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Characterization of Fatigue in Primary Mitochondrial Myopathies

Findings From a Qualitative Interview Study

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Abstract

Background and Objectives

Primary mitochondrial myopathies are genetic disorders that primarily affect peripheral skeletal muscles. Patients with primary mitochondrial myopathies often experience muscle weakness, fatigue, and other significant impacts on health-related quality of life. The aim of this non-interventional qualitative study was to collect the most bothersome fatigue-related symptoms and impacts reported by patients with primary mitochondrial myopathies and determine whether the questions included in an existing patient-reported outcome measure, the Modified Fatigue Impact Scale, are relevant and interpretable for this population.

Methods

The interviews contained a concept elicitation exercise to understand the most bothersome primary mitochondrial myopathies symptoms and impacts and a cognitive debriefing section to review the questions included in the Modified Fatigue Impact Scale for relevance and interpretability. Transcripts were coded using ATLAS.ti software.

Results

Interviews were conducted with 16 patients who were aged 16 years and older with a genetically confirmed and clinical diagnosis of symptomatic primary mitochondrial myopathies. Concept elicitation interviews established that while patients with mitochondrial myopathies reported a wide variety of symptoms and impacts, one of the most impactful symptoms discussed was fatigue. Cognitive debriefing interview results confirmed that the Modified Fatigue Impact Scale items were relevant, were interpretable, and largely captured patients' experience with fatigue.

Discussion

Fatigue was one of the most widely discussed experiences discussed by participants and was considered the most important symptom/impact to treat by most of the participants. The Modified Fatigue Impact Scale could be used in future clinical trials to measure treatment benefit in fatigue-related impacts.

Introduction

Primary mitochondrial diseases (PMDs) are a group of debilitating genetic disorders caused by alterations in nuclear (nDNA) or mitochondrial (mtDNA) genes that negatively affect mitochondrial oxidative phosphorylation.[1] Patients with PMDs can experience severe

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morbidity, reduced health-related quality of life, and premature death.[2] PMDs primarily manifest in tissues with high energy demand, and many patients will present with a myopathy or myopathic features.[3] Individuals with primary mitochondrial myopathies (PMM) have a PMD that primarily affects their muscles; prominent symptoms include fatigue, muscle weakness, weakness of ocular and lid muscles, and significant impacts on health-related quality of life. Patients with mtDNA alterations have varying degrees of tissue heteroplasmy causing more symptom-heterogeneity and a wider range of disease impact. Reports from a Delphi panel involving clinicians treating PMM and a Food and Drug Administration meeting with patients with PMM have provided valuable input regarding the identification of functional outcome and patient-reported measures, outcome scales, and the need for biomarkers to monitor clinical trial efficacy in PMM.[4,5] In addition, fatigue was reported as highly prevalent and debilitating in a large survey of patients with mitochondrial disease.[6]

While there is growing interest in PMM, there are currently no approved PMM therapies. Clinical trials assessing PMM treatments for symptom management typically rely on measuring surrogate performance outcome measures and biomarkers. Walk tests have been identified by experts as useful performance outcome measures, given their established history of use in cardiovascular, pulmonary, and other neuromuscular diseases and the potential for their use as a surrogate to measure endurance-related changes.[7-9] Several patient-reported outcome (PRO) measures are in use in clinical practice and across mitochondrial disease registries.[10-12] Some have also been used in PMM clinical trials to capture the holistic experience of fatigue from the patient perspective.[13,14] Despite the multiple instruments used, there are no 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) is 1 PRO of interest for potential application in future PMM clinical trials. The MFIS is a modified form of the Fatigue Impact Scale,[15] and its items were derived from interviews with patients with multiple sclerosis (MS) concerning how fatigue affects their lives. This 21-item PRO assesses the effects of fatigue in terms of physical, cognitive, and psychosocial functioning; it allows for separate scoring of each of these domains and a total score as well.[16,17] The MFIS has been successfully used to assess fatigue in other patient populations such as traumatic brain injury and MS.[18]

The primary goal of this study was to develop an understanding of how patients with PMM caused by mtDNA alterations experience fatigue and how fatigue affects their health-related quality of life through qualitative unbiased research methods. An additional objective included determining whether the use of existing PRO measures such as the MFIS could be used in clinical research to assess fatigue in the population with PMM.

