Characterization of Fatigue in Primary Mitochondrial Myopathy: Findings from a Qualitative Interview Study

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BACKGROUND AND OBJECTIVES

Primary mitochondrial myopathies (PMM) are a group of debilitating genetic disorders caused by mutations in nuclear (nDNA) or mitochondrial (mtDNA) genes that encode for mitochondrial proteins. Patients with PMM experience muscle weakness, fatigue, and other significant impacts on health-related quality of life (HRQoL). Patient-reported outcome (PRO) measures can capture the holistic experience of fatigue directly from a patients' perspective, however, there are no existing PRO measures that have been successfully used to substantiate labeling claims or evidence of treatment benefit in fatigue for PMM. The Modified Fatigue Impact Scale (MFIS) has the potential for application in future PMM clinical trials.

The objectives of this non-interventional qualitative study were to:

1. Develop a thorough understanding of how patients with PMM experience fatigue, as well as how fatigue impacts their HRQoL via qualitative unbiased research methods
2. Determine whether the use of existing PRO measures like the MFIS could be utilized to assess fatigue in the PMM population in the setting of clinical research.

METHODS

Participants were recruited for open-ended qualitative interviews through patient association and advocacy groups and two clinical sites (Massachusetts General Hospital and Akron Children's Hospital).

Study participants were recruited if they met the following inclusion criteria:

- Participants had PMM as defined by the International Workshop: Outcome measures and clinical trial readiness in primary mitochondrial myopathies in children and adults;
- A pathologic genetic mitochondrial DNA mutation associated with PMM and expected to impair function of the mitochondria;
- Currently or recently symptomatic (symptoms experienced within the past six months); and
- 16 years of age or older at the time of screening.

There were no formal exclusion criteria; however, inclusion of participants was subject to final approval by Reneo depending on the genetic diagnosis provided by the clinicians.

The interviews contained a concept elicitation method to understand the most bothersome PMM symptoms and impacts, as well as a cognitive debriefing section to review the questions included in the MFIS for relevance and interpretability. All interviews were conducted via telephone and audio-recordings, transcribed verbatim and anonymized. Transcripts were coded using the ATLAS.ti software.

Table 1. Demographic and health information for concept elicitation interview participants

Characteristic	Total sample (N=16) n (%)
Age (in years)	
Average (standard deviation [SD])	37.3 (15.6)
Minimum – maximum	16 – 65
Sex	
Female	11 (68.8%)
Male	5 (31.3%)
Race (all that apply selected)	
White	15 (93.8%)
South Indian	1 (6.3%)
Ethnicity	
Not Hispanic/Latino	15 (93.8%)
Hispanic/Latino	1 (6.3%)
Work status (all that apply selected)	
On disability	7 (43.8%)
Working part-time	3 (18.8%)
Working full-time	2 (12.5%)
Student	2 (12.5%)
Retired	2 (12.5%)
Unemployed	2 (12.5%)
Age at diagnosis (in years)	
Average (SD)	28.2 (15.4)
Minimum – maximum	8 – 55
Length of time since diagnosis (in years)	
Average (SD)	8.4 (7.8)
Minimum – maximum	0.2 – 31.0
Clinician reported mutation	
Single large-scale mtDNA deletion)	9 (56.3%)
MT-TL1 m.3243A>G	6 (37.5%)
MT-ND5 m.14453G>A	1 (6.3%)

RESULTS

A total of 16 patients with PMM qualified for interviews (Table 1). All participants completed the concept elicitation exercise, and 10 participants completed the cognitive debriefing exercise. The majority of interview participants were female, non-Hispanic white; age range was from 16-65 years old. Patients with PMM included in this study represented a demographically diverse set of the PMM population and had a broad array of PMM mutations and conditions.

