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Fatigue in young people with Duchenne muscular dystrophy

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ABBREVIATIONS

CNDR	Canadian Neuromuscular Disease Registry
DMD	Duchenne muscular dystrophy
NIV	Non-invasive ventilation
PAQ-C/A	Physical Activity Questionnaire for Children and Adolescents
PedsQL	Pediatric Quality of Life Inventory
MFS	Multidimensional Fatigue Scale

AIM To describe fatigue in Duchenne muscular dystrophy (DMD) from patients' and parents' perspectives and to explore risk factors for fatigue in children and adolescents with DMD.

METHOD A multicentre, cross-sectional study design was used. Seventy-one patients (all males; median age 12y, age range 5–17y) identified via the Canadian Neuromuscular Disease Registry, and their parents completed questionnaires. Subjective fatigue was assessed using the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale by child self-report and parent proxy-report.

RESULTS Patients with DMD across ages and disease stages experienced greater fatigue compared to typically developing controls from published data. Sleep disturbance symptoms were associated with greater fatigue by child self-report ($\rho=-0.42$; $p=0.003$) and parent proxy-report ($\rho=-0.51$; $p<0.001$). Depressive symptoms were associated with greater fatigue by child self-report ($\rho=-0.46$; $p<0.001$) and parent proxy-report ($\rho=-0.45$; $p<0.001$). Lower functional ability was associated with greater fatigue by parent proxy-report ($\rho=0.26$; $p=0.03$). Physical activity level, and musculoskeletal, respiratory, and cardiac function were not associated with fatigue.

INTERPRETATION In paediatric DMD, sleep disturbance symptoms and depressive symptoms are potentially modifiable factors associated with fatigue, warranting additional investigation to facilitate the development of therapeutic strategies to reduce fatigue.

Duchenne muscular dystrophy (DMD) is an X-linked recessive disease characterized by the absence of, or defect in, the sarcolemma protein dystrophin, resulting in progressive muscle degeneration and loss of ambulation. Additional musculoskeletal, respiratory, and cardiac complications emerge as DMD advances.¹ Children and adolescents with DMD are at increased risk of developmental, emotional, and behavioural problems.² Improved management with corticosteroid therapy and non-invasive ventilation (NIV) has prolonged survival. There is no cure for DMD; therapeutic strategies aim to delay disease progression and improve quality of life.¹ Fatigue recently emerged as the strongest predictor of poor health-related quality of life in children and adolescents with DMD, from both patients' and caregivers' perspectives.³

Subjective fatigue, the focus of this study, is defined as a lack of energy or the existence of weakness or exhaustion — mentally, physically, or both.⁴ Subjective fatigue differs from physiological fatigue or fatigability, which refer to difficulty maintaining physical or mental activity at a desired level.⁵ In neuromuscular disorders, physiological fatigue is related to functioning of the central or peripheral nervous system (lower motor neuron, neuromuscular junction, or muscle), and assessed objectively in a laboratory setting.⁵ Subjective fatigue is ideally assessed using

validated standardized questionnaires addressing the patient perspective.

Fatigue is frequent and among the most disabling symptoms in adult neuromuscular disorders, but it is not well characterized in paediatric neuromuscular disorders, including DMD. Fatigue may limit children's participation in age-related recreational and school activities, and consequently delay development, which is already problematic in children and adolescents with DMD. This may, in turn, ultimately impact social, educational, and occupational pursuits during adulthood.⁶

Data on mechanisms, prevention, and management of fatigue in neuromuscular disorders and paediatric chronic health conditions are limited, with most studies of the latter population focusing on childhood cancer.^{7,8} To our knowledge, no study has explored factors associated with fatigue in DMD. Therefore, identifying fatigue and understanding its determinants may facilitate the development of therapeutic strategies to reduce fatigue and improve health-related quality of life.

To facilitate best clinical practice for the prevention and management of fatigue in children and adolescents with DMD, an understanding of patients' and parents' perspectives of fatigue is needed. Parents' perceptions of their child's health influences healthcare utilization — particularly

when the child is too young, too cognitively impaired, or too ill to self-manage his or her own health.⁹ This study aimed to describe fatigue in DMD from patients' and parents' perspectives, and to explore associations of patient characteristics with child/adolescent self-reported and parent proxy-reported fatigue.