Methods

This noninterventional qualitative study was submitted to a central institutional review board (Copernicus Group Independent Review Board [IRB]) for ethical review and approval before any contact with study participants. Approval was granted on April 1, 2020.

Participants were recruited through patient association and advocacy groups, social media postings (e.g., within patient groups on Facebook), and 2 US clinical sites (the Massachusetts General Hospital and Akron Children's Hospital mitochondrial disease clinics). All participants completed Informed Consent and Health Insurance Portability and Accountability Act (HIPAA) Authorization Forms (ICF) and Assent Forms (applicable for patients younger than 18 years). Participants were enrolled if they met the following key eligibility criteria: an established diagnosis of PMM (as previously defined[4]); with a disease-causing mitochondrial DNA alteration that was known to be associated with PMM; current PMM symptoms experienced at least within the past 6 months; and in the judgment of the recruiting clinician, the participant had adequate communication skills to reflect on his or her experience with PMM.

Interviews were conducted through telephone, and interviewers used a semistructured concept elicitation interview guide consisting of open-ended questions encouraging spontaneous responses. The concept elicitation interview guide included topics and questions designed to understand PMM signs and symptoms, and impacts and experiences related to the condition from a participant's perspective. The guide included targeted probes that focused particularly on fatigue-related symptoms and impacts. An amended interview guide included a cognitive debriefing exercise in which participants were asked to complete and provide feedback on the MFIS to ensure the measure is interpretable and relevant to the interview participants' experience with PMM-related fatigue. Two clinicians with significant experience treating patients with PMM provided feedback on the interview guide before finalization. Interviews were audio-recorded with participants' consent and lasted approximately 60 minutes. Participants were compensated following interview completion.

Fifteen participants were interviewed in the first set of interviews, which contained only the concept elicitation exercise. A preliminary review of the first set of patients enrolled disclosed that 4 participants had polymerase gamma mutations (nuclear genetic alterations) instead of the required mitochondrial DNA alterations. These 4 participants were removed from further analysis. Based on the interim analysis, it was determined that a second set of interviews, specifically mixed concept elicitation/cognitive debriefing interviews, should be conducted with 5 additional participants. This resulted in 16 participants who qualified with concept elicitation data. A third and final round of cognitive debriefing-

only interviews was conducted with 5 participants who participated in the first set of concept elicitation interviews, resulting in 10 of the 16 participants having completed the MFIS cognitive debriefing portion of the interview.

Audio recordings of the interviews were transcribed and anonymized by removing identifying information. Each transcript was considered a unit of analysis, and data from all transcripts were aggregated following coding. An initial coding scheme was developed based on the interview guide and research objectives. Coding is an iterative process, and the initial code list was updated as necessary to incorporate newly emerging data. The coding scheme was applied and operationalized using ATLAS.ti version 8.4.24 or higher (Atlas.ti GmbH, Berlin). Codes were applied to specific text within each transcript and then queried for frequency across transcripts. The coding process was guided by established qualitative research methods, including grounded theory and constant comparative method.[19-22]

A total of 4 coders were used in this study. Intercoder reliability (ICR) (i.e., the extent to which independent coders are concordant in coding) was evaluated by dividing the total number of concordant codes by the total number of codes used and then multiplying by 100. Greater than or equal to 90% agreement among all 4 coders was considered an acceptable threshold for ICR (i.e., percent coder agreement) based on benchmarks outlined in the literature (i.e., 70%–94%).[23]

Qualitative data from the concept elicitation portion of the interviews were assessed for conceptual saturation of PMM symptoms and impacts with focus on fatigue-related concepts. Saturation was considered achieved when additional interviews were unlikely to yield new concepts of importance and relevance to participants.[22] To evaluate conceptual saturation, concepts spontaneously emerging from the interviews were analyzed in cohorts based on the order in which the interviews were conducted. Data from the MFIS debriefing exercise were analyzed to assess respondents' ability to correctly interpret the measure's items and whether the items were relevant to interview participants' experience with PMM-related fatigue.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was submitted to Copernicus Group IRB for ethical review and approval before any contact with study participants. IRB approval was granted on April 1, 2020. After screening, eligible potential participants were asked for consent through an electronic ICF. Endpoint Outcomes was responsible for screening and enrolling participants with the assistance of participants' clinicians.

