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Fatigue in primary genetic mitochondrial disease: No rest for the weary

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Abstract

Rates of perceived fatigue, anxiety, depression, sleepiness and mitochondrial disease severity were assessed prospectively in 2017–2018 using established validated questionnaires in 48 adult patients with genetically confirmed primary mitochondrial disease. Fatigue was found to be very common among patients with primary mitochondrial disease, with 34 to 48 (71–100%) patients reporting fatigue depending on the measure used, and the severity of fatigue correlating with the severity of disease. Moderate-to-severe depression (10/48; 20.8%) anxiety (28/48; 58.3%) and sleep problems (16/48; 33.3%) were frequent in our patients with fatigue and these conditions were even more prevalent in those with severe fatigue. In conclusion, perceived fatigue was common in patients with primary mitochondrial disease and appeared to correlate with disease severity. Depression, anxiety and sleep disorders were more common in the cohort than those with other chronic diseases but with rates similar to that seen in multiple sclerosis. The severity of perceived fatigue correlated with an increased risk of these comorbid conditions. The Fatigue Severity Scale may more selectively measure non-anxiety/sleep-related fatigue in primary mitochondrial disease and additional testing is planned.

keywords: Mitochondrial disease; Fatigue; Depression; Anxiety; Sleep disorder.

1. Introduction

Primary Mitochondrial Diseases (PMD) are genetic disorders that arise as a result of a direct or indirect dysfunction of mitochondrial oxidative phosphorylation (OxPhos) and comprise one of the most frequent genetic metabolic disorders with an incidence of 1 in 5000 individuals [1–5]. PMDs are caused by mutations in mitochondrial DNA (mtDNA) or one of over 350 nuclear encoded genes [6]. While these disorders may be multisystemic or involve only a single organ, they typically impact the neurologic system.

Fatigue, poor endurance, and exercise intolerance are some of the most common complaints in both adult and pediatric patients with PMDs and impact quality of life and level of disability but has not been extensively studied [7–9].

Fatigue may include both perceived and physiological fatigue. Perceived fatigue has been described as an overwhelming sense of tiredness, lack of energy, or feeling of exhaustion [7,10]. In contrast, physiological fatigue, or exercise intolerance, refers to a muscle's inability to generate

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and maintain power [8]. Perceived fatigue has been identified as one of the commonest symptoms that patients with PMD would like to improve, [11] and is also a core symptom targeted in current PMD clinical trials as an outcome measure for treatment efficacy.

Fatigue is common in individuals with chronic diseases and even more so in chronic neurologic diseases including multiple sclerosis (MS), [12–16] neuromuscular junction disorders, myotonic dystrophy, muscular dystrophy, post-stroke, and post-myelitis. [10,17] Little is known about the etiology, extent or severity of perceived fatigue in PMDs. Fatigue might be multifactorial, partly due to concomitant systemic disease, medication effects and the psychological burden of chronic disease. Common comorbidities such as anxiety, depression and sleep disorders may also worsen fatigue in patients with PMDs though the true prevalence of these symptoms in PMD patients is not known. Due to the complex pathophysiology of PMD, concern exists that it is a symptom due to factors not yet characterized. A better understanding of these issues and the potential mechanisms of fatigue in PMDs is needed and may lead to improved treatments, prevention and quality of life for patients. Despite the numerous clinical fatigue scales available, it is not yet clear if one will best capture this symptom in PMD.

The objective of our study was to assess self-reported or perceived fatigue and fatigue-associated comorbid conditions in a cohort of patients with PMD to better characterize these symptoms and investigate their interrelationships. We also preliminarily assessed whether one specific measure may better gauge fatigue in patients with PMD.

2. Methods

2.1. Participants and procedures

Forty-eight adults with PMD were voluntarily recruited from 10 national centers and completed a number of established questionnaires assessing fatigue, anxiety, depression, and sleep problems. Any adult patient with genetically confirmed PMD expressing variable multisystem phenotypes seen in a Mitochondrial Clinic for routine care was eligible to participate. Subjects were all current patients of the investigators and recruited over 2017–2018 via an IRB-approved written recruitment information sheet handed out at the office visit.

Physicians completed a modified mitochondrial disease severity score, using a portion of the Newcastle Mitochondrial Disease Adult Scale (NMDAS) for each subject. Patient demographics are provided in Table 1. Measures completed are outlined in Table 2. More detailed descriptions of the various common measures chosen are in Table 3. Data were collected and maintained using an online database system (REDCap). All study procedures were approved by the Cleveland Clinic Institutional Review Board (IRB) and participants were provided a written information sheet reviewing the purpose of the study.

Table 1
Patient Characteristics, $n = 48$.

Gene/Locus	Number	Symptoms
Mitochondrial DNA		
m.3243A>*G*	13	MELAS, MIDD plus, ataxia, CPEO & myopathy or multisystem disease
m.8344A>*G*	3	MERRF, multisystem disease
m.10466C>*T*	1	CPEO & Myopathy
mtDNA deletion	14	CPEO Plus, KSS, myopathy
m.11778G>*A*	1	LHON plus
Nuclear DNA		
ACAD9	1	Myopathy and Cardiomyopathy
ADCK3	1	Multisystem disease
ANT1	1	CPEO and myopathy
COX10	1	Myopathy
CYTB	1	Myopathy
MFN2	1	Neuropathy
NUBPL	1	Leigh
OPA1	2	Multisystem disease
POLG	2	Ataxia Neuropathy Spectrum, CPEO
RRM2B	1	CPEO
TK2	2	Myopathy Plus
TWNK	2	CPEO plus

CPEO: Chronic Progressive Externa Ophthalmoplegia.
KSS: Kearns Sayre Syndrome.
LHON: Leber Hereditary Optic Neuropathy.