METHOD

A multicentre cross-sectional study design was used. Eligible patients were identified via the Canadian Neuromuscular Disease Registry (CNDR), a clinic-based registry that includes patients from nine paediatric neuromuscular clinics across Canada.¹⁰ Data were collected using mailed paper questionnaires and registry data collected at patients' routine clinic visits. Eligible patients and their primary caregivers were sent questionnaires between July 2016 and November 2016. Patients and parents were instructed to complete their respective questionnaires independently. If a patient was unable to complete their questionnaire independently, the parent was instructed to read the questions to the patient verbatim without providing interpretation, and to indicate the patient's answers on the questionnaire without providing guidance on how to respond. Parents of young children were instructed to act as interviewers for their child. A four-contact mailing strategy was used to maximize the response rate in accordance with the Tailored Design Method.¹¹ Patient clinical characteristics were retrieved from the CNDR database. Implied consent was assumed for patients and parents who returned completed questionnaires.

Approval for the study was obtained from the Research Ethics Board at Western University and the CNDR.

Participants

Eligible patients were identified according to the following inclusion criteria: (1) patients have consented, or a parent or guardian has consented on their behalf, to be notified by the CNDR of research opportunities; (2) patients with a DMD diagnosis confirmed by genetic testing or muscle biopsy, and clinical presentation consistent with DMD; (3) patients are males; (4) patients are between 5 and 17 years of age; and (5) patients have a primary caregiver available to complete a parent questionnaire. Patients were ineligible according to the following exclusion criteria: (1) both patient and parent were unable to complete questionnaires, even with assistance, due to limited literacy, a communication disorder, or cognitive impairment; and (2) patient has a comorbidity unrelated to DMD, which may influence study outcomes.

Measures

Age, musculoskeletal characteristics (ambulatory status, wheelchair use, scoliosis status, corticosteroid therapy status), respiratory characteristics (forced vital capacity, ventilatory status), and cardiac characteristics (left ventricular ejection fraction) were retrieved from the CNDR database. Fatigue, physical activity level, functional ability related to

What this paper adds

- Fatigue is a major issue in paediatric Duchenne muscular dystrophy (DMD) across ages and disease stages.
- Sleep disturbance and depressive symptoms are significantly associated with fatigue in paediatric DMD.

activities of daily living, depressive symptoms, and sleep disturbance symptoms were assessed using survey measures.

Fatigue was measured using the Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale (MFS) by child self-report and parent proxy-report. Parent proxy-report forms are parallel to child self-report forms and assess parents' perceptions of their child's fatigue. The PedsQL MFS is composed of three domains: General Fatigue (six items, e.g. 'I feel tired'; 'I feel too tired to do things that I like to do'), Sleep/Rest Fatigue (six items, e.g. 'I feel tired when I wake up in the morning'), and Cognitive Fatigue (six items; e.g. 'It is hard for me to keep my attention on things'; 'It is hard for me to think quickly'). Respondents were asked to indicate how much of a problem each item had been in the past month. A total score and domain scores were computed, each ranging from 0 to 100, with higher scores indicating less fatigue due to reverse scoring. Total scores were computed if 50% or more items were completed. Domain scores were computed if 50% or more items were completed within each domain.⁹ PedsQL MFS scores of our sample were compared with scores of typically developing children derived from a previous study.¹² Data exclusively on typically developing males aged 5 to 17 years were provided by the developers of the PedsQL MFS and authors of the previously published study¹² for our comparison.

Physical activity level was assessed by child self-report using an adapted Physical Activity Questionnaire for Children and Adolescents (PAQ-C/A). The PAQ-C/A was adapted such that all items were applicable to ambulant and non-ambulant patients with DMD. Respondents were instructed to consider any activity that causes them to sweat, breathe hard, or causes their legs or arms to feel tired. The PAQ-C/A measures physical activity level during the past 7 days. PAQ-C/A scores range from 1 (low physical activity) to 5 (high physical activity).¹³ In the case of missing items, a score was not computed.

