PCR174

Characterizing Progressive Disease Burden amid Heterogeneity: Data Visualizations for Ambulatory Motor Function in Duchenne Muscular Dystrophy (DMD)

Anna Mayhew[1], James Signorovitch[2,3], Michaela Johnson[2], Molly Frean[2], Susan J. Ward[3], Nate Posner[4], Valeria Merla[4], Matthias Mahn[4], Georgia Stimpson[5], Michela Guglieri[1], Volker Straub[1], Robert Muni Lofra[1], Adnan Manzur[5], Giovanni Baranello[5], Francesco Muntoni[5], and the North Star Clinical Network

[1] The John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK [2] Analysis Group, Inc., Boston, MA, USA [3] Collaborative Trajectory Analysis Project (cTAP), Cambridge, MA, USA
[4] Pfizer Inc., New York, NY, USA [5] The Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health, London, UK

Introduction

- DMD is a neuromuscular disorder that follows a recessive, sex-linked pattern of inheritance and results from genetic mutations affecting the dystrophin gene[1]
- DMD primarily impacts males with an estimated prevalence of 15.9 to 19.5 per 100,000 live births[2]
- Patients with DMD experience a gradual weakening of their muscles, leading to impairments in motor function, including walking, as well as pulmonary and cardiac function[3]
  - Research has shown that functional ability is significantly correlated with quality of life in DMD[4]
- While initial symptoms typically manifest by age 3, there is considerable variability in age at symptom onset and in the rate of functional decline thereafter[2]
- DMD currently has no known cure, and treatment objectives focus on symptom management and slowing disease progression
  - Corticosteroids are commonly used and have been shown to preserve function in multiple domains[5]

Objective

- Given variation in ages at symptom onset and rates of motor function decline, this study aimed to develop data visualizations characterizing typical patterns of disease progression amid heterogeneity

Methods

Data and Measures

- Data were obtained from the North Star Clinical Network database, which includes information on regular assessments of patients with DMD from 24 pediatric specialist neuromuscular centers in the UK[6]
- Ambulatory function was measured using the North Star Ambulatory Assessment (NSAA), a validated functional rating scale, which was designed to assess the ambulatory performance of individuals with DMD[7]
  - The NSAA is composed of 17 items: stand, walk, stand up from chair, stand on right leg, stand on left leg, climb step with right leg, climb step with left leg, descend step with right leg, descend step with left leg, get to sitting, rise from floor, lift head, stand on heels, jump, hop on right leg, hop on left leg, and run for 10 meters
    - Prior work has identified six NSAA items, which together accurately reflect disease progression and may be prioritized in practice: walk, rise from floor, stand on one leg, hop on one leg, jump, and climb box step[8]
  - Each NSAA item is scored on a scale of 0 to 2 where 0 indicates inability to perform the test, 1 indicates ability to perform the test with assistance, and 2 indicates ability to perform the test without assistance
  - The NSAA total score ranges from 0 to 34 with higher scores indicating better performance

Sample

- The overall study sample included boys with at least two visits with complete NSAA data between ages 4 and 16
- A subgroup of patients experiencing similar disease progression was identified based on the following additional criteria and contrasted with the overall sample:
  - NSAA total score below 10 between ages 11 and 13
  - NSAA total score above 20 during at least one visit
- We consider the subgroup to be a "centrally representative" sample as the first criterion is consistent with loss of ambulation around age 12, the DMD population median[2]
  - We hypothesized that focusing on patients who lose ambulation around this median age would provide an average rate of decline that is not confounded by variability in the age at which this milestone is reached

Analysis

- Spaghetti plots were used to illustrate trajectories in NSAA total scores for individual patients over time
- Mean NSAA total scores were modeled as a quadratic function of age
- Average performance on specific NSAA functional tasks was described using heatmaps

Results

Sample

- The overall sample included 376 patients with DMD with an average of 5.1 NSAA assessments per patient (**Table 1**)
  - 34 patients were eligible for inclusion in the centrally representative sample
- At the time of their first assessment, the average age of patients in the overall sample was 7.1 years, and the average NSAA total score was 22.2 units
  - Respective values for patients in the centrally representative sample were 6.9 and 24.0
- Mean scores for the six NSAA priority items ranged from 0.7 to 1.7 and 0.8 to 1.8 in the overall and centrally representative samples, respectively
  - In both groups, mean scores were lowest for hop and highest for walk