2.2. Statistical analysis

Patient demographics, diagnoses, patient-reported outcomes, and provider-reported NMDAS were summarized using descriptive statistics. Summary scores are reported as mean with standard deviation and median with interquartile range, while severity thresholds are presented as frequency count with percentage. Spearman correlation coefficients were computed to determine the association between patient- and provider-reported measures. Rates of concomitant depression, anxiety, and sleepiness within patients with extreme fatigue were examined; extreme fatigue was defined as a Fatigue Impact Scale (FIS) $\geq$ 40, CIS $\geq$ 35, or Fatigue Severity Scale (FSS) $\geq$ 36, and clinically significant depression (BDI $\geq$ 20), anxiety (BAI $\geq$ 16), and sleepiness (ESS $\geq$ 10) [18–23]. Average item scores (total score/9) on the FSS were also calculated for comparison with research in other populations. Statistical significance was established throughout at $p < 0.05$. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Patient characteristics

Adult patients older than age 18 years with genetically confirmed mitochondrial diseases were included with the majority (13/48) carrying the common m.3243A > *G* pathogenic variant or having a large-scale mitochondrial DNA deletion (14/48). (Table 1) To facilitate participation via

Table 2
Measures Administered.

Measure	Construct	# Items	Score Interpretations	Subscales*
Fatigue Impact Scale (FIS)	Fatigue	40	40+ excessive symptomatic fatigue 80+ severe symptomatic fatigue	Cognitive, Physical, Psychosocial Fatigue
Checklist Individual Strength (CIS)	Fatigue	20	35+ severe fatigue	Fatigue, Concentration, Motivation, Activity
Fatigue Severity Scale (FSS)	Fatigue	9	36+ abnormal fatigue	–
FCS Panic Scale	Fatigue	10	Higher scores indicate worse fatigue	–
Beck Depression Inventory-II (BDI-II)	Depression	21	0–13 Minimal 14–19 Mild 20–28 Moderate 29 + Severe depression	–
Beck Anxiety Inventory (BAI)	Anxiety	21	0–7 Minimal 8–15 Mild 16–25 Moderate 26+ Severe anxiety	–
Epworth Sleepiness Scale (ESS)	Sleep problems	8	0–7 low likelihood of abnormal sleepiness 8–9 average 10–15 excessive sleepiness 16–24 excessive sleepiness requiring potential medical attention	–
Newcastle Mitochondrial Disease Adult Scale (NMDAS)ł	Disease severity	29	1–5 Mild 6–20 Moderate 21 + Severe	General physical functioning, System specific involvement, Clinical assessment

items refers to the number of questions on the measurement survey. Score interpretations includes known thresholds for discriminating across the measurement construct.

* In addition to the overall measured construct on the scale, subscales measure a smaller construct and contribute to the overall rating. For example, the 40 symptoms measured on the FIS form 3 subscales and 1 overall measure of fatigue. "–" indicates the items rate one overall measure and no subscales.

łProvider-reported.

Table 3
List of Measures Used.

The *Newcastle Mitochondrial Disease Adult Scale* (NMDAS) is a validated disease-specific survey that assesses mitochondrial disease manifestation [29] by monitoring the clinical expression of the disease and consists of the following three sections: (1) current functioning: general physical functioning in the past 4 weeks, (2) system specific involvement: functioning of individual organ-systems, (3) current clinical assessment. NMDAS scores of 1–5 indicate mild clinical manifestation, scores 6–20 moderate, and scores 20+ severe.

The *Beck Anxiety Inventory* (BAI) consists of 21 items designed to assess common features of anxiety (Beck et al., 1988). Items are rated on a 4-point scale. Scores of 0–21 indicate low anxiety, 22–35 moderate anxiety, and 36+ severe anxiety.

The *Beck Depression Inventory* (BDI) consists of 21 items designed to assess common symptoms of depression (Beck et al., 1996). It includes somatic and cognitive-affective symptoms, and each item is rated on a 4-point scale. Scores of 0–13 indicate minimal depression, 14–19 mild, 20–28 moderate depression, and 29+ severe depression.

The *Epworth Sleepiness Scale* (ESS) is an 8-item measure of patient's sleepiness. Items are scored on a 4-point Likert scale with a maximum score of 24 (Johns 1991). Scores of 0–7 indicate low likelihood of abnormal sleepiness, 8–9 average, 10–15 excessive sleepiness, and 16–24 indicates excessive sleepiness requiring potential medical attention.

The *Checklist Individual Strength* (CIS) is a 20 item questionnaire and measures the following four separate aspects of fatigue during the previous two weeks: fatigue severity (eight items, score range 8–56), concentration problems (five items, score range 5–35), reduced motivation (four items, score range 4–28), and reduced activity (three items, score range 3–21). Each item is scored on a 7-point Likert scale. High scores indicate high levels of fatigue, high levels of concentration problems, low motivation, and low levels of activity (Vercoulen et al., 1994). It shows good reliability and consistency in neuromuscular patients. A CIS fatigue score of 35 or more is used to identify severe fatigue.