Functional ability related to activities of daily living was assessed by parent proxy-report using the DMD Functional Ability Self-Assessment Tool, which assesses physical and respiratory functioning at all disease stages in patients with DMD. Respondents were asked to rate their current level of functioning in relation to common activities of daily living, upper and lower extremities, and ventilation status. DMD Functional Ability Self-Assessment Tool scores range from 0 (low functional ability) to 23 (high functional ability).¹⁴ In the case of missing items, a total score was computed by dividing the sum of completed items by the maximum possible score of completed items, and multiplying this fraction by the maximum possible score of all items.

Depressive symptoms were assessed by child self-report using the Center for Epidemiological Studies Depression Scale for Children. Respondents were asked to indicate how strongly they experienced certain feelings during the past week. The Center for Epidemiological Studies Depression Scale for Children scores range from 0 to 60, with higher scores indicating more depressive symptoms.¹⁵ In the case of missing items, a total score was computed after imputing the mean of completed items as the response for missing items.

Sleep disturbance symptoms were assessed by parent proxy-report using the Sleep Disturbance Scale for Children, which is composed of six domains: disorders of initiating and maintaining sleep, sleep-related breathing disorders, disorders of arousal, sleep-wake transition disorders, disorders of excessive somnolence, and sleep hyperhidrosis. Respondents were asked to consider their child's sleep behaviour during the past 6 months. A total score and domain scores were computed. Possible Sleep Disturbance Scale for Children total scores range from 26 to 130, with higher scores indicating more sleep disturbance symptoms.¹⁶ In the case of missing items, the total and domain scores were not computed.

Statistical analysis

For patient characteristics, median and interquartile range (IQR) were computed for continuous variables, and frequencies and percentages were computed for categorical variables. Mean and standard deviations (SD) or median and IQR were computed for child self-report and parent proxy-report PedsQL MFS scores. Associations between child self-reports and parent proxy-reports of PedsQL MFS scores were examined using pairwise correlation analyses with Spearman's rank correlation coefficient.

Bivariate analyses were conducted to explore associations of patient characteristics with child self-reported and parent proxy-reported fatigue. Associations of continuous variables with PedsQL MFS scores were examined using pairwise correlation analyses with Spearman's rank correlation coefficient. For dichotomous variables, unpaired two-sample *t*-tests or Mann-Whitney *U* test were used to assess differences in PedsQL MFS scores between categories. For categorical variables of more than two categories, one-way analysis of variance (ANOVA) or Kruskal-Wallis tests were used to assess differences in PedsQL MFS scores between categories. Bivariate analyses were performed using pairwise deletion. Exploratory multivariable linear regression analyses were used to explore the adjusted associations of patient characteristics with child self-reported and parent proxy-reported fatigue. Multivariable analyses were performed using complete case analysis (listwise deletion).

Statistical analyses were performed using Stata version 13.0 (StataCorp LP, College Station, TX, USA). A two-sided level of significance at $p=0.05$ was assumed.

RESULTS

Of 193 eligible participants identified and sent questionnaires, 71 patient-parent pairs returned completed

questionnaires. Both patient and parent questionnaires were completed by 64 patient-parent pairs, while for five participants only the parent questionnaire was completed and for two participants only the patient questionnaire was completed. Patient clinical characteristics for participants and non-participants are summarized in Table I. Participating and non-participating patients were similar with respect to age and musculoskeletal, respiratory, and cardiac characteristics, including scoliosis and invasive ventilation (data not presented). The ratio of ambulant to non-ambulant patients was lower for participating patients compared to non-participating patients.

Descriptive statistics for PedsQL MFS scores are presented in Table II, along with PedsQL MFS scores of typically developing males for comparison.¹² Males with DMD experienced greater fatigue (lower scores) compared with typically developing peers from published data across domains, by child self-report and parent proxy-report.¹² Mean (SD) age of typically developing males was 12 years 11 months (3y 2mo) and ranged from 5 to 17 years. PedsQL MFS scores by child self-report were significantly associated with PedsQL MFS scores by parent proxy-report: total fatigue ($\rho=0.69$; $p<0.001$), general fatigue ($\rho=0.63$; $p<0.001$), sleep/rest fatigue ($\rho=0.50$; $p<0.001$), and cognitive fatigue ($\rho=0.68$; $p<0.001$).

