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Mobility and Upper Extremity Function in Duchenne Muscular Dystrophy: A Longitudinal Survey Using PROMIS

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Background

- Measures such as the Patient-Reported Outcomes Measurement Information Systems (PROMIS) play a crucial role in assessing functional ability and symptom burden from a patient or caregiver perspective[1]
- Duchenne muscular dystrophy (DMD) is characterized by progressive muscular weakness leading to loss of ambulation (LOA), scoliosis, respiratory insufficiency, cardiomyopathy, and ultimately, premature mortality[2-5]
  - Wheelchair dependency commonly occurs by late childhood[6]
  - As DMD progresses, upper limb function deteriorates, resulting in difficulties with reaching, lifting, and manipulating objects[7]
- Functional decline progressively impairs ability to perform activities of daily living such as feeding, self-care and communication, all of which severely impact patient autonomy and health-related quality-of-life[8,9,10]
- At present, there is limited real-world evidence examining patient-reported mobility and upper extremity function in DMD over time

Objectives

- To characterize the progression of mobility and upper extremity function after 36 months in patients with DMD in a real-world setting, as measured by PROMIS Mobility and Upper Extremity scores
- To examine whether PROMIS Mobility and Upper Extremity scores reflect differences in health states defined by varying levels of lower and upper limb function

Methods

Study design and data collection

- Caregivers of individuals with DMD up to 40 years of age were recruited through Parent Project Muscular Dystrophy, a patient advocacy organization in the United States (US), between August 2021-February 2022
- Participants, reporting on one individual with DMD, completed an online survey at baseline and 36 months later, which included a demographic and clinical questionnaire,[11] PROMIS Parent Proxy (PP) Mobility– Short Form 8a, and PROMIS PP Upper Extremity – Short Form 8a[1]
  - Responses to each item ranged from 1 (reflecting the ability to complete tasks with no trouble) to 5 (being unable to perform the tasks)
  - Responses to the PROMIS Mobility form were exclusively provided by caregivers of ambulatory patients
- Data from the clinical questionnaire were used to classify individuals into ambulatory-focused health states[11] defined by level of upper and lower limb function[12,13]

Analysis

- Mean (standard deviation [SD]) PROMIS 'raw summed scores' and T-scores at baseline and month 36 were calculated, stratified by baseline health state
  - Mean raw summed PROMIS scores are calculated by dividing the summed raw score by the number of non-missing item-responses, and range from 1 to 5, with higher scores indicating better mobility and upper limb function[14]
  - PROMIS T-scores were obtained using the "HealthMeasures Scoring Service"; Higher T-scores reflect better mobility or upper extremity function
- Changes in PROMIS scores over time were analyzed using linear regression
  - The model is adjusted for PROMIS score at baseline, age at baseline, and any steroid, PMO, or gene therapy at 36 months (entered as unique covariates)
  - Estimates of mean change, with 95% confidence intervals [CI], from baseline to month 36 were obtained using least squares means extracted from the model

Results

Baseline cohort

- One hundred caregivers were included; the mean (SD) patient age was 12.6 (6.2) years at baseline, and most patients were White (77%)
  - For respiratory support, 13% reported use of nighttime ventilation and 5% night and daytime ventilation; cardiomyopathy was reported by 36%
- At baseline, 85% of participants reported use of corticosteroids
  - Over the course of the 3-year follow-up, 40 patients were administered phosphorodiamidate morpholino oligomers (PMO) and 10 patients received gene therapy at different timepoints
  - The clinical status of the cohort declined over time. While 45% were in the early ambulatory state and 19% in the late non-ambulatory state at baseline, by month 36, only 27% remained early ambulatory and 26% were now in the late non-ambulatory state (**Figure 1**)
  - At baseline 60% had preserved upper limb function, 21% mildly impaired upper limb function, 15% moderately impaired upper limb function, and 4% a loss of upper limb function; these numbers at month 36 were 35%, 39%, 15% and 11%, respectively

Figure 1 *Health states and sample sizes at baseline and month 36*

Health state	Early ambulatory	Late ambulatory	Early non-ambulatory	Late non-ambulatory
Baseline n (%)	45 (45%)	15 (15%)	21 (21%)	19 (19%)
Month 36 n (%)	27 (27%)	13 (13%)	34 (34%)	26 (26%)

Note: Level of lower limb function was used to classify patients as early ambulatory, late ambulatory, or non-ambulatory. Within the non-ambulatory category, patients were further classified as early non-ambulatory if their level of upper limb involvement was considered none or minimal and late non-ambulatory if their level of upper limb involvement was moderate or severe