The *Fatigue Impact Scale* (FIS) was developed to assess the symptom of fatigue as part of an underlying chronic disease or condition. It consists of 40 items scored on a 5-point Likert scale, evaluating the effect of fatigue on 3 domains of daily life: cognitive functioning, physical function, and psychosocial functioning [19]. Scores are tallied to produce an overall score with a maximum of 160. Subscale scores can also be calculated. Scores of 40+ indicate excessive symptomatic fatigue and scores of 80+ indicate severe, symptomatic fatigue.

The *Daily Fatigue Impact Scale* (D-FIS) is a shorter 8-item measure that is used to monitor daily changes in fatigue (Fisk et al., 2002). Each item is scored on a 5-point Likert scale and indicates how much of a problem fatigue has been for the patient today.

The *Fatigue Severity Scale* (FSS) is a 9-item instrument designed to assess fatigue as a symptom of a variety of different chronic conditions and disorders [20]. Each item is scores on a 7-point Likert scale with higher scores indicated worse fatigue.

The *FCS Panic Scale* is a 10-item measure to assess thoughts people have when they are fatigued based on the most recent time they were fatigued. Items are scored on a 5-point Likert scale.

an information sheet alone for consent and online Redcap survey mechanism additional protected health information and demographics were not collected.

3.2. Patient-reported outcome scores

Descriptive statistics of patient-reported scores for fatigue, depression, anxiety, and sleep problems measures are presented in Table 4. High levels of fatigue were reported across patients with abnormal levels of fatigue found in the vast majority of patients across all fatigue measures. In comparison, patients reported relatively lower average levels of depression ($M_{BDI\text{-}II} = 13.7 \pm 8.5$) and anxiety ($M_{BAI} = 17.6 \pm 9.9$). 31.3% of patients reported mild depressive symptoms while 20.8% reported moderate or severe symptoms. 58.3% reported moderate or severe symptoms of anxiety. Sleep problems were similarly common with 33.3% of patients reporting elevated scores.

3.3. Associations

Fatigue scores were highly correlated with depression, anxiety, and sleep problems for the FIS, CIS, and FCS Panic Scale. Surprisingly, there was no significant association between the FSS and anxiety or sleep. The FIS, FSS, and CIS were positively correlated with disease severity (NMDAS). See Table 5 for the full list of correlations.

We also examined rates of concomitant depression, anxiety, and sleepiness within patients with severe fatigue. As shown in Table 6, 20.0–26.5% of patients with extreme fatigue also reported clinically significant depression. There were greater rates of clinically significant anxiety (57.5–61.8%) and sleepiness (33.3–47.1%) within patients with extreme fatigue.

4. Discussion

Fatigue in PMD may include both perceived and physiological fatigue. The aim of this study was to examine the prevalence and severity of self-reported fatigue among patients with genetically-confirmed PMD and to investigate the relationship between fatigue and comorbidities including depression, anxiety, and sleep problems. We also assessed whether a specific fatigue measure may better capture perceived fatigue in adult patients with PMD.

4.1. Fatigue is common in PMD and may correlate with disease severity

Our results demonstrated that fatigue is very common among patients with PMD, with 71–100% of patients reporting fatigue, depending on the measure used, and that the severity of fatigue correlates with the severity of mitochondrial disease as measured by the NMDAS. Interestingly the severity of fatigue did not correlate with the severity of myopathy as scored on a section of the NMDAS. Abnormal fatigue scores were most commonly observed on the CIS (100% of patients endorsing severe fatigue). When examining subscales of the FIS, the most commonly reported problems involved physical and psychosocial functioning.

When compared to other medical populations, levels of reported fatigue in patients with PMD are somewhat variable.

Table 4
Patient- and Provider-Reported Fatigue Outcomes, $n = 48$.