Correlation analysis between continuous variables and PedsQL MFS scores by child self-report and parent proxy-report are presented in Tables III and IV respectively. Scatter plots of total fatigue versus physical activity level, functional ability, depressive symptoms, and sleep disturbance symptoms can be seen in Figures S1 to S8

Table I: Comparison of clinical characteristics retrieved from the Canadian Neuromuscular Disease Registry between participating and non-participating patients

	Participating patients ($n=71$)	Non-participating patients ($n=122$)
Age, y	12 (9–15)	12 (10–14)
Musculoskeletal characteristics		
Unsupported ambulation		
Ambulant	42 (59)	84 (69)
Non-ambulant	28 (39)	31 (25)
Wheelchair use		
Never	30 (42)	47 (39)
Intermittent	16 (23)	38 (31)
Permanent	17 (24)	27 (22)
Corticosteroid therapy		
Never	9 (13)	8 (7)
Past	1 (1)	2 (2)
Current	52 (73)	101 (83)
Respiratory characteristics		
Forced vital capacity	88 (72–99)	82.5 (67–94.5)
Non-invasive ventilatory support		
No	66 (93)	105 (86)
Part-time	2 (3)	6 (5)
Full-time	2 (3)	–
Cardiac characteristics		
Left ventricular ejection fraction	64 (60–67.2)	63.9 (59.5–68.5)

Data are frequency (%) or median (IQR).

Table II: Descriptive statistics for the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale by child self-report and parent proxy-report

	DMD sample			Typically developing sample ¹²	
	<i>n</i>	Median (IQR)	Mean (SD)	<i>n</i>	Mean (SD)
Child self-report					
Total fatigue	66	69.4 (62.5–81.9)	71.6 (15.2)	110	82.6 (13.2)
General fatigue	66	70.8 (58.3–83.3)	70.2 (19.7)		87.5 (14.4)
Sleep/rest fatigue	66	75.0 (64.6–87.5)	74.0 (17.5)		76.9 (17.9)
Cognitive fatigue	65	70.8 (54.2–91.7)	70.9 (23.0)		83.4 (15.8)
Parent proxy-report					
Total fatigue	69	69.4 (58.3–84.7)	70.8 (16.0)	121	88.3 (11.6)
General fatigue	69	62.5 (45.8–79.2)	64.2 (20.1)		88.8 (13.6)
Sleep/rest fatigue	69	79.2 (66.7–91.7)	76.9 (18.0)		87.8 (14.5)
Cognitive fatigue	69	75.0 (54.2–91.7)	69.7 (24.6)		88.1 (15.3)

DMD, Duchenne muscular dystrophy.

(online supporting information). Greater physical activity level was significantly associated with greater general fatigue by child self-report. Lower functional ability was significantly associated with greater general fatigue by child self-report, and with greater total fatigue, general fatigue, and sleep/rest fatigue by parent proxy-report. More depressive symptoms were significantly associated with greater total fatigue, general fatigue, sleep/rest fatigue, and cognitive fatigue by child self-report and parent proxy-report. More total sleep disturbance symptoms were significantly associated with greater total fatigue, general fatigue, sleep/rest fatigue, and cognitive fatigue by child self-report and parent proxy-report. Significant correlations with fatigue were most frequently observed for disorders of initiating and maintaining sleep, disorders of arousal, sleep/wake transition disorders, and disorders of excessive somnolence (Tables SI and SII, online supporting information).

Parent proxy-reported sleep/rest fatigue was greater for patients treated with part-time NIV compared with patients not treated with NIV, as demonstrated by Kruskal–Wallis test ($\chi^2=7.02$; $df=2$; $p=0.03$), followed by post hoc analysis using Dunn's test ($p=0.03$).¹⁷ NIV status was not associated with other domains of fatigue (data not presented). Musculoskeletal characteristics (ambulatory status, wheelchair use, scoliosis status, corticosteroid therapy status) were not associated with fatigue (data not presented).