Data Availability

Anonymized data not published within this article will be made available to qualified investigators by request to the authors.

Table 1 Participant-Reported Demographic and Health Information for Concept Elicitation Interview

Characteristic	Total sample (N = 16) n (%)
Age (y)	
Average (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[a]	1 (6.3)
Ethnicity	
Not Hispanic/Latino	15 (93.8)
Hispanic/Latino	1 (6.3)
Highest level of education	
Currently in high school	1 (6.3)
High school graduate (or equivalent)	3 (18.8)
Some college (no degree)	2 (12.5)
Associate's degree	1 (6.3)
Bachelor's degree	4 (25.0)
Master's degree	3 (18.8)
Other[b]	2 (12.5)
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

[a] Participant selected "other" and specified: "South Indian".
[b] Participants selected other and specified: "technical school" (n = 2 of 16, 12.5%).

Results

Interview data from 16 participants were included in the analysis. All 16 participants completed concept elicitation interviews, and 10 of these participants completed the cognitive debriefing portion of the interview. The demographic characteristics and results for study participants are summarized in Table 1. Specific PMM DNA alterations reported by clinicians and participants are listed in Table 2.

Signs and Symptoms of PMM

Fifty-three unique signs and symptoms of PMM were reported across 7 domains (i.e., musculoskeletal, cognitive, neurologic, gastrointestinal, ocular, systemic, and other including auditory, respiratory, cardiac, and other diverse issues) either spontaneously or following probing by interviewers. The following symptoms were reported by at least 10 of the 16 participants (62.5%): exhausted, fatigued, or experiencing a lack of energy (n = 16, 100.0%), muscle weakness (n = 15, 93.8%), blurry vision (n = 12, 75.0%), muscle cramping (n = 12, 75.0%), headaches or migraines (n = 11, 68.8%), muscle spasms (n = 11, 68.8%), drooping eyelids (n = 10, 62.5%), tremors in the hand or other parts of the body (n = 10, 62.5%), trouble concentrating (n = 10, 62.5%), and dizziness (n = 10, 62.5%).

Table 2 Specific DNA Alterations Reported (Clinician Reported)

ID	Clinician-reported alteration	Type of mitochondrial disease reported by participant[a]
02-01	Single large-scale mtDNA deletion	Kearns-Sayre syndrome
02-02	Single large-scale mtDNA deletion	CPEO
01-02	Single large-scale mtDNA deletion	CPEO
02-03	Single large-scale mtDNA deletion	Do not know
01-03	MT-TL1 m.3243A>G	MELAS
01-04	MT-TL1 m.3243A>G	MELAS
03-03	MT-TL1 m.3243A>G	MELAS
01-08	Single large-scale mtDNA deletion	CPEO
01-09	MT-ND6 m.14453G>A	MELAS
02-04	Single large-scale mtDNA deletion	Do not know
01-10	Single large-scale mtDNA deletion	CPEO
02-05	MT-TL1 m.3243A>G	MELAS
04-01	Single large-scale mtDNA deletion	Kearns-Sayre syndrome and CPEO
03-12	MT-TL1 m.3243A>G	MELAS
03-15	MT-TL1 m.3243A>G	MELAS
03-02	Single large-scale mtDNA deletion	CPEO

[a] Patients reporting having MELAS is often inaccurate. This is a misnomer referring to the presence of the m.3243A > G alteration and not the clinical phenotype of MELAS.

For each reported sign or symptom, participants were asked to rate "how bothered were you by [sign/symptom]" on an 11-point numeric rating scale that ranged from "0" to "10," where "0" meant not at all bothered and "10" meant extremely bothered. The most bothersome symptoms reported by n ≥ 8 participants included the following: feeling exhausted, fatigued, or experiencing a lack of energy (n = 16; mean = 8.0); muscle weakness (n = 13; mean = 7.6); headaches or migraines (n = 11; mean = 7.4); blurry vision (n = 8; mean = 7.4); and muscle cramping (n = 8; mean = 5.6). Participants most commonly reported their fatigue bothersome ratings as an 8 (n = 5 of 16, 31.3%) of 10. Bothersome ratings for fatigue ranged from 6 of 10 (n = 3 of 16, 18.8%) to 10 of 10 (n = 4 of 16, 25.0%). When asked to explain why fatigue was bothersome, one participant explained, "I'm constantly tired" and another participant noted, "[the exhaustion is] overwhelming … it's the thing that I most often get frustrated with, because it is exhausting being exhausted all the time."