Patient-Reported Fatigue Outcomes	
Fatigue Impact Scale (FIS), Overall Score, mean ± SD	61.5 ± 36.4
Median (Q1, Q3)	64 (28, 78)
Excessive Symptomatic Fatigue (score 40+), n (%)	34 (70.8%)
Severe Symptomatic Fatigue (score 80+), n (%)	11 (22.9%)
FIS Subscales	
Cognitive functioning, mean ± SD	12.5 ± 9.9
Physical functioning, mean ± SD	20.5 ± 10.7
Psychosocial functioning, mean ± SD	28.5 ± 18.2
Checklist Individual Strength (CIS), Overall Score, mean ± SD	93.8 ± 23.1
Median (Q1, Q3)	91 (81, 113)
Severe Fatigue (score 35+), n (%)	48 (100.0%)
CIS Subscales	
Fatigue, mean ± SD	41.4 ± 10.1
Concentration, mean ± SD	21.0 ± 7.8
Motivation, mean ± SD	15.9 ± 5.0
Activity, mean ± SD	15.6 ± 5.2
Fatigue Severity Scale (FSS), Overall Score, mean ± SD	48.3 ± 14.9
Median (Q1, Q3)	54 (41, 58)
Average Items Score, mean ± SD	2.63 ± 1.65
Median (Q1, Q3)	2.0 (1.5, 3.4)
Abnormal Fatigue (score 36+), n (%)	40 (83.3%)
FCS Panic Scale, Overall Score, mean ± SD	1.95 ± 0.73
Median (Q1, Q3)	1.80 (1.30, 2.30)
Beck Depression Inventory –II,, mean ± SD	13.7 ± 8.5
Median (Q1, Q3)	14 (8, 18)
Minimal (score 0–13), n (%)	23 (47.9%)
Mild (score 14–19), n (%)	15 (31.3%)
Moderate (score 20–28), n (%)	6 (12.5%)
Severe (score 29+), n (%)	4 (8.3%)
Beck Anxiety Inventory, mean ± SD	17.6 ± 9.9
Median (Q1, Q3)	17 (11, 23)
Minimal (score 0–7)	10 (20.8%)
Mild (score 8–15), n (%)	10 (20.8%)
Moderate (score 16–25), n (%)	19 (39.6%)
Severe (score 26+), n (%)	9 (18.8%)
Epworth Sleepiness Scale, mean ± SD	8.3 ± 4.4
Median (Q1, Q3)	8 (5, 11)
Low (score 0–7), n (%)	23 (47.9%)
Average (score 8–9), n (%)	9 (18.7%)
Excessive (score 10–15), n (%)	13 (27.1%)
Requires medical attention (score 16+), n (%)	3 (6.2%)
Provider-Reported NMDAS Disease Score, mean ± SD	25.8 ± 12.2
Median (Q1, Q3)	25 (17, 33)
Mild (score 1–5), n (%)	1 (2.1%)
Moderate (score 6–20), n (%)	14 (29.2%)
Severe (score 21+), n (%)	33 (68.7%)
NMDAS Subscales	
Section 1 score: current function, mean ± SD	11.2 ± 6.6
Section 2 score: system specific involvement, mean ± SD	6.1 ± 5.0
Section 3 score: current clinical assessment, mean ± SD	8.5 ± 5.9

For each construct, both the continuous measurement is presented as the mean with standard deviation as well as the median with interquartile range (quartile 1 (Q1), quartile 3 (Q3)); and as the number of patients who have met reported thresholds. For example, 34 patients had FIS scores of 40+, which equates to excessive symptomatic fatigue.

Table 5
Spearman Correlations between Patient- and Provider-Reported Outcomes.

	CIS	FSS	FCS	BDI	BAI	ESS	NMDAS
FIS	0.79**	0.56**	0.57**	0.64**	0.45**	0.50**	0. 31*
CIS	**X**	0.62**	0.55**	0.64**	0.43**	0.38**	0.31*
FSS		**X**	0.45**	0.41**	0.20	0.14	0.46**
FCS Panic Scale			**X**	0.72**	0.62**	0.45**	0.23
BDI				**X**	0.61**	0.52**	0.06
BAI					**X**	0.20	0.09
ESS						**X**	−0.06
NMDAS							**X**

* $p < 0.05$;.
** $p < 0.01$; FIS = Fatigue Impact Scale; CIS=Checklist Individual Strength; FSS = Fatigue Severity Scale; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; ESS = Epworth Sleepiness Scale; FCS = FCS Panic Scale.

Table 6
Rates of concomitant depression, anxiety, and sleepiness within patients with extreme fatigue, $n = 48$.

	FIS 40+*N* (%)	CIS 35+*N* (%)	FSS 36+*N* (%)
Total # of Patients	*34 (70.8)*	*48 (100.0)*	*40 (83.3)*
Depression (BDI 20+)	9 (26.5)	10 (20.8)	8 (20.0)
Anxiety (BAI 16+)	21 (61.8)	28 (58.3)	23 (57.5)
Sleepiness (ESS 10+)	16 (47.1)	16 (33.3)	14 (35.0)

Fatigue is a common finding in neurological diseases and has been studied extensively in patients with MS [12–17,24]. Centrally mediated fatigue has also been described in many other neurologic diseases [17,25]. Fatigue and exercise intolerance are also commonly seen in patients with a variety of chronic non-neurologic diseases including heart failure or diabetes, seen 33–45% of the time [25]. Our sample reported higher levels of fatigue when compared to a group of 50 patients with post-stroke fatigue, [26] and lower levels when compared to patients with fibromyalgia (FM) and rheumatoid arthritis (RA) as measured by the FSS [27]. In comparison with the FM and RA samples, our patients with PMD reported greater impact of fatigue on psychosocial functioning, similar impact on physical functioning, and lower impact on cognition, based on the FIS, though it is not clear why this is.

These results are consistent with a prior report of fatigue in PMD. Specifically, in a cohort of 132 adult patients with genetically confirmed PMD, [7] 62% of patients with a PMD reported perceived fatigue when assessed by the Fatigue Impact Scale (score > 40) with 32% reporting severe, functionally limiting fatigue symptoms (score > 80), comparable to findings in patients with Chronic Fatigue Syndrome [17]. Severe fatigue was noted regardless of age, gender or genotype and correlated with disease severity scales. Severity of fatigue in this report did not correlate with the associated severity of myopathy as measured by the NMDAS.