Because bivariate analyses did not consistently demonstrate significant associations between objective measures of musculoskeletal, respiratory, and cardiac function and fatigue, overall functional ability may be more related to fatigue than any single musculoskeletal, respiratory, or cardiac characteristic. Thus, functional ability measured using the DMD Functional Ability Self-Assessment Tool was included as a covariate in the multivariable linear regression analyses, rather than single measures of musculoskeletal, respiratory, and cardiac function.

Multivariable analyses ($n=41$) demonstrated that physical activity level, functional ability, depressive symptoms, and sleep disturbance symptoms explained 38% of the variability in child self-reported total fatigue and 44% of the variability in parent proxy-reported total fatigue. Physical activity level was not associated with total fatigue by child self-report ($\beta=2.50$; $p=0.37$) or parent proxy-report ($\beta=-1.37$; $p=0.61$), while adjusting for functional ability, depressive symptoms, and sleep disturbance symptoms. Functional ability was significantly associated with greater total fatigue by parent proxy-report ($\beta=0.68$; $p=0.03$), but not child self-report ($\beta=-0.18$; $p=0.57$), while adjusting for physical activity level, depressive symptoms, and sleep disturbance symptoms. Depressive symptoms were not associated with total fatigue by child self-report ($\beta=-0.32$; $p=0.31$) or parent proxy-report ($\beta=-0.28$; $p=0.36$), while adjusting for physical activity level, functional ability, and sleep disturbance symptoms. More sleep disturbance symptoms were significantly associated with greater total fatigue by child self-report ($\beta=-0.84$; $p=0.001$) and parent proxy-report ($\beta=-0.91$; $p<0.001$), while adjusting for physical activity level, functional ability, and depressive symptoms.

Table III: Correlation analyses between child characteristics and Pediatric Quality of Life Inventory Multidimensional Fatigue Scale scores by child self-report, using Spearman's rank correlation coefficient (ρ)

	Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue
Clinical characteristics				
Age, y	0.01 (66)	-0.19 (65)	-0.06 (66)	0.23 (66)
Forced vital capacity	0.29 (40)	0.34 ^a (39)	0.15 (40)	0.03 (40)
Left ventricular ejection fraction	0.00 (42)	0.10 (41)	-0.22 (42)	0.08 (42)
Child self-report or parent proxy-report measures				
Physical Activity Questionnaire for Children and Adolescents	0.13 (58)	0.27 ^a (57)	0.12 (58)	-0.06 (58)
Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool	0.05 (64)	0.30 ^a (63)	-0.01 (64)	-0.13 (64)
Center for Epidemiological Studies Depression Scale for Children	-0.46 ^b (66)	-0.30 ^a (65)	-0.30 ^a (66)	-0.46 ^b (66)
Sleep Disturbance Scale for Children	-0.42 ^a (46)	-0.32 ^a (45)	-0.30 ^a (46)	-0.33 ^a (46)

Data are ρ (*n*). ^a $p<0.05$; ^b $p<0.001$.

Table IV: Correlation analyses between child characteristics and Pediatric Quality of Life Inventory Multidimensional Fatigue Scale scores by parent proxy-report, using Spearman's rank correlation coefficient (ρ)

	Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue
Clinical characteristics				
Age, y	0.06 (69)	-0.10 (69)	-0.18 (69)	0.20 (69)
Forced vital capacity (%)	0.12 (40)	0.22 (40)	0.07 (40)	-0.01 (40)
Left ventricular ejection fraction (%)	0.06 (41)	0.22 (41)	-0.07 (41)	0.02 (41)
Child self-report or parent proxy-report measures				
Physical Activity Questionnaire for Children and Adolescents	0.09 (57)	0.16 (57)	0.18 (57)	-0.11 (57)
Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool	0.26 ^a (69)	0.30 ^a (69)	0.3 ^a (69)	0.08 (69)
Center for Epidemiological Studies Depression Scale for Children	-0.45 ^b (64)	-0.37 ^a (64)	-0.35 ^a (64)	-0.32 ^a (64)
Sleep Disturbance Scale for Children	-0.51 ^b (50)	-0.45 ^a (50)	-0.48 ^a (50)	-0.34 ^a (50)

Data are ρ (n). ^a $p < 0.05$; ^b $p < 0.001$.