Most of the participants (n = 10 of 16, 62.5%) considered fatigue to be the important symptom to treat. One participant explained, "I feel like if there was enough energy even just to feel awake, that it would be easier to deal with everything else physically, emotionally and otherwise to deal with all the symptoms that follow. … it's the most limiting symptom. It's the most frustrating symptom." Other symptoms identified as most important to treat included headaches or migraines, muscle weakness, and vision issues, each endorsed by 3 participants (n = 3 of 16, 18.8%).

Impacts of PMM

Fifty-nine unique impacts of PMM were reported across 8 domains (i.e., activities of daily living, cognitive fatigue, communication, emotional, physical fatigue, psychosocial fatigue, social or relationship, and other including related to work or school, sleep, appearance, finances, and body weight), either spontaneously or following probing by interviewers. The following impacts were reported by at least 10 of the 16 participants (62.5%): limit physical activities or exercise (n = 16, 100.0%), need to pace self in physical activities (n = 13, 81.3%), less able to complete tasks requiring physical effort (n = 12, 75.0%), lack of independence or reliance on others (n = 12, 75.0%), affects work or school performance (n = 11, 68.8%), difficulty with housekeeping (n = 11, 68.8%), less motivated to participate in social activities (n = 11, 68.8%), less motivation for physical effort (n = 11, 68.8%), need to rest more often or for longer periods (n = 11, 68.8%), clumsy and uncoordinated (n = 10, 62.5%), difficulty communicating with others (n = 10, 62.5%), and trouble maintaining physical effort for long periods (n = 10, 62.5%). Signs, symptoms, and impacts of PMM, reported both spontaneously and following probing by ≥ 50% of participants, are summarized by frequency of report and listed in Table 3.

For each reported impact, participants were asked to rate how bothered they were on the same bothersome scale used for the

Table 3 Summary of Most Frequently Reported Signs, Symptoms, and Impacts

	Spontaneous n (%)	Probed n (%)	Total sample (N = 16) n (%)
Sign/symptom			
Exhausted, fatigued, or experiencing a 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 or migraines	7 (43.8)	4 (25.0)	11 (68.8)
Muscle spasms	2 (12.5)	9 (56.3)	11 (68.8)
Drooping eyelids	9 (56.3)	1 (6.3)	10 (62.5)
Tremors in the hand or other parts of the body	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)
Muscle pain	7 (43.8)	2 (12.5)	9 (56.3)
Forgetful or loss of memory	4 (25.0)	5 (31.3)	9 (56.3)
Brain fog	2 (12.5)	7 (43.8)	9 (56.3)
Impact			
Limit physical activities or 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 or 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 or 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)
Difficulty communicating with others	4 (25.0)	6 (37.5)	10 (62.5)
Clumsy and uncoordinated	3 (18.8)	7 (43.8)	10 (62.5)
Negatively affects sleep	8 (50.0)	1 (6.3)	9 (56.3)
Socially isolated	4 (25.0)	5 (31.3)	9 (56.3)
Difficulty reading	1 (6.3)	8 (50.0)	9 (56.3)
Difficulty driving	8 (50.0)	0 (0.0)	8 (50.0)
Depressed or sad	3 (18.8)	5 (31.3)	8 (50.0)
Negatively affects appearance	2 (12.5)	6 (37.5)	8 (50.0)

symptom ratings. The most bothersome impacts reported by ≥ 8 participants included the following: limit on physical activities or exercise (n = 9; mean = 7.4) and less motivation to participate in social activities (n = 8; mean = 7.4).

ICR and Conceptual Saturation

ICR was achieved with 98.2% after coding one of the concept elicitation transcripts.