In a single large Italian cohort [8] of patients with likely PMD, not all molecularly defined, 25–35% of the patients with genetically confirmed PMD including those with the m.3243A > *G* and m.8344A > *G* pathogenic variants reported fatigue. Other studies in patients with PMD also show self-reported fatigue as being severe [28,29]. A smaller study [9] of exertional tolerance and fatigue in six ambulatory pediatric patients with "mitochondrial myopathy" that was not genetically defined showed a lower activity level, higher level of fatigue as measured by the Pictorial Children's Effort Rating Scale and a self-reported level of fatigue, and lower quality of life relative to a control group of ten age-matched healthy children.

It is not surprising that both pediatric and adult patients with PMD report fatigue. While the etiology is multifactorial, OxPhos deficiency in PMDs appears to be an important risk factor as supported by objective exercise testing in patients with PMDs [28,30–35]. PMD patients have reduced oxygen extraction, an increase in free radical production, phosphocreatine depletion and more anaerobic metabolism in muscle [28]. Exercise testing shows a reduction in maximal oxygen consumption and excessive carbon dioxide production [30,35]. Some PMD patients may have reduced cardiac output and a hyperdynamic circulatory response – even without concomitant cardiomyopathy [25]. Presumably, central nervous system disease may also impact fatigue though this has been less studied. Comorbid conditions in mitochondrial disease such as neuropathy, myopathy, cardiac dysfunction, endocrinopathies and renal disease likely further exacerbate fatigue. Deconditioning worsens endurance and quality of life further [29]. Regular aerobic exercise may help reverse exercise intolerance and improve quality of life [32,33,35–41].

4.2. Severe fatigue in PMD correlates with depression, anxiety and sleepiness

Depression, anxiety and sleep problems were common in our patients with PMD. Our cohort had elevated scores for depression (20.8% with moderate to severe symptoms and an additional 31.3% with mild symptoms), anxiety (58.3% with moderate to severe symptoms and an additional 20.8% with mild symptoms), and sleep problems (33.3%) [see Fig. 1]. These comorbid conditions were even more prevalent in those with severe fatigue, with up to 61.8% with clinically significant anxiety and 47.1% with sleepiness. (Table 6)

These rates are clearly higher than what is reported in patients with chronic disease but not necessarily in chronic neurologic disease. In MS, using the same measures as employed in our study, elevated depression (BDI-II ≥ 14) was found in 33.9% of patients (compared to our 52.1%) [42] and elevated anxiety (BAI ≥ 8) was found in 73.3% (compared to our 79.2%) [43]. Using the Hospital Anxiety and Depression Scale (HADS), depression has been found in up to 46.9% of MS patients [44]. Similarly, excessive sleepiness, as reported on the ESS, has been found in up to 53% [45]. Comorbid depression and anxiety has been previously noted in studies of small cohorts of pediatric and adult patients with genetically confirmed PMD [46–50]. It was previously not clear if these symptoms were present at a higher prevalence than in patients with other neurologic or

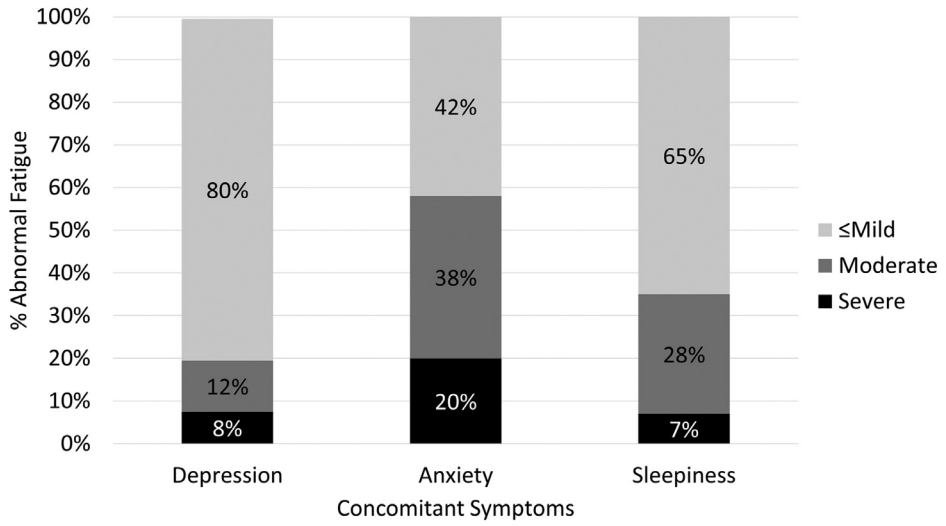

Fig. 1. Concomitant depression, anxiety, and sleepiness in patients with fatigue defined by FSS 36+, $n = 40$.
This figure presents the percentage of concomitant levels of depression, anxiety, and sleepiness stratified by level: none-mild, moderate, and severe for the 40 patients with fatigue defined by FSS 36+. Among patients with abnormal fatigue, 20% have depression (8% moderate and 12% severe), 58% have anxiety (38% moderate and 20% severe), and 35% have sleepiness (28% moderate and 7% severe). These comorbidity frequencies are comparable to that of the total study sample (20.8% depression, 58.3% anxiety, and 33.3% sleepiness from Table 4).

chronic diseases [48,51]. The prevalence is clearly higher than what is seen in the general population [49].

Thus, concomitant depression, anxiety and sleep problems may be common for patients with PMD and should not be overlooked – especially as the severity of perceived fatigue increase. It is not yet clear if the underlying disease severity or intensity of the fatigue alone is contributing to these comorbidities or how the symptoms impact each other. It is likely that these comorbidities are under-recognized and under-treated in this population. Routine assessments of these comorbidities are needed with consideration of further consultation with psychology and sleep medicine when appropriate.