Table 1. Baseline Characteristics

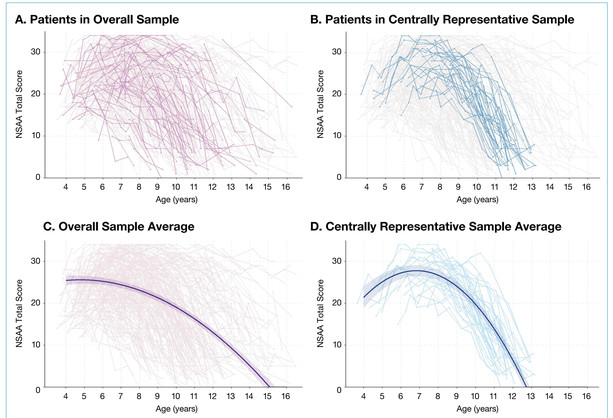
	Overall Sample N = 376	Centrally Representative Sample N = 34
Age	7.1 (2.4)	6.9 (1.7)
Weight	27.7 (12.1)	25.7 (7.2)
Height	118.0 (13.2)	120.9 (8.5)
Body Mass Index	18.6 (3.6)	17.8 (3.0)
NSAA Total Score	22.2 (7.0)	24.0 (4.6)
NSAA Priority Items		
Walk	1.7 (0.5)	1.8 (0.4)
Climb step	1.6 (0.6)	1.7 (0.5)
Stand, one leg	1.5 (0.6)	1.6 (0.5)
Jump	1.3 (0.8)	1.4 (0.8)
Rise from floor	1.1 (0.5)	1.1 (0.3)
Hop	0.7 (0.8)	0.8 (0.7)

Notes: The baseline visit is defined as the first eligible visit for each patient. For NSAA priority items, the best of the left and right side was used for bilateral tasks (stand on one leg; climb step; hop).

Ambulatory Function

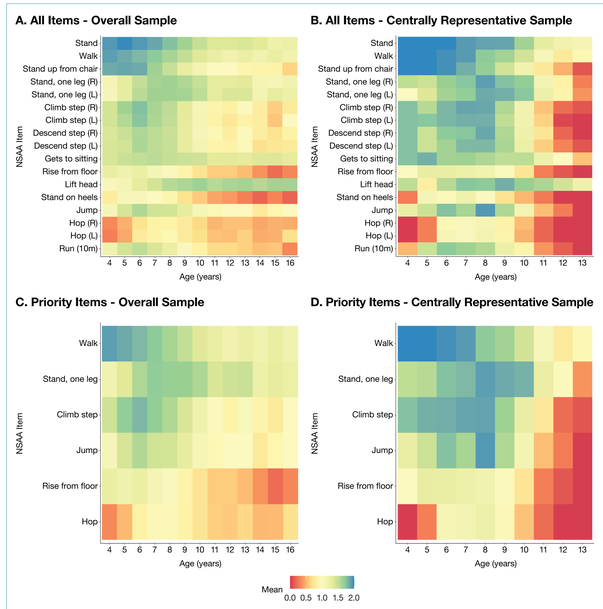
- There was significant heterogeneity in disease progression for the overall sample (**Figure 1-A**), with more similar trajectories observed for the centrally representative sample (**Figure 1-B**)
- Average ambulatory performance in both samples resembled an arc pattern of early improvement followed by later decline (**Figure 1-C** and **Figure 1-D**)
  - Mean NSAA total score declines were more rapid among centrally representative patients than in the overall sample, with the last 15 points of the NSAA total score lost in 2 vs. 4 years
- Performance on specific NSAA tasks exhibited more abrupt declines among centrally representative patients than observed in the overall population (**Figure 2-A** and **Figure 2-B**)
  - Heat maps limited to the six NSAA priority items showed similar patterns for the centrally representative versus overall sample (**Figure 2-C** and **Figure 2-D**)

Figure 1. NSAA Total Score Trajectories



Note: Panels A and B show NSAA total score trajectories for individual patients in the overall and centrally representative samples, respectively. Each line plots an individual patient's NSAA total score over time; darker lines are used to illustrate trajectories for a random sample of 100 patients in Panel A, and to contrast the centrally representative sample from the overall sample in Panel B. Panels C and D show average NSAA total scores by age in the overall and centrally representative samples, respectively. In each panel, the solid line represents the fitted mean score, while the shaded region represents the 95% confidence interval.