Conceptual saturation was considered met for all fatigue-related symptoms and impacts, except "less motivation for physical effort." However, this concept was reported frequently by participants when probed (n = 10 of 16, 62.5%). Eight symptoms unrelated to fatigue (gallstones, constipation, nausea, lactic acid "buildup," vascular pain, dysautonomia, sensitivity to light, and ophthalmoplegia) were mentioned spontaneously in the last group of participants (i.e., did not meet saturation). The saturation results attributed to PMM signs, symptoms, and impacts are presented in Figures 1 and 2.

Cognitive Debriefing of MFIS

All physical subscale items of the MFIS (Items 4, 6, 7, 10, 13, 14, 17, 20, and 21) were interpreted as intended by all participants and considered relevant by all participants. For the cognitive subscale, all except 1 item (item 2, "difficulty paying attention") were interpreted as intended by all participants; the one participant (n = 1 of 10, 10.0%) who did not interpret the item as intended reported that the concept of having difficulty paying attention (item 2) was the same as the concept of being less alert (item 1). Most of the participants (>66.7%) found the cognitive subscale items (items 1, 3, 5, 11, 12, 15, 16, 18, and 19) to be relevant. The psychosocial subscale items (items 8–9) were interpreted as intended by all participants and found relevant by all participants.

All participants with evaluable data noted that response options were appropriate (n = 10 of 10, 100.0%) and easy to use (n = 9 of 9, 100.0%). Almost all participants (n = 9 of 10,

90.0%) confirmed that the MFIS captured their overall experience with fatigue, while 1 participant (n = 1 of 10, 10.0%) noted that the cognitive impact items were less relevant than the physical impact items.

Discussion

The participants included in this study represent a demographically diverse set of the population with PMM. The specific alterations reported by clinicians included some of the most common mtDNA alterations; with the single large mtDNA deletion (n = 9 of 16, 56.2%) and the $tRNA^{Leu}$ point mutation m.3243A>G (n = 6 of 16, 37.5%) being the most prevalent. Notably, participants with the m.3243A>G alteration consistently self-referred as having MELAS despite not always meeting criteria for this syndrome.

While interview participants reported a variety of symptoms and impacts, the most prevalent and impactful symptom discussed was fatigue. All participants reported feeling fatigued, and all but 1 participant reported fatigue spontaneously. Participants generally described fatigue similarly as feeling exhausted all the time, having a lack of energy, and/or feeling tired from performing physical activity. In addition, fatigue was reported by most of the participants as the most important symptom to treat (n = 10 of 16, 62.5%). The findings of this study align with previous research conducted with patients with PMM, where fatigue was described as one of the most common symptoms, and a "reduction in chronic fatigue" was identified as an important unmet need that should be considered for new PMM treatments.[5] In addition, a Delphi panel of 26 PMM investigators concluded that patient-reported outcome measures of fatigue were important to include in clinical research.[4]

While saturation was met for fatigue-related symptoms and impacts, there were several less frequent signs and symptoms unrelated to fatigue (e.g., constipation, visual issues) that did not reach saturation. This is not surprising given the phenotypic heterogeneity observed in patients with PMM, even among family members with similar genetic defects.[24] The well-established heterogeneity of the disease, corroborated in this study, indicates that if less frequent symptoms unrelated to fatigue were being considered for labeling claims, additional concept elicitation interviews would need to be conducted. Of importance, symptoms and impacts related to fatigue were discussed more frequently and prominently than the other symptoms in all 16 concept elicitation interviews conducted, and therefore, it is expected that no novel information related to fatigue would arise from additional concept elicitation interviews.