4.3. The FSS may better quantify mitochondrial fatigue

Bivariate correlations showed significant associations between fatigue and depression, anxiety, and sleep problems for most fatigue scales, which is consistent with research in other populations with chronic illness [52–57]. The exception was the FSS which was not significantly associated with anxiety or sleepiness, suggesting that the FSS may more closely measure non-anxiety/sleep-related fatigue than the other measures. There is no clear explanation for this lack of association. If proven accurate and consistent, then the FSS may provide a more specific assessment of mitochondrial fatigue though given the modest sample size of this study further sampling is needed prior to reaching any conclusions.

This paper presents findings related to self-reported fatigue in a large cohort of patients with genetically confirmed PMD. No single mitochondrial phenotype was sufficiently to allow for disease, genotype- or phenotype-specific conclusions to be reached. While the established measures we used are commonly utilized to quantify symptoms in patients with neurologic disease, we do not yet know if they are specific to mitochondrial disease.

4.4. Limitations

This paper is not without limitations. While small sample sizes are common in MD research, our relatively small and heterogeneous sample limits generalizability of these findings. The study did not have the power to assess differences in patient- or provider-reported outcomes across individual disease type. The methodology utilized limited the ability to collect robust data points. As such, this study should encourage future research to clarify the prevalence of fatigue and its relationship with psychological functioning in PMD. However, this study does add to the existing small body of literature on this topic and is one of the very few that include only patients with genetically confirmed MD and uses multiple measures of fatigue. Our study validates previously reported findings from the United Kingdom in a distinct population in the United States [7].

4.5. Conclusion

In summary, perceived fatigue is a significant finding in patients with PMD, appears to be correlated with disease severity and severely impacts psychosocial functioning. Depression, anxiety and sleep disorders are more common in PMD than those with other chronic diseases but with rates similar to that seen in MS. The severity of perceived fatigue correlates with an increased risk of these comorbid conditions. Routine assessment of fatigue severity and these comorbidities is needed as addressing these concerns will likely directly impact the quality of life of PMD patients. As the FSS may better capture fatigue in PMD, additional testing

of the FSS with concomitant measures of anxiety, mood and sleep symptoms is planned. Effective treatments are clearly needed to decrease the burden of fatigue in this disease.

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Abbreviations

BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CIS	Checklist Inidividual Strength
ESS	Epworth Sleep Scale
FIS	Fatigue Impact Scale
FM	Fibromyalgia
FSS	Fatigue Severity Scale
mtDNA	Mitochonrial DNA
MS	Multiple Sclerosis
NMDAS	Newcastle Mitochondrial Disease Adult Scale
OxPhos	Oxidative Phosphroylation
PMD	Primary Mitochondrial Disease
RA	Rheumatoid Arthritis

References

[1] Sallevelt SCEH, de Die-Smulders CEM, Hendrickx ATM, Hellebrekers DMEI, de Coo IFM, Alston CL, et al. De novo mtDNA point mutations are common and have a low recurrence risk. J Med Genet 2017;54:73–83. doi:10.1136/jmedgenet-2016-103876.

[2] Darin N, Oldfors A, Moslemi AR, Holme E, Tulinius M. The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA abnormalities. Ann Neurol 2001;49:377–83.

[3] McKiernan P, Ball S, Santra S, Foster K, Fratter C, Poulton J, et al. Incidence of primary mitochondrial disease in children younger than 2 years presenting with acute liver failure. J Pediatr Gastroenterol Nutr 2016;63:592–7 [doi]. doi:10.1097/MPG.0000000000001345.

[4] Chinnery PF. Mitochondrial disorders overview. GeneReviews. Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, editors, SeattleWA: University of Washington; 1993. Seattle.

[5] Gorman GS, Schaefer AM, Ng Y, Gomez N, Blakely EL, Alston CL, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol 2015. doi:10.1002/ana.24362.

[6] Rahman J, Rahman S. Mitochondrial medicine in the omics era. Lancet 2018;391:2560–74 (London, England). doi:10.1016/S0140-6736(18)30727-X.

[7] Gorman GS, Elson JL, Newman J, Payne B, McFarland R, Newton JL, et al. Perceived fatigue is highly prevalent and debilitating in patients with mitochondrial disease. Neuromuscul Disord 2015. doi:10.1016/j.nmd.2015.03.001.

[8] Mancuso M, Angelini C, Bertini E, Carelli V, Comi GP, Minetti C, et al. Fatigue and exercise intolerance in mitochondrial diseases. literature revision and experience of the Italian network of mitochondrial diseases. Neuromuscul Disord 2012. doi:10.1016/j.nmd.2012.10.012.

[9] Martens A-M, Gorter H, Wassink RG V, Rietman H. Physical activity of children with a mitochondrial disease compared to children who are healthy. Pediatr Phys Ther 2014. doi:10.1097/PEP.0000000000000016.

[10] Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. Curr Opin Neurol 1996. doi:10.1097/00019052-199612000-00011.

[11] Zolkipli-Cunningham Z, Xiao R, Stoddart A, McCormick EM, Holberts A, Burrill N, et al. Mitochondrial disease patient motivations and barriers to participate in clinical trials. PLoS One 2018. doi:10.1371/journal.pone.0197513.