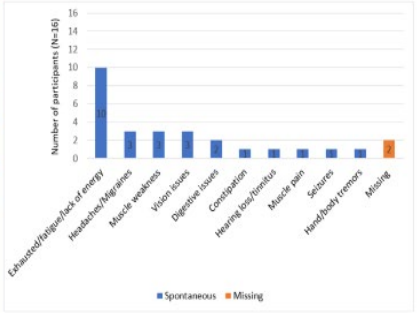
- A total of 53 unique signs and symptoms of PMM were reported across seven domains (i.e., musculoskeletal, cognitive, neurologic, gastrointestinal, ocular, systemic, and other including auditory, respiratory, cardiac, and autoimmune issues) either spontaneously or following probing by interviewers.
- Across all domains the most commonly reported symptoms (Table 2) included **feeling fatigued** (n=16, 100%), **muscle cramping** (n=12, 75.0%), and **blurry vision** (n=12, 75.0%).
- The most commonly reported impacts included **limitations in physical activities/exercise** (n=16, 100%), **needing to pace self during physical activities** (n=13, 81.3%), and **lack of independence/reliance on others** (n=12, 75%).
- In addition to fatigue, participants also reported symptoms such as muscle/nerve pain and vision loss. While saturation was met for fatigue-related symptoms and impacts, there were several less frequent signs/symptoms unrelated to fatigue (e.g., constipation, sensitivity to light) that did not reach saturation. Saturation was considered achieved when additional interviews were unlikely to yield new information (i.e., new concepts of importance and relevance to participants).
- A majority of participants noted that **fatigue was the most important symptom to treat** (Figure 1), while limitations on physical activities/exercise was the most bothersome impact.
- All participants who took part in cognitive debriefing of the MFIS noted that the response options were appropriate, and easy to use. Almost all participants confirmed that the MFIS captured their overall experience with fatigue.

Table 2. Summary of most frequently reported signs, symptoms, and impacts*

Sign/symptom	Spontaneous n (%)	Probed n (%)	Total sample (N=16) n (%)
Exhausted/fatigue/lack of energy	15 (93.8%)	1 (6.3%)	16 (100.0%)
Muscle weakness	9 (56.3%)	6 (37.5%)	15 (93.8%)
Blurry vision	11 (68.8%)	1 (6.3%)	12 (75.0%)
Muscle cramping	5 (31.3%)	7 (43.8%)	12 (75.0%)
Headaches/migraines	7 (43.8%)	4 (25.0%)	11 (68.8%)
Muscle spasms	2 (12.5%)	9 (56.3%)	11 (68.8%)
Drooping eyelids/ptosis	9 (56.3%)	1 (6.3%)	10 (62.5%)
Hand/body tremors	6 (37.5%)	4 (25.0%)	10 (62.5%)
Trouble concentrating	3 (18.8%)	7 (43.8%)	10 (62.5%)
Dizziness	0 (0.0%)	10 (62.5%)	10 (62.5%)
Impact	**Spontaneous n (%)**	**Probed n (%)**	**Total sample (N=16) n (%)**
Limit physical activities/exercise	16 (100.0%)	0 (0.0%)	16 (100.0%)
Need to pace self in physical activities	4 (25.0%)	9 (56.3%)	13 (81.3%)
Less able to complete tasks requiring physical effort	8 (50.0%)	4 (25.0%)	12 (75.0%)
Lack of independence/reliance on others	4 (25.0%)	8 (50.0%)	12 (75.0%)
Less motivated to participate in social activities	10 (62.5%)	1 (6.3%)	11 (68.8%)
Need to rest more often or for longer periods	7 (43.8%)	4 (25.0%)	11 (68.8%)
Difficulty with housekeeping	6 (37.5%)	5 (31.3%)	11 (68.8%)
Affects work/school performance	5 (31.3%)	6 (37.5%)	11 (68.8%)
Less motivation for physical effort	1 (6.3%)	10 (62.5%)	11 (68.8%)
Trouble maintaining physical effort for long periods	5 (31.3%)	5 (31.3%)	10 (62.5%)

*The table includes the ten most frequently reported signs/symptoms and the ten most frequently reported impacts.

Figure 1. Most important PMM symptoms to treat



CONCLUSIONS

Concept elicitation interviews established that while PMM patients reported a wide variety of symptoms and impacts, the most prevalent and impactful symptoms reported is fatigue. All participants reported feeling fatigued and all but one participant reported fatigue spontaneously. In general, all participants described fatigue similarly as: feeling exhausted all the time, having a lack of energy, and/or feeling tired from performing physical activity. Additionally, fatigue was reported by a majority of participants as the most important symptom to treat (n=10 of 16, 62.5%).

In addition to fatigue, participants also reported symptoms such as muscle/nerve pain, vision loss, and several less frequent signs/symptoms unrelated to fatigue (e.g., constipation, sensitivity to light) that did not reach saturation. This is not surprising given that in PMM patients with mtDNA mutations, inheritance and clinical presentation are complicated by the presence of a mixture of mutated and wild-type genomes (heteroplasmy) in the same cell or tissue that can result in significant phenotypic heterogeneity, even among siblings with similar genetic defects.

