PATTERNS OF CLINICAL PROGRESSION AMONG PATIENTS WITH AUTOSOMAL RECESSIVE LIMB-GIRDLE MUSCULAR DYSTROPHY (LGMDR): A SYSTEMATIC REVIEW

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BACKGROUND

- Limb-girdle muscular dystrophy (LGMD) is a group of rare muscular dystrophies primarily characterized by proximal muscle weakness.[1]
- Over 30 subtypes have been identified, of which 90% are autosomal recessive (LGMDR).[2,3]
  - The most common are: LGMDR1, LGMDR2/Miyoshi myopathy (MM), LGMDR3-6, LGMDR9, LGMDR12.
- The course of LGMDR is highly variable between patients; some are severely affected from a young age while others have mild impacts in advanced age.[4,5]
- Worsening of muscle weakness over time may lead to loss of ambulation (LOA) as well as severe cardiac and respiratory involvement (i.e. cardiomyopathy or respiratory failure).[2,6]
- Although such clinical manifestations have been described in various LGMDR subtypes, it is unclear how clinical progression compares between subtypes, and whether these more severe manifestations occur together.
- Characterizing clinical progression by subtype is crucial to understand the specific disease burden and unmet needs of patients with LGMDR.

OBJECTIVE

- To characterize the frequency of and age at progression (including development of LOA, cardiac and respiratory involvement); and the frequency of cardiac or respiratory involvement among those with or without LOA in LGMDR, according to subtype.

METHODS

- A systematic literature review (SLR) was conducted to identify published data on the frequency of LOA, cardiac & respiratory involvement in patients with LGMDR1, LGMDR2/MM, LGMDR3-6, LGMDR9, and LGMDR12.
- A study-specific search strategy was implemented in MEDLINE and EMBASE in September 2019.

METHODS, CONT.

- Patient-level data from epidemiologic studies, clinical trials, as well as case series and reports were included.
- Outcomes of interest for the overall sample, and for each LGMDR subtype, were:
  - N patients with ambulatory status & age at ambulation assessment reported.
  - From those, the n (%) patients with LOA or who remained ambulatory at the age at assessment. Not all included patients had experienced LOA at the time of assessment.
  - n (%) of patients with LOA and without LOA who experienced cardiac or respiratory involvement.
  - Mean (standard deviation [SD]) age at LOA, cardiac & respiratory involvement.
- Patients were analyzed based on the subgroup reported by study authors; e.g. if authors did not report LGMDR2 and MM separately, this was analyzed as LGMDR2/MM.

RESULTS

- 2,929 abstracts were identified and screened.
- 418 patients had both ambulatory status and age at ambulation assessment reported; 142 (34.0%) also had an assessment of cardiac and/or respiratory function.

RESULTS, CONT.

- LOA was reported in 265 (63.4%) patients, with counts by subtype ranging from 5 (23.8%; LGMDR12) to 105 (92.9%; LGMDR3-6; Table 1).
- Of patients with LOA assessed for cardiac and/or respiratory function, cardiac involvement was most frequent in LGMDR9 (11; 73.3%) and respiratory involvement was most frequent in LGMDR3-6 (20; 74.1%).

Figure 1. Mean age (years) at clinical manifestations for patients with LOA

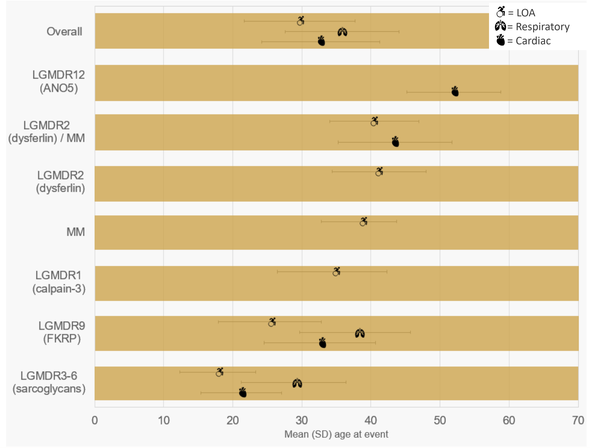

Table 1. LGMDR patients with clinical manifestations among those with ambulation and age data