[12] Leocani L, Colombo B, Comi G. Physiopathology of fatigue in multiple sclerosis. Neurol Sci 2008. doi:10.1007/s10072-008-0950-1.

[13] Comi G, Leocani L, Rossi P, Colombo B. Physiopathology and treatment of fatigue in multiple sclerosis. J Neurol 2001. doi:10.1007/s004150170222.

[14] Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep 2010. doi:10.1093/sleep/33.8.1061.

[15] Induruwa I, Constantinescu CS, Gran B. Fatigue in multiple sclerosis - a brief review. J Neurol Sci 2012. doi:10.1016/j.jns.2012.08.007.

[16] Krupp LB, Serain DJ. Multiple sclerosis-associated fatigue. Mult Scler Ther 2011. doi:10.1017/CBO9781139023986.059.

[17] Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004. doi:10.1016/S0140-6736(04)15794-2.

[18] Beck AT, Steer RA. Manual for the beck anxiety inventory. Behav Res Ther 1990. doi:10.1017/CBO9781107415324.004.

[19] Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis 1994. doi:10.1093/clinids/18.Supplement_1.S79.

[20] Krupp LB. The fatigue severity scale. Arch Neurol 1989. doi:10.1001/archneur.1989.00520460115022.

[21] Michielsen HJ, De Vries J, Van Heck GL, Van de Vijver FJR, Sijtsma K. Examination of the dimensionality of fatigue: the construction of the fatigue assessment scale (FAS). Eur J Psychol Assess 2004. doi:10.1027/1015-5759.20.1.39.

[22] Beck AT, Steer RA, Brown GK. Manual for the beck depression inventory-II. San Antonio: TX Psychol Corp; 1996. doi:10.1002/(SICI)1097-0142(19991215)86:123.3.CO;2-I.

[23] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991. doi:10.1093/sleep/14.6.540.

[24] Bol Y, Duits AA, Hupperts RM, Vlaeyen JW, Verhey FR. The psychology of fatigue in patients with multiple sclerosis: a review. J Psychosom Res 2009. doi:10.1016/j.jpsychores.2008.05.003.

[25] McCoy J, Bates M, Eggett C, Siervo M, Cassidy S, Newman J, et al. Pathophysiology of exercise intolerance in chronic diseases: the role of diminished cardiac performance in mitochondrial and heart failure patients. Open Hear 2017. doi:10.1136/openhrt-2017-000632.

[26] Nadarajah M, Mazlan M, Abdul-Latif L, Goh H-T. Test-retest reliability, internal consistency and concurrent validity of fatigue severity scale in measuring post-stroke fatigue. Eur J Phys Rehabil Med 2017. doi:10.23736/S1973-9087.16.04388-4.

[27] Öncü J, Başoğlu F, Kuran B. A comparison of impact of fatigue on cognitive, physical, and psychosocial status in patients with fibromyalgia and rheumatoid arthritis. Rheumatol Int 2013. doi:10.1007/s00296-013-2825-x.

[28] Taivassalo T, Jensen TD, Kennaway N, DiMauro S, Vissing J, Haller RG. The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients. Brain 2003;126:413–23.

[29] Taivassalo T, Gardner JL, Taylor RW, Schaefer AM, Newman J, Barron MJ, et al. Endurance training and detraining in mitochondrial myopathies due to single large-scale mtDNA deletions. Brain 2006;129:3391–401. doi:10.1093/brain/awl282.

[30] Tarnopolsky M. Exercise testing as a diagnostic entity in mitochondrial myopathies. Mitochondrion 2004. doi:10.1016/j.mito.2004.07.011.