DISCUSSION

To our knowledge, this is the first study to describe fatigue and to identify factors associated with fatigue in paediatric DMD across the full spectrum of ages and disease stages from patients' and parents' perspectives. Fatigue is a prominent concern in children and adolescents with DMD, highlighting the need for fatigue to be addressed in routine care of affected males. Males with DMD experienced greater fatigue than typically developing males in a previous study,¹² from both patients' and parents' perspectives. Child self-reported and parent proxy-reported fatigue scores of males with DMD in our study were comparable to previously published scores of a multicentre cohort of ambulant males with DMD¹⁸, as well as scores of children and adolescents with cancer, for whom fatigue is recognized as a frequent and debilitating symptom.¹⁹

Of the patient characteristics explored in our study, sleep disturbance symptoms and depressive symptoms emerged as the strongest correlates of fatigue. Lower functional ability was associated with greater fatigue from parents' perspective only. Thus, parents may be more likely to perceive their child's fatigue as an outcome of, or contributor to, the progressive functional decline associated with DMD than patients themselves. Physical activity level and clinical characteristics including age and musculoskeletal, respiratory, and cardiac function were not consistently associated with fatigue. These findings should be interpreted with caution, considering that fatigue may not manifest as a symptom of musculoskeletal and cardiorespiratory decline until the late ambulatory to non-ambulatory stages, or in adulthood. Patients in our sample had relatively preserved cardiorespiratory function.

Because sleep disturbances are frequent in paediatric DMD, and variations exist in their assessment and management in clinical practice, sleep disturbance symptoms may be a modifiable factor associated with fatigue.^{20,21} More sleep disturbance symptoms were associated with greater fatigue from both patients' and parents' perspectives. Sleep-related breathing disorders, of non-obstructive and obstructive origin, are common in DMD.²⁰ In our study, symptoms of sleep-related breathing disorders did not emerge as a correlate of fatigue. However, the accuracy of parent

proxy-reported symptoms of sleep-related breathing disorders compared with objective sleep measurements is unclear.²⁰ Moreover, symptoms such as restless sleep, nightmares, morning confusion, and excessive daytime sleepiness may be related to sleep-related breathing disorders, but were scored as items of other domains in the Sleep Disturbance Scale for Children.¹⁶ Thus, the lack of association between sleep disordered breathing and fatigue should be interpreted cautiously. Symptoms of disorders of initiating and maintaining sleep, disorders of arousal, sleep-wake transition disorders, and disorders of excessive somnolence demonstrated the strongest associations with fatigue. Disorders of initiating and maintaining sleep and disorders of excessive somnolence are prevalent in an estimated 30% and 11% of males with DMD respectively.²⁰ Thus, clinical sleep evaluations in males with DMD should not be limited to detecting sleep-related breathing disorders.

Sleep evaluations in patients with DMD are recommended as early as the ambulatory stage, or at the onset of daytime symptoms of sleep disordered breathing or abnormal pulmonary function tests.²² Because overnight pulse oximetry with capnography has limited utility for detecting sleep disturbances not associated with hypoxemia or hypercapnia, and because there is a poor correlation between daytime symptoms, abnormal pulmonary function, and sleep disturbances, a 'polysomnography for all policy' has been proposed.²³ Polysomnography is important for indicating the need for timely intervention with NIV, which can reduce symptoms of sleep disordered breathing and potentially confer a beneficial effect on fatigue.

Sleep can be further complicated by disease-related, psychological, and social factors. Muscle weakness and the need to be turned by a caregiver during the night have been reported to be associated with sleep disturbance symptoms.²⁰ Emotional and behavioural problems also contribute to sleep disturbance symptoms. Parental exhaustion, sleep deprivation, and poor mental health associated with caring for a child with DMD, can contribute to vulnerability of families and interfere with development of effective sleep hygiene practices in affected males. Recommendations for the assessment and management of sleep disturbances in DMD should be interdisciplinary and extend beyond sleep

disordered breathing to include other sleep disorders, as well as disease-related, psychological, and social factors.