Figure 2. NSAA Item Mean Score by Age



Note: Panels A and B show mean NSAA item scores by age in the overall and centrally representative samples, respectively. Panels C and D show mean scores by age in each sample for the six NSAA priority items only. For bilateral tasks (stand on one leg; climb step; hop), the best of the left and right side was used.

Acknowledgments

This study was conducted by the collaborative Trajectory Analysis Project (cTAP) – a precompetitive coalition of academic clinicians, drug developers, and patient foundations formed in 2015 to overcome the challenges of high variation in clinical trials in DMD – with funding from Pfizer. cTAP has received sponsorship from Astellas (Mitobridge), Avidity Biosciences, BioMarin Pharmaceutical, Bristol Meyers Squibb, Catabasis, Daiichi Sankyo, Edgewise Therapeutics, Entrada Therapeutics, FibroGen, Italfarmaco SpA, Marathon Pharmaceuticals, NS Pharma, Pfizer, PTC Therapeutics, Roche, Sarepta Therapeutics, Shire, Solid Biosciences, Summit Therapeutics, Ultragenyx, Vertex Pharmaceuticals, Parent Project Muscular Dystrophy, Charley's Fund, and CureDuchenne, a founding patient advocacy partner and provider of initial seed funding to cTAP.

References

1. Hoffman, E. P., Brown Jr, R. H., & Kunkel, L. M. (1987). Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell*, *51*(6), 919-928.
2. Ryder, S., Leadley, R. M., Armstrong, N., Westwood, M., De Kock, S., Butt, T., ... & Kleijnen, J. (2017). The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. *Orphanet journal of rare diseases*, *12*, 1-21.
3. National Institute of Neurological Disorders and Stroke (NINDS). Muscular Dystrophy Information. Available from: https://www.ninds.nih.gov/Disorders/All-Disorders/Muscular-Dystrophy-Information-Page.
4. Messina, S., Vita, G. L., Sframeli, M., Mondello, S., Mazzone, E., D'Amico, A., ... & Mercuri, E. (2016). Health-related quality of life and functional changes in DMD: a 12-month longitudinal cohort study. *Neuromuscular Disorders*, *26*(3), 189-196.
5. Matthews, E., Brassington, R., Kuntzer, T., Jichi, F., & Manzur, A. Y. (2016). Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database of Systematic Reviews*, (5).
6. UK National Neuromuscular Database. Available from: http://www.northstardmd.com.
7. Mazzone, E. S., Messina, S., Vasco, G., Main, M., Eagle, M., D'Amico, A., ... & Mercuri, E. (2009). Reliability of the North Star Ambulatory Assessment in a multicentric setting. *Neuromuscular Disorders*, *19*(7), 458-461.
8. Mayhew, A., Signorovitch, J., Straub, V., Marini-Bettolo, C., Muni-Lofra, R., Sodhi, J., ... & Muntoni, F. (2022). A Concisely Recorded Ambulatory Assessment for Enhancing Real-World Outcomes Research in Duchenne Muscular Dystrophy: Development and Validation (P13-13.003). *Presented at the 27th International Hybrid Annual Congress of the World Muscle Society*, October 11–15, 2022, Halifax, Nova Scotia, Canada.
9. Mercuri, E., Coratti, G., Messina, S., Ricotti, V., Baranello, G., D'Amico, A., ... & Pane, M. (2016). Revised North Star Ambulatory Assessment for young boys with Duchenne muscular dystrophy. *PLoS One*, *11*(8), e0160195.

Limitations

- The present study focused on motor function, future research should characterize heterogeneity in decline of other functions in DMD, such as respiratory and/or cardiac function
- NSAA item and total scores are unavailable for patients with especially poor ambulatory function, which may bias results towards a more optimistic picture of disease progression
- Certain NSAA items are less appropriate for assessing function in younger boys (i.e., ages 3-5)[9]
- We identified a single centrally representative sample to illustrate how overall averages obscure real rates of functional decline, however, even greater heterogeneity exists in the disease course and is worth exploring further (e.g., in a clustered analysis)

Conclusions

- When patterns of disease progression are heterogeneous, as in DMD, the population average trajectory obscures the more rapid pace of decline experienced by centrally representative individuals
- As the pace of progression can have profound impacts on patients and caregivers, visualizations characterizing representative individual experiences amid population heterogeneity are important to understanding and communicating disease burden
- Understanding the varied nature of disease progression in DMD can provide decisionmakers with better understanding of the burden of the disease for the affected individuals and their families

Presented at the ISPOR 2023 Conference, May 7-10, 2023, Boston, MA, USA