Patient-Reported Outcomes in LGMD2E/R4, 2D/R3, and 2C/R5: Descriptive Analysis of Baseline PROMIS Data From the JOURNEY Natural History Study

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Background

- Limb-girdle muscular dystrophies (LGMDs) are a group of rare genetic disorders characterized by progressive weakness and wasting of the shoulder and pelvic girdle musculature[1–3]
- Sarcoglycanopathies are ultra-rare LGMD subtypes that account for ~15% of LGMD cases in the US[4] and are caused by defects in the genes encoding 1 of the 4 cell membrane glycoproteins contributing to the sarcoglycan complex (SGCB, SGCA, SGCG, and SGCD)[2,3]
- The progressive nature of sarcoglycanopathies has a devastating impact on patients and caregivers[5,6]
- There are limited data on the patient/caregiver-reported impact of sarcoglycanopathies on physical function and aspects of health-related quality of life

Objective

To describe baseline Patient-Reported Outcomes Measurement Information System (PROMIS) data from patients with sarcoglycanopathy subtypes LGMD2E/R4, 2D/R3, and 2C/R5 enrolled in JOURNEY (NCT04475926)

Methods

- JOURNEY is a global, multicenter, prospective, longitudinal study of the natural history of patients with LGMD2E/R4, LGMD2D/R3, LGMD2C/R5, and LGMD2A/R1[7]
  - This analysis reports only data from patients with sarcoglycanopathy subtypes (2E/R4, 2D/R3, 2C/R5); data from patients with LGMD2A/R1 are not shown

Study population

- Male or female ≥4 years of age
- Clinical diagnosis (muscle weakness, loss of function, delayed milestones) and genetic confirmation (1 homozygous or 2 heterozygous pathogenic and/or likely pathogenic sarcoglycans, ie, β-SG, α-SG, or γ-SG) of LGMD sarcoglycanopathy

Patient/observer-reported outcome-related study endpoints

- PROMIS scores
- PROMIS measures included age-appropriate proxy or self-reported versions of items of Mobility, Strength Impact, Upper Extremity, Fatigue, Sleep Disturbance, and Positive Affect (**scan QR code for additional methods details**)
- Mean scores (0–5, with higher scores indicating more of the concept being measured) were derived for each measure by taking an average of all items

Results

Baseline characteristics

- PROMIS data were available for 91 of 137 patients enrolled in JOURNEY at the time of data analysis
- Sarcoglycanopathy subtypes included 2C/R5 (n=34), 2D/R3 (n=32), and 2E/R4 (n=25) (**Table 1**)
- Overall, 58 (63.7%) were female, and 45 (49.5%) were ambulatory
- Mean (SD) age was 19.1 (14.48) years for ambulatory and 26.0 (12.50) years for nonambulatory patients
- Additional baseline characteristics are shown in **Supplemental Table 1**

PROMIS scores

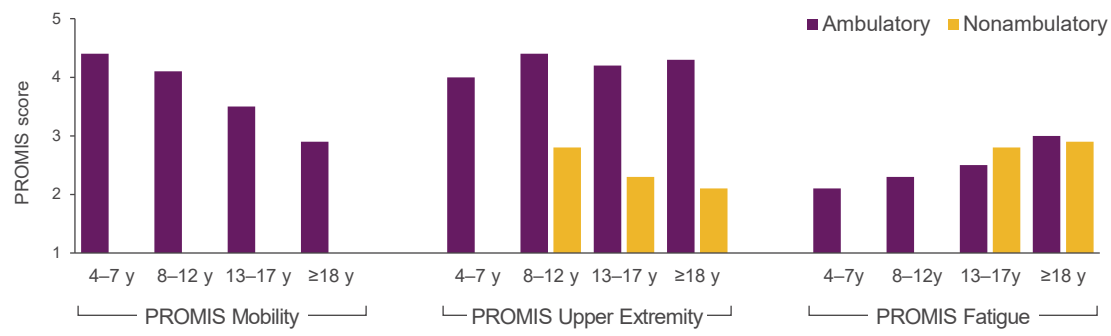
- PROMIS Mobility mean scores suggested that mobility is more limited in older age groups, consistent with an irreversibly progressive degenerative neuromuscular disease such as LGMD (**Figure 1, Table 2A**)
- PROMIS Upper Extremity mean scores were higher in ambulatory vs nonambulatory patients
  - Scores of ambulatory patients slightly increased between the 4–7-year age group and older age groups, which may be due to physiological fine motor development
  - Following the expected disease course, nonambulatory patients exhibited lower PROMIS Upper Extremity mean scores compared with ambulatory patients (**Figure 1, Table 2B**)
- PROMIS Fatigue mean scores increased with age, indicating that older patients may experience higher levels of fatigue compared with younger patients (**Figure 1, Table 2C**)
- PROMIS Strength Impact mean scores indicated that strength tended to decrease with age across LGMD subtypes, with a more pronounced impact observed in nonambulatory patients (**Supplemental Table 2A**)
- Sleep Disturbance and Positive Affect mean scores were generally similar between ambulatory and nonambulatory patients (**Supplemental Table 2B, C**)