Consistent with findings in other paediatric patient populations,²⁴ our results demonstrated more depressive symptoms were associated with greater fatigue in males with DMD from patients' and parents' perspectives. Males with DMD are at increased risk of depression compared with their typically developing peers or other paediatric patient populations with physical disabilities.²⁵ In a cross-sectional study of adults with DMD, fatigue and affective disorders coexisted in 24% of patients.²⁶

Fatigue, sleep disturbance symptoms, and depressive symptoms can occur independently, or coexist and exacerbate one another. Distinguishing fatigue from sleep disturbance symptoms and depressive symptoms, and understanding causal relationships of this triad is essential for developing targeted therapeutic strategies to achieve satisfactory outcomes. Fatigue implies mental or physical exhaustion, independent of exertion or amount of sleep, whereas excessive daytime sleepiness implies a problem with the sleep-wake cycle.⁶ Depression is characterized by a general lack of interest in daily activities that are typically enjoyed; however, this motivational component is unaffected in fatigue.²⁷

Because we used a cross-sectional study design, multivariable regression analyses do not allow for conclusions about directionality to be made, but serve to explore adjusted associations between related factors and fatigue. Fatigue, sleep disturbance symptoms, and depressive symptoms have complex bidirectional relationships. Despite a strong association between depression and fatigue, causal relationships between depression and fatigue remain to be elucidated in longitudinal studies.²⁸

Physical activity level was not associated with fatigue in males with DMD, in contrast to previous findings whereby physical inactivity was associated with fatigue in children and adolescents with physical disabilities.²⁹ It is possible that the PAQ-C/A did not adequately capture variability in physical activity level of males with DMD, reducing the magnitude of association between physical activity level and fatigue. Because most measures of physical activity level are intended for use in typically developing children, there is a need to develop feasible, valid, and reliable measures for use in patients with neuromuscular disorders, which quantify lower and upper limb activity.

The following limitations of our study should be considered when interpreting the results. The cross-sectional study design does not allow for temporality or causality of associations to be established. Lack of statistical power may have resulted in failure to detect associations between clinical characteristics and fatigue. It is unclear whether participants differ from non-participants with respect to survey measures, or whether males enrolled in the CNDR systematically differ from affected males not enrolled in the CNDR with respect to clinical characteristics or care practices. Nevertheless, the use of a national registry facilitated the inclusion of patients from multiple clinics and

regions within Canada, enhancing generalizability. Because questionnaires were not completed in a supervised setting, we cannot be certain that patients and parents independently completed their respective questionnaires.

Our findings contribute to the limited literature on fatigue in paediatric neuromuscular disorders. We identified fatigue to be a prominent issue in paediatric DMD, emphasizing the need for healthcare providers to become more familiar with fatigue in this population and to engage in dialogue about fatigue with patients and caregivers. We identified sleep disturbance symptoms and depressive symptoms to be associated with fatigue in paediatric DMD, contributing to our understanding of the subjective experience of fatigue as a complex, multi-causal, and multi-dimensional phenomenon. Sleep disturbance symptoms and depressive symptoms may be overlooked in routine management of children and adolescents with DMD, warranting further investigation as potentially modifiable risk factors for fatigue in this population. Child self-report and parent proxy-report symptom-based measures are easy to administer and are associated with a low participation burden. However, measures of sleep disturbance symptoms and depressive symptoms provide limited information on the associations of formal diagnoses of sleep disturbances and depression with fatigue. To further understand these relationships, polysomnographic data and psychiatric evaluations conducted by clinicians are required in future studies. Prospective cohort studies are required to establish causality between patient characteristics and fatigue, to facilitate the development of targeted therapeutic strategies to reduce fatigue, and to improve health-related quality of life. Qualitative studies can also provide insight into the origin, severity, patterns, and impact of fatigue.