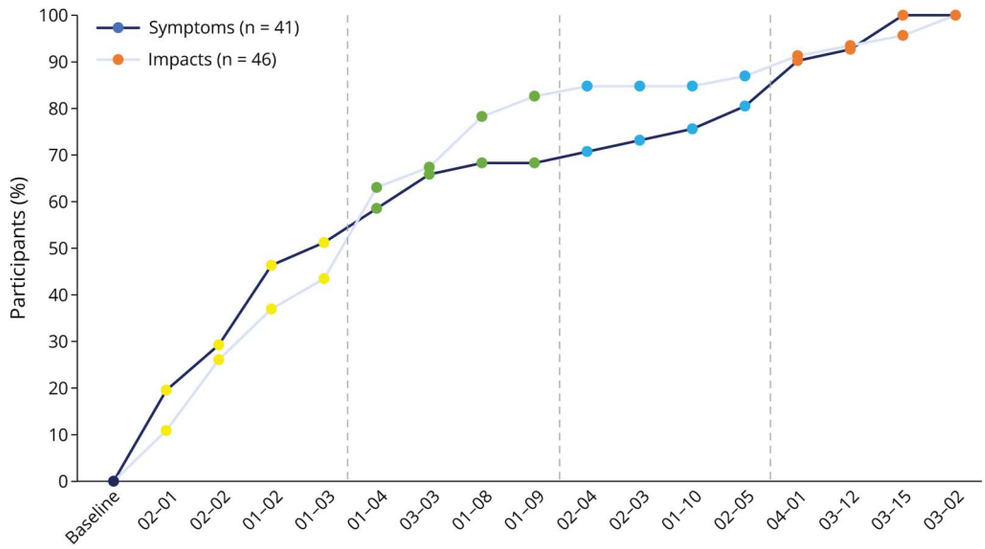
An interim analysis conducted on the first 11 interviews demonstrated that fatigue-related impacts participants discussed were conceptually similar to concepts in the existing MFIS PRO instrument, and therefore, a novel PRO assessing fatigue was unnecessary. Although the MFIS was developed initially with patients with MS, the domain structure and item content are appealing from a scoring and conceptual perspective.[15] In addition, the MFIS includes response options that measure fatigue on a frequency scale, which makes it unique among fatigue instruments being used in PMM clinical trials.[16,17] Because participants in the interviews often described their fatigue in terms of frequency (e.g., "I feel tired *all of the time*"), it is important to ensure response options are reflective of patient experiences.

The results of the MFIS cognitive debriefing interviews confirmed that almost all the MFIS items were relevant and interpretable to participants, including 1 participant as young as 16 years of age. Participants also confirmed that the MFIS captured their overall experience with fatigue. If the MFIS is to be used in future clinical trials, the "physical fatigue" subscale may be of particular interest because it was shown to be more relevant to participants (and therefore less likely to see floor effects with clinical trial data). The cognitive and psychosocial fatigue items were not as relevant or frequently discussed by participants compared with the physical fatigue items. While 3 participants (n = 3 of 10, 30.0%) reported that they would have issues with the recall period in the MFIS, most of the participants (n = 7 of 10; 70.0%) said it would be easy to recall their fatigue over the past 4 weeks. Nevertheless, a shorter recall period could help ensure participants in future clinical research can accurately recall their fatigue-related impacts.

There are several fatigue scales available and some currently in use for patients with mitochondrial diseases. The Primary Mitochondrial Myopathy Symptom Assessment (PMMSA) tool was specifically designed for clinical trial purposes and demonstrated strong reliability and construct-related validity.[14] However, it failed to capture minimally important difference (MID) of fatigue and was thus not as relevant as a clinical trial PRO.[13,14] The Fatigue Severity Scale (FSS) is being used in a large PMM Italian cohort and was significantly impaired at baseline, correlating with other functional tests such as the 6 MWT.[10] FSS scores remained stable after a 12-month reassessment within the same cohort.[11] Comparison of the FSS and MFIS in conditions where fatigue is a prominent feature found that both scales are equivalent in measuring physical fatigue, but the psychosocial and the cognitive impact of fatigue are better assessed by the MFIS.[25] These impacts were deemed relevant in a subset of patients in our cohort.

The MFIS may also be more responsive to clinically significant changes in fatigue when compared with the FSS. This is likely related to the multiple domains measured by the scale, which affords it a stronger association with global function in patients,[26] which was deemed appropriate for the population with PMM. There is probably more than 1 suitable fatigue