	LOA [a]		Cardiac				Respiratory			
LGMDR subtype	n (%) with LOA	Mean (SD) age at LOA	n (%) with cardiac assessment [b]	n (%) with involvement	Mean (SD) age at involvement	Mean (SD) age at no involvement [c]	n (%) respiratory assessment [b]	n (%) with involvement	Mean (SD) age at involvement	Mean (SD) age at no involvement [c]
Overall	**265 (63.4)**	**28.6 (15.8)**	**91 (34.3)**	**45 (49.5)**	**28.0 (16.5)**	**30.7 (14.9)**	**49 (18.5)**	**28 (57.1)**	**28.1 (14.6)**	**37.7 (15.0)**
LGMDR1 (calpain-3)	37 (68.5)	33.8 (15.7)	8 (21.6)	2 (25.0)	30.5 (29.0)	40.2 (16.0)	5 (13.5)	1 (20.0)	27.0	40.0 (22.9)
LGMDR2 (dysferlin)/MM	77 (68.1)	39.9 (12.7)	11 (14.3)	6 (54.5)	51.8 (15.1)	40.6 (14.7)	6 (7.8)	2 (33.3)	59.5 (2.1)	41.0 (9.8)
LGMDR2 (dysferlin)	49 (67.1)	40.2 (13.1)	7 (14.3)	4 (57.1)	44.3 (11.3)	48.3 (13.4)	4 (8.2)	1 (25.0)	58.0	43.3 (10.5)
MM	23 (82.1)	38.3 (10.9)	3 (13.0)	1 (33.3)	61.0	29.0 (7.1)	2 (8.7)	1 (50.0)	61.0	34.0
LGMDR3-6 (sarcoglycans)	105 (92.9)	18.9 (10.5)	53 (50.5)	26 (49.1)	24.2 (10.8)	22.6 (9.7)	27 (25.7)	20 (74.1)	23.9 (11.0)	25.9 (5.5)
LGMDR9 (FKRP)	41 (35.0)	24.3 (15.4)	15 (36.6)	11 (73.3)	23.7 (17.7)	37.0 (0.0)	7 (17.1)	5 (71.4)	32.4 (16.0)	38.5 (2.1)
LGMDR12 (ANO5)	5 (23.8)	55.0 (12.5)	4 (80.0)	0 (0.0)	N/A	52.5 (13.0)	4 (80.0)	0 (0.0)	N/A	52.5 (13.0)

[a] Among patients without LOA, 12 had cardiac and 6 had respiratory involvement (further analysis not shown); [b] Cardiac and respiratory involvement was only assessed among those with LOA; [c] Patients with no involvement at time of assessment may have developed additional clinical manifestations after follow-up (the age shown is the last known age at which they did not have cardiac or respiratory involvement).

RESULTS, CONT.

- Data for patients without LOA were sparse. Of 153 without LOA, 39 (25.5%) had cardiac & 24 (15.7%) had respiratory assessments. Data were only available for LGMDR9, LGMDR12, and LGMDR3-6, hence not shown in Table 1. Twelve patients had cardiac (11 LGMDR9, 1 LGMDR4) and 6 had respiratory (5 LGMDR9, 1 LGMDR4) involvement. No patients with LGMD12 had either cardiac or respiratory involvement.
- Among those experiencing progression to clinical manifestations, this tended to occur earliest for patients with LGMDR3-6, and latest for patients with LGMDR12 (Figure 1).

DISCUSSION

- This study described the clinical progression to LOA, cardiac & respiratory involvement, and the frequency of cardiac or respiratory involvement among those with or without LOA, in LGMDR by subtype.
- Patients with LOA often experienced cardiac and respiratory involvement; these were less common among patients without LOA except for those with LGMDR9, suggesting that these manifestations may precede LOA in some cases for LGMDR9.
- Variability in the occurrence of cardiac and respiratory involvement among patients with LOA was observed across LGMDR subtypes.
- Mean age at involvement was also variable, and was earliest among those with LGMDR3-6 and latest among those with LGMDR12.
- Small sample sizes of individual subtypes and the lack of standardized reporting in case report data limit the generalizability of these findings.
- Nevertheless, this SLR provides insight through the synthesis of available data on clinical progression for a rare disease.

CONCLUSIONS

This study described the clinical progression to LOA, cardiac, and respiratory involvement in LGMDR. Despite limited data, these findings help characterize the clinical progression of LGMDR by subtype.

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ACKNOWLEDGEMENTS & DISCLOSURES

This study was funded by Sarepta Therapeutics, Inc. IFA and KLG are employees of Sarepta Therapeutics, Inc. AC, SMS and MF are employees of Broadstreet HEOR, which received funds from Sarepta for the conduct of this study. CCW received consulting fees as part of this study. Contact: sszabo@broadstreetheor.com

Presented at the MDA 2021 Virtual Congress
March 15 – 21, 2021