[31] Haller RG, Lewis SF. Pathophysiology of exercise performance in muscle disease. Med Sci Sports Exerc 1984;16:456–9.
[32] Taivassalo T, Haller RG. Implications of exercise training in mtDNA defects–use it or lose it? Biochim Biophys Acta 2004;1659:221–31. doi:10.1016/j.bbabio.2004.09.007.
[33] Taivassalo T, Haller RG. Exercise and training in mitochondrial myopathies. Med Sci Sports Exerc 2005;37:2094–101.
[34] Taivassalo T, De Stefano N, Argov Z, Matthews PM, Chen J, Genge A, et al. Effects of aerobic training in patients with mitochondrial myopathies. Neurology 1998;50:1055–60.
[35] Siciliano G, Simoncini C, Lo Gerfo A, Orsucci D, Ricci G, Mancuso M. Effects of aerobic training on exercise-related oxidative stress in mitochondrial myopathies. Neuromuscul Disord 2012;22(3):S172–7 Suppl. doi:10.1016/j.nmd.2012.10.00510.1016/j.nmd.2012.10.005.
[36] Schreuder L, Peters G, Nijhuis-van der Sanden R, Morava E. Aerobic exercise in children with oxidative phosphorylation defects. Neurol Int 2010;2:e4. doi:10.4081/ni.2010.e410.4081/ni.2010.e4.
[37] Marcuello A, Martínez-Redondo D, Dahmani Y, Terreros JL, Aragonés T, Casajús JA, et al. Steady exercise removes VO2max difference between mitochondrial genomic variants. Mitochondrion 2009;9:326–30. doi:10.1016/j.mito.2009.04.007.
[38] Cao X, Zhao ZW, Zhou HY, Chen GQ, Yang HJ. Effects of exercise intensity on copy number and mutations of mitochondrial DNA in gastrocnemus muscles in mice. Mol Med Rep 2012;6:426–8. doi:10.3892/mmr.2012.913.
[39] Jeppesen TD, Orngreen MC, van Hall G, Haller RG, Vissing J. Fat metabolism during exercise in patients with mitochondrial disease. Arch Neurol 2009;66:365–70. doi:10.1001/archneurol.2009.24.
[40] Jeppesen TD, Schwartz M, Olsen DB, Wibrand F, Krag T, Duno M, et al. Aerobic training is safe and improves exercise capacity in patients with mitochondrial myopathy. Brain 2006;129:3402–12. doi:10.1093/brain/awl149.
[41] Tarnopolsky MA, Raha S. Mitochondrial myopathies: diagnosis, exercise intolerance, and treatment options. Med Sci Sports Exerc 2005;37:2086–93.
[42] Solaro C, Trabucco E, Signori A, Martinelli V, Radaelli M, Centonze D, et al. Depressive symptoms correlate with disability and disease course in multiple sclerosis patients: an Italian multi-center study using the beck depression inventory. PLoS One 2016. doi:10.1371/journal.pone.0160261.
[43] Askari F, Ghajarzadeh M, Mohammadifar M, Azimi A, Sahraian MA, Owji M. Anxiety in patients with multiple sclerosis: association with disability, depression, disease type and sex. Acta Med Iran 2014.
[44] Jones KH, Ford D V, Jones PA, John A, Middleton RM, Lockhart-Jones H, et al. A large-scale study of anxiety and depression in people with multiple sclerosis: a survey via the web portal of the UK MS register. PLoS One 2012. doi:10.1371/journal.pone.0041910.
[45] Popp RFJ, Fierlbeck AK, Knüttel H, König N, Rupprecht R, Weissert R, et al. Daytime sleepiness versus fatigue in patients with multiple sclerosis: a systematic review on the Epworth sleepiness scale as an assessment tool. Sleep Med Rev 2017. doi:10.1016/j.smrv.2016.03.004.
[46] Rosebush PI, Anglin RE, Rasmussen S, Mazurek MF. Mental illness in patients with inherited mitochondrial disorders. Schizophr Res 2017. doi:10.1016/j.schres.2017.05.010.
[47] Koene S, Kozicz TL, Rodenburg RJ, Verhaak CM, de Vries MC, Wortmann S, et al. Major depression in adolescent children consecutively diagnosed with mitochondrial disorder. J Affect Disord 2009;114:327–32 [doi]. doi:10.1016/j.jad.2008.06.023.
[48] Fattal O, Link J, Quinn K, Cohen BH, Franco K. Psychiatric comorbidity in 36 adults with mitochondrial cytopathies. CNS Spectr 2007;12:429–38.
[49] Mancuso M, Orsucci D, Ienco EC, Pini E, Choub A, Siciliano G. Psychiatric involvement in adult patients with mitochondrial disease. Neurol Sci 2013;34:71–4 [doi]. doi:10.1007/s10072-011-0901-0.
[50] Anglin RE, Tarnopolsky MA, Mazurek MF, Rosebush PI. The psychiatric presentation of mitochondrial disorders in adults. J Neuropsychiatry Clin Neurosci 2012. doi:10.1176/appi.neuropsych.11110345.
[51] Inczedy-Farkas G, Remenyi V, Gal A, Varga Z, Balla P, Udvardy-Meszaros A, et al. Psychiatric symptoms of patients with primary mitochondrial DNA disorders. Behav Brain Funct 2012;8:9 [doi]. doi:10.1186/1744-9081-8-9.
[52] Skorvanek M, Gdovinova Z, Rosenberger J, Ghorbani Saeedian R, Nagyova I, Groothoff JW, et al. The associations between fatigue, apathy, and depression in Parkinson's disease. Acta Neurol Scand 2015. doi:10.1111/ane.12282.
[53] Amtmann D, Askew RL, Kim J, Chung H, Ehde DM, Bombardier CH, et al. Pain affects depression through anxiety, fatigue, and sleep in multiple sclerosis. Rehabil Psychol 2015. doi:10.1037/rep0000027.
[54] Simpson S, Tan H, Otahal P, Taylor B V. Ponsonby AL, lucas RM, et al. anxiety, depression and fatigue at 5-year review following CNS demyelination. Acta Neurol Scand 2016. doi:10.1111/ane.12554.
[55] Ho SY, Rohan KJ, Parent J, Tager FA, McKinley PS. A longitudinal study of depression, fatigue, and sleep disturbances as a symptom cluster in women with breast cancer. J Pain Symptom Manag 2015. doi:10.1016/j.jpainsymman.2014.09.009.
[56] Cohen BL, Zoega H, Shah SA, Leleiko N, Lidofsky S, Bright R, et al. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. Aliment Pharmacol Ther 2014. doi:10.1111/apt.12659.
[57] Bosse-Henck A, Koch R, Wirtz H, Hinz A. Fatigue and excessive daytime sleepiness in sarcoidosis: Prevalence, predictors, and relationships between the two symptoms. Respiration 2017. doi:10.1159/000477352.