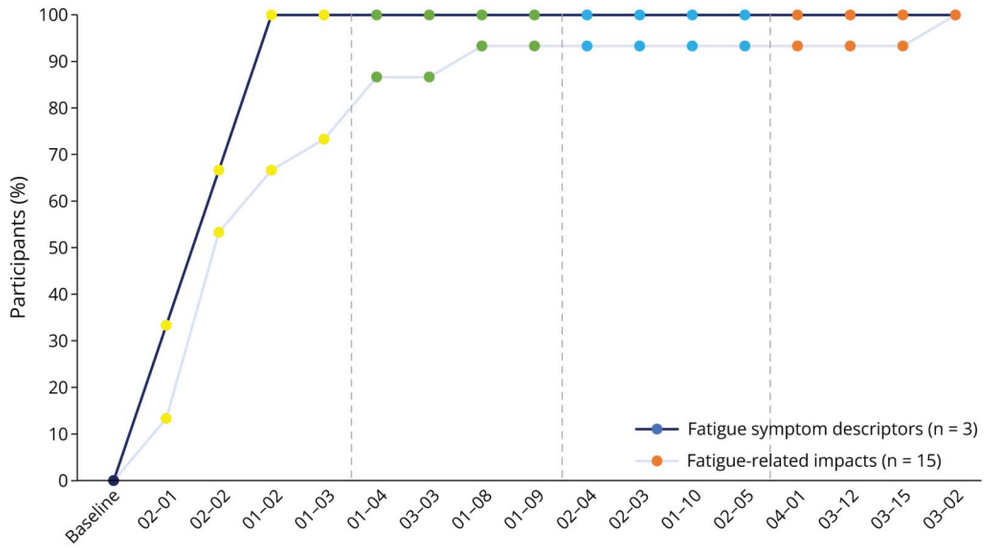
Figure 1 Saturation Graph for the Signs/Symptoms and Impacts of PMM (N = 16)*



* Each cohort is represented by a colored marker: yellow represents the first approximately 25% of participants (n = 4 of 16, 25.0%), green represents the second approximately 25% of participants (n = 4 of 16, 25.0%), blue represents the third approximately 25% of participants (n = 4 of 16, 25.0%), and orange represents the last approximately 25% of participants (n = 4 of 16, 25.0%). The X-axis is temporal and based on when the interviews occurred. Each colored marker represents the cumulative number of concepts reported by all participants interviewed up to that time point.

PRO for patients with PMM, and the selection of the "best" PRO will require further studies comparing them head-to-head and validating them specifically for mitochondrial disorders. This study used a thorough and methodical evaluation of an existing fatigue PRO, the MFIS to assess its suitability for patients with PMM.

Figure 2 Saturation Graph for Fatigue-Related Signs/Symptoms and Impacts of PMM (N = 16)*



* Each cohort is represented by a colored marker: yellow represents the first approximately 25% of participants (n = 4 of 16, 25.0%), green represents the second approximately 25% of participants (n = 4 of 16, 25.0%), blue represents the third approximately 25% of participants (n = 4 of 16, 25.0%), and orange represents the last approximately 25% of participants (n = 4 of 16, 25.0%). The X-axis is temporal and based on when the interviews occurred. Each colored marker represents the cumulative number of concepts reported by all participants interviewed up to that time point.

TAKE-HOME POINTS

- Qualitative interviews were conducted with patients with primary mitochondrial myopathies to understand fatigue-related symptoms and impacts.
- Of all symptoms discussed, patients most frequently reported experiencing fatigue and considered it one of the most bothersome aspects of PMM.
- Patients experience significant limitations in physical activities and require frequent rest because of fatigue.
- Patient fatigue can be self-reported and measured over the course of a clinical intervention using the Modified Fatigue Impact Scale.

A limitation of this study is the small sample size. Although the sample was sufficient for achieving conceptual saturation with fatigue-related concepts, additional psychometric work should be completed to assess the reliability and validity of the MFIS in PMM. In addition, interviews in a wider range of mitochondrial diseases could examine whether the findings are generalizable beyond PMM.

Through qualitative interviews with participants with PMM, the study investigators gained a thorough understanding of the patient experience with fatigue-related symptoms and impacts and determined that the items in the MFIS PRO measure were relevant and interpretable for those with PMM. Fatigue was one of the most common experiences discussed by participants, and it was considered the most important symptom/impact to treat by most of the participants. The MFIS could be used in future clinical trials to measure treatment benefit in fatigue-related impacts, particularly in terms of physical fatigue.

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Nathan Johnson, MPH	Endpoint Outcomes, Boston, MA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Ian Clarkson, BA	Endpoint Outcomes, Boston, MA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
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