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SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Relationship between physical activity level and total fatigue by child self-report

Figure S2: Relationship between functional ability and total fatigue by child self-report

Figure S3: Relationship between depressive symptoms and total fatigue by child self-report

Figure S4: Relationship between sleep disturbance symptoms and total fatigue by child self-report

Figure S5: Relationship between physical activity level and total fatigue by parent proxy-report

Figure S6: Relationship between functional ability and total fatigue by parent proxy-report

Figure S7: Relationship between depressive symptoms and total fatigue by parent proxy-report

Figure S8: Relationship between sleep disturbance symptoms and total fatigue by parent proxy-report

Table SI: Correlation analyses between sleep disturbance symptoms and Pediatric Quality of Life Inventory Multidimensional Fatigue Scale scores by child self-report

Table SII: Correlation analyses between sleep disturbance symptoms and Pediatric Quality of Life Inventory Multidimensional Fatigue Scale scores by parent proxy-report

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RESUMEN**FATIGA EN JÓVENES CON DISTROFIA MUSCULAR DE DUCHENNE**

OBJETIVO Describir la fatiga en la distrofia muscular de Duchenne (DMD) desde la perspectiva de los pacientes y los padres, y explorar los factores de riesgo de fatiga en niños y adolescentes con DMD.

MÉTODO Se utilizó un diseño transversal, con información de diversos centros. En total 71 pacientes (todos varones; edad media 12 años, rango de edad 5 a 17 años) identificados a través del Registro Canadiense de Enfermedades Neuromusculares, y sus padres completaron cuestionarios. La fatiga subjetiva se evaluó utilizando la Escala de Fatiga Multidimensional del Inventario de Calidad de Vida Pediátrica usando la información provista por los niños y por los padres.

RESULTADOS Los pacientes con DMD en todas las edades y etapas de la enfermedad experimentaron una mayor fatiga en comparación con los datos publicados en grupo de niños que se desarrollan típicamente (controles). Los síntomas de alteración del sueño se asociaron con mayor fatiga reportada por el niño ($\rho = -0,42$; $p = 0,003$) y por los padres ($\rho = -0,51$; $p < 0,001$). Los síntomas de depresión se asociaron con mayor fatiga reportada por el niño ($\rho = -0,46$; $p < 0,001$) y por los padres ($\rho = -0,45$; $p < 0,001$). La capacidad funcional más baja se asoció con mayor fatiga reportada por los padres ($\rho = 0,26$; $p = 0,03$). El nivel de actividad física y la función musculoesquelética, respiratoria y cardíaca no se asociaron con la fatiga.

INTERPRETACIÓN En la DMD pediátrica, los síntomas de alteración del sueño y los síntomas de depresión son factores asociados con la fatiga. Estos factores son potencialmente modificables, lo que justifica una investigación adicional para facilitar el desarrollo de estrategias terapéuticas para reducir la fatiga.

RESUMO**FADIGA EM JOVENS COM DISTROFIA MUSCULAR DE DUCHENNE**

OBJETIVO Descrever a fadiga na distrofia muscular de Duchenne (DMD) pela perspectiva de pacientes e pais, e explorar fatores de risco para fadiga em crianças e adolescentes com DMD.

MÉTODO Um desenho de estudo multicêntrico e transversal foi usado. Setenta e um pacientes (todos do sexo masculino; idade mediana 12a, variação da idade 5–17a) identificados via Registro Canadense de Doenças Neuromusculares, e seus pais, completaram os questionários. A fadiga subjetiva foi avaliada usando a Escada de Fadiga do Inventario Pediátrico de Qualidade de Vida Multidimensional por auto-relato da criança e relato dos pais.

RESULTADOS Pacientes com DMD de várias idades e estágios da doença apresentaram mais fadiga comparados os controles com desenvolvimento típico de dados publicados. Sintomas de distúrbios do sono foram associados com maior fadiga pelo auto-relato das crianças ($\rho = -0,42$; $p = 0,003$) e pelo relato dos pais ($\rho = -0,51$; $p < 0,001$). Sintomas depressivos foram associados com maior fadiga no auto-relato das crianças ($\rho = -0,46$; $p < 0,001$) e pelo relato dos pais ($\rho = -0,45$; $p < 0,001$). Menor capacidade funcional se associou com maior fadiga de acordo com o relato dos pais ($\rho = 0,26$; $p = 0,03$). Nível de atividade física, e função músculo-esquelética, respiratória, e cardíaca não foram associadas com a fadiga.

INTERPRETAÇÃO Na DMD pediátrica, sintomas de distúrbios do sono e sintomas depressivos são fatores potencialmente modificáveis, que merecem investigação adicional para facilitar o desenvolvimento de estratégias terapêuticas para reduzir a fadiga.