Table 1 *Baseline Characteristics by LGMD Subtype and Ambulatory Status*

Characteristic	2C/R5 (n=34)	2D/R3 (n=32)	2E/R4 (n=25)	Overall (N=91)
Age, years				
Mean (SD)	18.5 (9.64)	25.6 (16.68)	24.2 (14.01)	22.6 (13.87)
Gender, n (%)				
Female	23 (67.6)	20 (62.5)	15 (60.0)	58 (63.7)
Ambulatory, n (%)	11 (32.4)	20 (62.5)	14 (56.0)	45 (49.5)
4–7 y	2 (5.9)	3 (9.4)	3 (12.0)	8 (8.8)
8–12 y	5 (14.7)	3 (9.4)	3 (12.0)	11 (12.1)
13–17 y	4 (11.8)	4 (12.5)	2 (8.0)	10 (11.0)
≥18 y	0 (0.0)	10 (31.3)	6 (24.0)	16 (17.6)
Nonambulatory, n (%)	23 (67.6)	12 (37.5)	11 (44.0)	46 (50.5)
4–7 y	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
8–12 y	2 (5.9)	1 (3.1)	0 (0.0)	3 (3.3)
13–17 y	9 (26.5)	3 (9.4)	3 (12.0)	15 (16.5)
≥18 y	12 (35.3)	8 (25.0)	8 (32.0)	28 (30.8)

LGMD=limb-girdle muscular dystrophy; y=years of age.

Figure 1 *PROMIS Scores by Age and Ambulatory Status*



PROMIS=Patient-Reported Outcome Measurement Information System; y=years of age.

Table 2 *Baseline PROMIS Scores by LGMD Subtype and Ambulatory Status*

			2C/R5 (n=34)	2D/R3 (n=32)	2E/R4 (n=25)	Ambulatory (n=45)	Nonambulatory (n=46)
A PROMIS Mobility	4–7 y	n	2	3	3	8	NA
		Mean (SD)	4.6 (0.28)	4.4 (0.55)	4.2 (0.26)	4.4 (0.38)	NA
	8–12 y	n	5	3	3	11	NA
		Mean (SD)	3.9 (0.50)	4.4 (0.32)	4.1 (0.73)	4.1 (0.51)	NA
	13–17 y	n	4	4	2	10	NA
		Mean (SD)	2.8 (0.77)	3.8 (0.97)	4.5 (0.38)	3.5 (1.03)	NA
	≥18 y	n	NA	10	6	16	NA
		Mean (SD)	NA	3.1 (0.99)	2.7 (0.91)	2.9 (0.94)	NA
B PROMIS Upper Extremity	4–7 y	n	2	3	3	8	NA
		Mean (SD)	4.7 (0.20)	3.3 (1.72)	4.1 (1.08)	4.0 (1.23)	NA
	8–12 y	n	7	4	3	11	3
		Mean (SD)	3.9 (1.04)	3.8 (1.07)	4.7 (0.47)	4.4 (0.74)	2.8 (0.38)
	13–17 y	n	13	7	5	10	15
		Mean (SD)	2.8 (1.19)	3.4 (1.39)	3.1 (1.76)	4.2 (1.02)	2.3 (0.95)
	≥18 y	n	12	18	14	16	28
		Mean (SD)	1.8 (0.37)	3.3 (1.34)	3.2 (1.24)	4.3 (0.56)	2.1 (0.76)
C PROMIS Fatigue	4–7 y	n	2	3	3	8	NA
		Mean (SD)	1.5 (0.71)	1.6 (1.10)	3.0 (1.50)	2.1 (1.26)	NA
	8–12 y	n	7	4	3	11	3
		Mean (SD)	2.2 (0.58)	2.6 (1.21)	2.6 (0.76)	2.3 (0.79)	2.7 (0.90)
	13–17 y	n	13	7	5	10	15
		Mean (SD)	2.7 (1.05)	3.1 (1.39)	2.1 (0.66)	2.5 (1.00)	2.8 (1.20)
	≥18 y	n	12	18	14	16	28
		Mean (SD)	2.6 (0.58)	3.0 (0.66)	3.0 (0.65)	3.0 (0.68)	2.9 (0.62)

LGMD=limb-girdle muscular dystrophy; PROMIS=Patient-Reported Outcome Measurement Information System; y=years of age.

Key Finding

Baseline PROMIS Measure showed that younger and ambulatory patients with sarcoglycanopathies generally reported higher physical functioning scores compared with older or nonambulatory counterparts

Conclusions

While caution is necessary when interpreting data across age-specific measures, mean PROMIS scores can still provide insights into the differences between age groups since they measure the same construct

Mobility scores were lower for older ambulatory patients and Upper Extremity scores were lower in older nonambulatory patients, which aligns with the known progression of sarcoglycanopathy; older patients reported higher levels of fatigue across both ambulatory and nonambulatory groups

This analysis of baseline data is a pivotal step in understanding sarcoglycanopathies from both patient- and observer-reported perspectives; baseline data also serve as a benchmark, providing a reference point against which future changes and improvements can be measured

Future longitudinal analyses will help confirm cross-sectional trends and support interpretation of patient/caregiver-reported outcomes for different sarcoglycanopathy subtypes

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