PROMIS PP Mobility Scores

- Mean PROMIS Mobility raw scores were lower with increasing severity of health states, at baseline and month 36
  - Unadjusted PROMIS Mobility scores are presented in **Table 1**
- Over 36 months, mean (SD) unadjusted PROMIS Mobility scores showed notable declines among patients who were in the early ambulatory (-0.5 [0.5]) and late ambulatory (-0.7 [0.5]) health states at baseline (note, values may not sum exactly due to rounding)
- As anticipated, T-scores were also lower with increasing severity of health states, at baseline and month 36 (**see supplementary materials, QR code**)

Table 1 *Mean Mobility raw scores by health state at baseline and month 36*

DMD patient health state at baseline	N	Baseline		Month 36	
		Mean (SD)	Min, Max	Mean (SD)	Min, Max
Early ambulatory	45	3.3 (0.8)	1.5, 4.9	2.7 (1.0)	1.1, 4.6
Late ambulatory	15	2.4 (0.5)	1.6, 3.2	1.7 (0.5)	1.1, 2.6

Abbreviations: **Max**, maximum; **Min**, minimum; **SD**, standard deviation

- The linear regression model for PROMIS Mobility showed statistically significant declines after 36 months in:
  - Mean raw scores (-0.5 [-0.7, -0.4]; p<0.001) and T-scores (-3.3 [-4.4, -2.2]; p< 0.001) among patients in the early ambulatory health state at baseline
  - Mean raw scores (-0.7 [-1.0, -0.4]; p< 0.001) and T-scores (-5.7 [-7.7, -3.7]; p< 0.001) for patients in the late ambulatory health state at baseline

PROMIS PP Upper Extremity Scores

- Mean PROMIS Upper Extremity raw scores were lower with increasing severity of health states, at baseline and month 36
  - Unadjusted PROMIS Upper Extremity scores are presented in **Table 2**
- The largest declines in PROMIS Upper Extremity scores at 36 months were observed among patients in the late ambulatory (-0.8 [0.8]) and early non-ambulatory (-1.1 [0.9]) health states at baseline
- PROMIS Upper Extremity T-scores were also lower with increasing severity of health states (**see supplementary materials, QR code**)

Table 2 *Mean Upper Extremity raw summed scores by health state at baseline and month 36*

DMD patient health state at baseline	n	Baseline		Month 36	
		Mean (SD)	Min, Max	Mean (SD)	Min, Max
Early ambulatory	45	3.1 (1.0)	1.0, 4.9	3.1 (1.2)	1.0, 5.0
Late ambulatory	15	2.8 (1.0)	1.1, 4.6	2.0 (1.0)	1.1, 4.1
Early non-ambulatory	21	2.5 (1.2)	1.1, 4.4	1.4 (0.5)	1.0, 2.6
Late non-ambulatory	19	1.1 (0.1)	1.0, 1.5	1.0 (0.1)	1.0, 1.4

Abbreviations: **Max**, maximum; **Min**, minimum; **SD**, standard deviation

- The linear regression model for PROMIS Upper Extremity scores showed
  - A statistically significant decrease in mean raw scores (-0.9 [-1.3, -0.4]; p< 0.001) and T-scores (-5.6 [-9.0, -2.2]; p=0.002) after 36 months among patients who were in the early non-ambulatory health state at baseline
  - No significant changes among those in the early ambulatory, late ambulatory, and late non-ambulatory states at baseline, for both mean raw scores and T-scores

Discussion

- Understanding how lower and upper limb function change over time in DMD is essential to both better characterize DMD burden, but also to understand the validity of PROMIS measures for tracking outcomes in DMD
- These results highlight the burden experienced by patients with DMD and document caregiver-reported changes in mobility and upper extremity function related to DMD progression
  - The mobility impairment experienced by ambulatory individuals with DMD is considerable; T-scores indicate individuals in early and late ambulatory states experience severe impairment with mobility, compared to population norms
  - Upper extremity impairments manifest early in the clinical course of DMD; individuals in an early ambulatory state already report some challenges performing upper extremity tasks, and the degree of impairment increases as health states deteriorate
    - Only 15 individuals self-classified into the late ambulatory group, which may help explain why relatively large changes in score on unadjusted analyses, were not significant on adjusted analyses
  - At 36 months, notable and statistically significant declines were observed in mobility for those in both the early and late ambulatory health states while those in the early non-ambulatory showed notable decline in upper limb function
    - In contrast, upper extremity scores among individuals in the late non-ambulatory state remained relatively stable, likely reflecting the advanced disease stage at baseline and the tendency for fine motor function in fingers and hands to be preserved in DMD for an extended period of time before noticeable declines begin.
- The large sample size followed for 36 months is a key strength; limitations include that clinical status was self-reported and the potential for attrition bias to be affecting the generalizability of the study sample by 36 months

Conclusions

- **These results highlight that marked difficulties in upper and lower limb function emerge early in the clinical course of DMD, with impairments worsening with disease progression**
- **Even after mobility is lost, DMD continues to affect other critical motor functions**
- **PROMIS Mobility and Upper Extremity measures can effectively capture real-world changes in physical function over time in patients with DMD**

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