The results of the MFIS cognitive debriefing interviews confirmed that the MFIS items were relevant and interpretable to patients with PMM. Participants also confirmed that the MFIS accurately captured their overall experience with fatigue. This research supports the use of the MFIS in future PMM clinical trials to measure treatment benefit in fatigue-related impacts, particularly with respect to physical fatigue.

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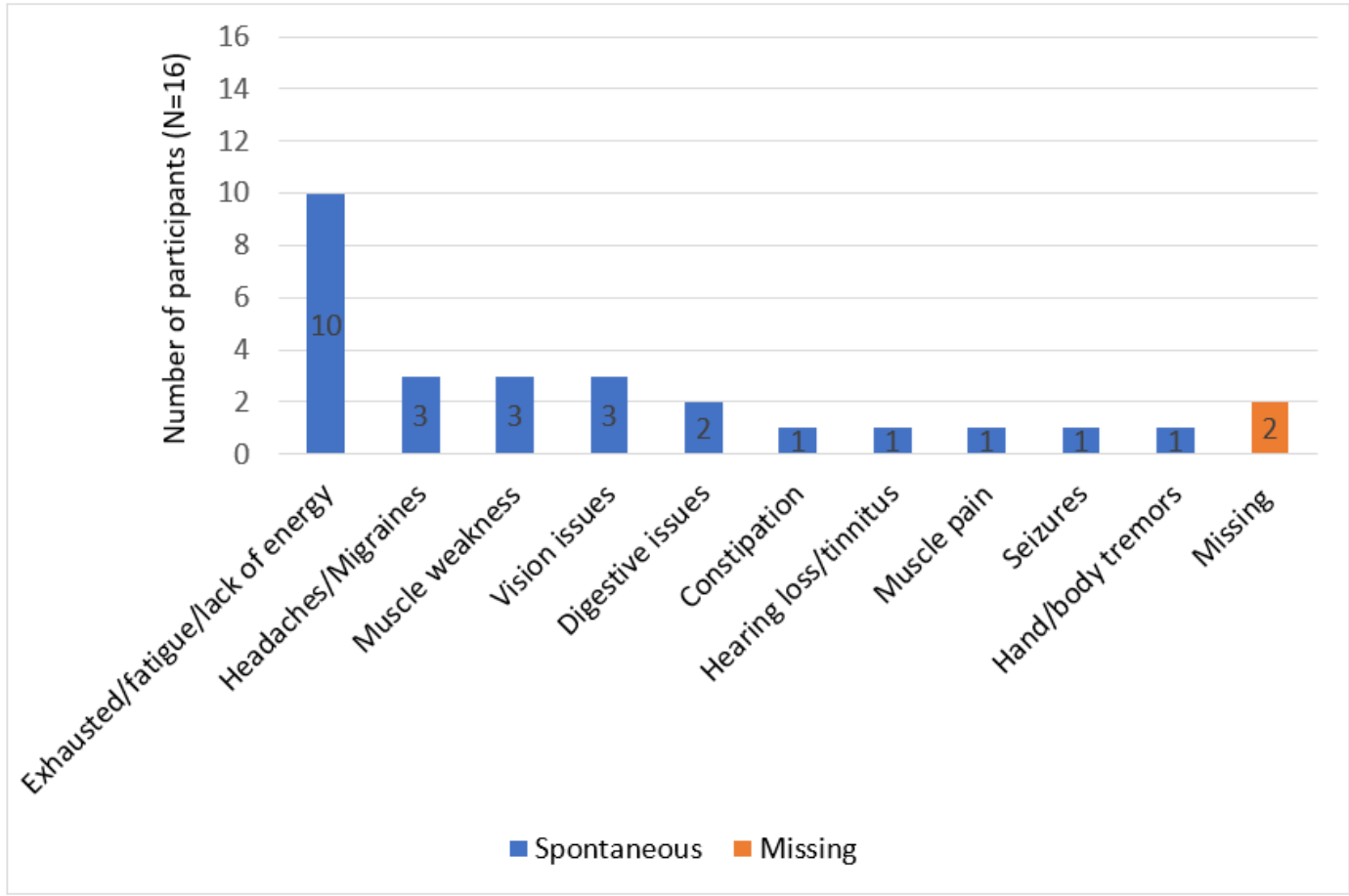

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