age	Ptosis Muscle issues Lack of vision Lack of hearing	ADHD Anxiety Seizures	Occupational Therapy Physical Therapy Speech Therapy	
≥22 years of age	Brain tumor Developmental delay Atypical virus Lupus Autonomic dysfunction	Chronic Fatigue Syndrome Lyme Disease Drug side effects (atorvastatin) Brain tumor	Adult day program Occupational Therapy Physical Therapy Social Worker Speech Therapy Chiropractic Treatment	Self-massager Acupuncture Water Therapy School UC Psychologist Counselor Equestrian Therapy

Medical Interventions

- Patients with PMM are currently being treated by multiple physicians throughout their lifespan (**Table 3**)
  - All respondents reported that they were routinely seeing 4 to 10 physicians (generalists and various specialists)

Table 3. Physicians Currently Treating Surveyed Patients with PMM

Age Group	Current Treating Physicians		
Birth to 3 years of age	Cardiologist Dysmorphologist	Metabolic Specialist Neurologist	Ophthalmologist Pediatrician
4 to 15 years of age	Cardiologist Dermatologist Dysmorphologist Endocrinologist Gastroenterologist	Gynecologist Hematologist Immunologist Neurologist Neuro-geneticist	Opthalmologist Orthodontist Pediatrician Primary Care Physician Psychiatrist
16 to 21 years of age	Allergist Cardiologist Ear Nose Throat	Gastroenterologist Geneticist Neurologist	Ophthalmologist Pediatrician Psychiatrist
≥22 years of age	Allergist Cardiologist Chiropractor Dermatologist Ear Nose Throat Endocrinologist Gastroenterologist	Geneticist Immunologist Internist Movement Specialist Neurologist Ophthalmologist Orthopedist	Pain Specialist Primary Care Physician Psychiatrist Rheumatologist Sleep Specialist Urologist

- All respondents reported being on a variety of supplements and prescription medications throughout the course of their disease (**Table 4**)

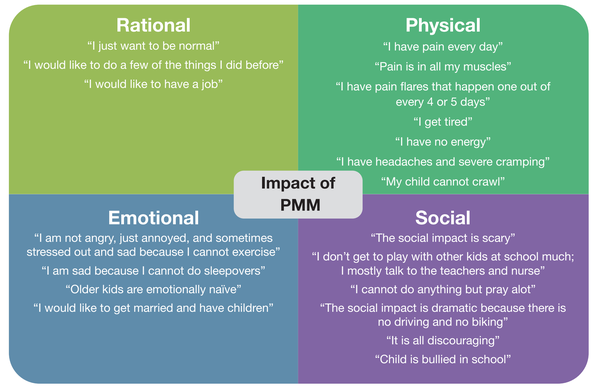
Table 4. Supplements and Prescription Treatments Prescribed for Patients with PMM

	Treatments		
Supplements	Co-enzyme Q10 (ubiquinone) Creatine L-Carnitine Thiamine – B1	Riboflavin – B2 B3, 6, and 12 Folic acid (B9) Antioxidants (Vitamins C and E)	Melatonin Valerian Root Vitamin D3
Prescription Medications	Leucovorin Calcium Omeprazole Divalproex Sodium Fluticasone Propionate Methylphenidate	Gabapentin Skeletal Muscle relaxant combinations Hydrocodone during pain flare	Lorazepam Mirtazapine Zolpidem Prednisone

Disease Burden

- Fatigue and muscle weakness were the most frequently experienced symptoms in respondents aged ≥3 years
  - Experienced by 80% to 100% of respondents
- The number of different symptoms experienced by patients increased with age
- In patients <3 years of age, caregivers noted delays in achieving expected developmental milestones
- As expected, the social and emotional impact of PMM is burdensome, affecting rational, emotional, physical, and social parameters (**Figure 3**)
- The older the patient, the greater the impact on day-to-day functioning

Figure 3. The Impact of Living with PMM Affects All Health Parameters



- Journal review showed more positivity in younger age groups and more problematic days in older groups (**Table 5**)

Table 5. Examples of Journal Responses by Age Group

Age Group	Face Showing Overall Feelings	Best Thing About the Day	Worst Thing About the Day	Today's Wish
Birth to 3 years of age		• Daughter showing us some yoga poses she learned at school • PT and Speech	• Daughter got mad and tried to push me • Not taking a nap • Going to the eye doctor	• To understand not to push • To speak at speech therapy
4 to 15 years of age		• Sitting on my teacher's lap • Helping at my school	• Mom had to give me a suppository • Taking a nap and waking up feeling terrible	• To not need suppositories • To not be so exhausted
16 to 21 years of age	 	• Spending time with my brother • Listening to music	• Frustrated with Medicaid • Not sleeping through the night	• Nothing • To go for a walk
≥22 years of age		• Got to do a bucket list item • Severe pain waited until evening • Going swimming and floating • Being outside with new people	• Thigh pain • Fatigue • Shooting nerve pain • Muscle pain • Sunburn	• To walk with others instead of riding an all-terrain vehicle • To make it through a week without a flare • To walk around the pool by myself and flirt

Supportive Care

- Involvement with support organizations or other PMM-related efforts is therapeutic, social, and a way of giving back to the PMM community
- Transitioning from pediatric care to adult care requires supportive care
  - Physician education was identified as a primary need by adult patients
- Support organizations, such as United Mitochondrial Disease Foundation, and charitable organizations were deemed to be therapeutic

CONCLUSIONS

- Our findings highlighted several continued difficulties faced by patients with PMM, including:
  - Long delays in diagnosis, multiple medical interventions, high number of doctor appointments, burdensome symptoms, and lack of supportive care, which emphasizes the need for continued research and educational efforts aimed at decreasing the burden of disease
- New patient-journey insights reinforced the need for a more timely diagnosis in PMM
- Specialists in neurogenetics, geneticists, and some neurologists are key to obtaining a diagnosis; generalist physicians and specialists wait too long to refer patients to other specialists
- Patients with PMM see numerous other specialists over the span of many years without obtaining a definitive diagnosis
- Generally, the younger the patient, the faster the PMM diagnosis
- 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 in all age groups

REFERENCES

1. 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.
2. Ahuja AS. Understanding mitochondrial myopathies: a review. *Peer J*. 2018;6:e4790.
3. 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.
4. Karaa A, Haas R, Goldstein A, Vockley J, Weaver WD, Cohen BH. Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy. *Neurology*. 2018;90(14):e1212-21.

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