PROGRESSION TO LOSS OF AMBULATION AMONG PATIENTS WITH AUTOSOMAL RECESSIVE LIMB-GIRDLE MUSCULAR DYSTROPHY: 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 clinical course of LGMDR subtypes is highly variable.
  - Onset can range from childhood through adulthood.
  - Signs and symptoms of muscle weakness may appear at any age and typically worsen over time.[2,4]
- Progression to severe mobility impairments such as loss of ambulation (LOA) has been described across LGMDR subtypes;[5,6,7] however, it is unclear how the frequency and timing of LOA compares between subtypes.
  - While there has been some indication that those with pediatric-onset LGMDR may experience a more severe progressive course than those with adult-onset disease,[8] the impact of age at onset on progression to LOA has not been well established.
- Understanding the natural history by subtype and age at onset is important to characterize disease burden and unmet need in LGMDR. Moreover, this data may help inform trial design, capturing the unique aspects of LGMDR that can have onset in childhood and adulthood.

OBJECTIVE

- To characterize the frequency and timing of LOA among patients with pediatric- and adult-onset LGMDR, by LGMDR subtype.

METHODS

- A systematic literature review was conducted to identify published data on the frequency and timing of LOA 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:
  - The n (%) with adult- (>18 years), late childhood- (10-18 years), and early childhood-onset (<10 years) LGMDR.
  - From those, the n (%) with ambulatory status reported. Not all included patients had experienced LOA at the time of assessment.
  - n (%) patients with LOA or who remained ambulatory at the age at assessment.
  - Among those with LOA and whose age at onset was reported numerically, mean (standard deviation [SD]) time from onset to LOA, stratified by age of onset (adult-, late childhood-, and early childhood-onset LGMDR).
- 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.
- 1,597 patients had a reported age at onset; overall, 695 (43.5%) had adult-, 531 (33.2%) had late childhood-, and 371 (23.2%) had early childhood-onset disease (Table 1).

Table 1. Patients with LOA by age at onset category and LGMDR subtype

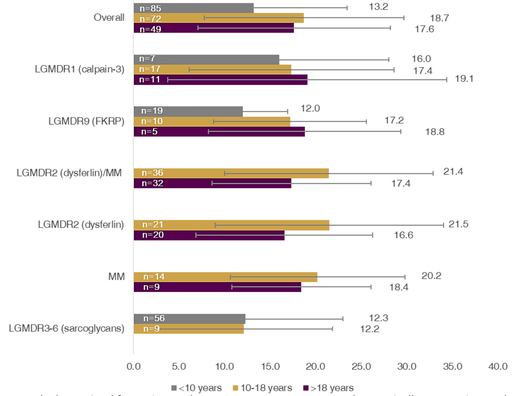
	Adult-onset (>18 years)			Pediatric-onset (10-18 years)			Pediatric-onset (<10 years)		
LGMDR subtype	**N in age group**	**n (%) with ambulatory status**	**n (%) with LOA**	**N in age group**	**n (%) with ambulatory status**	**n (%) with LOA**	**N in age group**	**n (%) with ambulatory status**	**n (%) with LOA**
Overall, N=1,597*	**695**	**122 (17.6)**	**64 (52.5)**	**531**	**132 (24.9)**	**78 (59.1)**	**371**	**121 (32.6)**	**86 (71.1)**
LGMDR1 (calpain-3), n=324	102	12 (11.8)	11 (91.7)	162	30 (18.5)	17 (56.7)	60	10 (16.7)	7 (70.0)
LGMDR2 (dysferlin)/MM, n=529	308	56 (18.2)	32 (57.1)	211	54 (25.6)	42 (77.8)	10	3 (30.0)	3 (100.0)
LGMDR2 (dysferlin), n=312	175	35 (20.0)	20 (57.1)	128	36 (28.1)	27 (75.0)	9	2 (22.2)	2 (100.0)
MM, n=144	83	14 (16.9)	9 (64.3)	61	14 (23.0)	14 (100.0)	0	N/A	N/A
LGMDR3-6 (sarcoglycans), n=289	22	11 (50.0)	11 (100.0)	59	13 (22.0)	9 (69.2)	206	60 (29.1)	57 (95.0)
LGMDR9 (FKRP), n=292	106	23 (21.7)	5 (21.7)	91	34 (37.4)	10 (29.4)	95	48 (50.5)	19 (39.6)
LGMDR12 (ANO5), n=165	157	20 (12.7)	5 (25.0)	8	1 (12.5)	0 (0.0)	0	N/A	0 (0.0)

*Sum of n's listed for each subtype exceeds 1,597 as patients reported as having LGMDR2 or MM are also represented in the grouped LGMDR2/MM category.

RESULTS, CONT.

- Of the 1,597 patients, 375 (23.5%) also had ambulatory status reported, ranging from 21 (12.7%; LGMDR12) to 113 (21.4%; LGMDR2/MM) patients.
- LOA was observed in 60.8% (228/375) and was most common among those with early childhood-onset LGMDR (71.1%, 86/121). This trend was generally consistent across subtypes, except in cases where low numbers of patients with ambulatory status were available (e.g. LGMDR1).
- n (%) of patients with LOA and adult- or late childhood-onset was highest for LGMDR2/MM (32 [57.1%] and 42 [77.8%], respectively); while n (%) with LOA and early childhood-onset was highest for LGMDR3-6 (57 [95.0%]).

Figure 1. Time (years) to LOA of adult- and pediatric-onset LGMDR, by subtype*



*Time to LOA was only determined for patients whose age at onset was reported numerically; e.g. patients who were reported as having onset "in adulthood" are not reflected. In addition, subtypes and age groups with n<5 are not reflected (e.g. LGMDR12).

RESULTS, CONT.

- Mean (SD) time to LOA varied between subtypes, being shortest for patients with early childhood-onset LGMDR9 (12.0 [4.9] years, n=19) and longest for those with late childhood-onset LGMDR2 (21.5 [12.5] years, n=21), suggesting that patients with earlier onset have faster progression to LOA (Figure 1).

DISCUSSION

- This study described the occurrence and timing of LOA in LGMDR according to age at disease onset and subtype.
- These findings suggest that LOA is more common among patients with early childhood- (71.1%) compared to late childhood- (59.1%) and adult-onset disease (52.5%). Moreover, patients with early childhood-onset disease tend to have faster progression to LOA than those with late childhood- or adult-onset disease, particularly in LGMDR9.
- The small sample sizes for some subtypes may limit the generalizability of these findings.
  - Selection and reporting bias may also have resulted in ambulatory status being preferentially investigated among those who progressed to LOA, which would further impact generalizability.
- Data informing this synthesis were primarily from cross-sectional studies. Large registries or observational studies that follow patients over time would be valuable to better characterize the natural history of LGMDR.

CONCLUSIONS

- This study described the frequency and timing of LOA among patients with adult- and pediatric-onset LGMDR. Despite limited data, these findings provide a greater understanding of progression to LOA by subtype in LGMDR, which may help inform clinical trial design and provide a basis for natural history studies.

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