THE AGE AT LOSS OF AMBULATION AMONG PATIENTS WITH LIMB-GIRDLE MUSCULAR DYSTROPHY SUBTYPE 2: A SYSTEMATIC REVIEW

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BACKGROUND

- Limb-girdle muscular dystrophy (LGMD) refers to a group of rare muscular dystrophies caused by mutations in genes encoding proteins involved with muscle maintenance, function, and repair.[1]
- Over 30 subtypes of LGMD have been identified, of which 90% are autosomal recessive (LGMD2).[2,3] The most common of these are calpainopathy (LGMD2A), dysferlinopathy (LGMD2B/Miyoshi myopathy [MM]), sarcoglycanopathies (LGMD2C-F), anoctaminopathy (LGMD2L), and dystroglycanopathy (LGMD2I).
- Patients with LGMD, including LGMD2, predominantly present with proximal muscle weakness.[4]
- The clinical course of different LGMD2 subtypes is highly variable.
  - Onset can range from childhood through adulthood.
  - Disease severity varies from mild forms in which patients have relatively normal function, to severe forms with rapid onset and progression.[1,4]
- Progression to severe mobility impairments such as loss of ambulation (LOA) has been described across LGMD2 subtypes;[5,6] however, it is unclear how the timing of LOA compares between subtypes.
  - Understanding the natural history by subtype is important to characterize disease burden and unmet need among those with LGMD2.

OBJECTIVE

- To synthesize data on the timing of LOA among patients with the most common LGMD2 subtypes.

METHODS

- A systematic literature review (SLR) was conducted to identify published data on the frequency and timing of LOA in patients with LGMD2A, LGMD2B/MM, LGMD2C-F, LGMD2L, and LGMD2I.

METHODS, CONT.

- A study-specific search strategy was implemented in MEDLINE and EMBASE in September 2019.
- This SLR captured data from epidemiologic studies, clinical trials, as well as case series and case reports.
- Outcomes of interest were:
  - N patients with ambulatory status & age at ambulation assessment reported
  - n (%) patients with LOA (including wheelchair dependency)
  - Mean (standard deviation [SD]) age at LOA (overall and by LGMD2 subtype).
- Eligible studies were required to present either individual or grouped estimates of LOA. Patients were included if both their ambulatory status and age at ambulation assessment were reported. Not all included patients had experienced LOA at the time of assessment.
- To calculate the timing of LOA, only patients who had experienced LOA/wheelchair dependency were included.

RESULTS

- 2,929 abstracts were identified and screened.
- Overall, 7147 patients were identified and 2107 had ambulatory status reported.

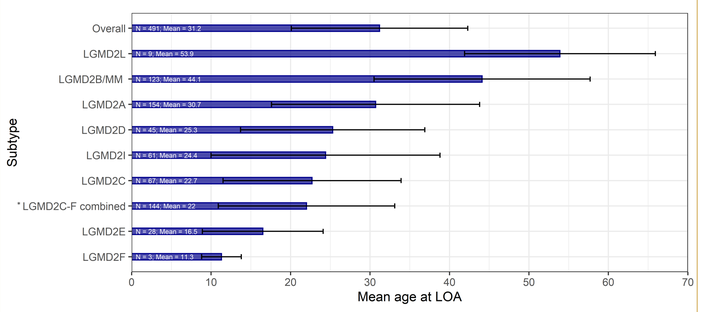
Table 1. LGMD2 patients with LOA among those with ambulation and age data

LGMD2 subtype	Total N	N with ambulatory status	N with ambulatory status & age	% with LOA*
Overall	7147	2107	661	74.3%
LGMD2E	222	73	29	96.6%
LGMD2D	354	97	49	91.8%
LGMD2C-F	1290	376	157	91.7%
LGMD2C	428	89	74	90.5%
LGMD2A	1819	603	171	90.1%
LGMD2B/MM	1971	856	159	77.4%
LGMD2F	32	16	4	75.0%
LGMD2I	1387	235	149	40.9%
LGMD2L	680	37	25	36.0%

* Of patients with ambulatory status and age reported

RESULTS, CONT.

Figure 1. Mean age at LOA by LGMD2 subtype



* Includes patients who were reported combined as LGMD2C-F, as well as patients reported individually as LGMD2C, 2D, 2E, and 2F.

- 661 patients were identified from 105 studies with ambulatory status and age at ambulation assessment available for the most common LGMD2 subtypes.
- The most data were available from patients with LGMD2B/MM (n=159; Table 1). The fewest data were reported on patients with LGMD2F (n=4).
- Overall, 491/661 (74.3%) of LGMD2 patients were reported to experience LOA/wheelchair dependency (Table 1).
  - All but one patient with LGMD2E were reported to have LOA/wheelchair dependency (28/29; 96.6%)
  - LOA/wheelchair dependency was also common among patients with LGMD2D (45/49; 91.8%) and sarcoglycanopathies (LGMD2C-F) as a whole (144/157; 91.7%), and least common among patients with LGMD2I (61/149; 40.9%) and LGMD2L (9/25; 36.0%).
- Of the 491 LGMD2 patients with LOA/wheelchair dependency, the mean (SD) age at LOA was 31.2 (11.1) years (Figure 1).
  - Mean (SD) age at LOA was earliest in LGMD2F (11.3 [2.5] years) and LGMD2E (16.5 [7.6] years), and latest in LGMD2L (53.9 [12.0] years).

DISCUSSION

- LOA is a severe and devastating complication of LGMD2 but its frequency and timing is unclear, particularly when comparing between subtypes.
- This study described the occurrence and timing of LOA among patients with the most common LGMD2 subtypes.
- Variability in the occurrence of LOA was observed across LGMD2 subtypes; in some subtypes, almost all patients were reported to have LOA (LGMD2E) while in others, less than half had LOA (LGMD2I, 2L).
- Mean age at LOA was also variable, ranging from 11.3 to 53.9 years.
- Limitations to reported data precluded calculating the proportion of patients remaining ambulant over time.
- Selection and reporting bias may result in studies describing ambulatory status particularly among patients with LOA, which would impact the generalizability of the findings.
- The requirement that age at ambulation assessment be reported limited data availability, with some subtypes having fewer than 30 patients in the analysis (LGMD2E, 2F, 2L). However, given the rarity of some subtypes, small sample sizes were expected.
- Large registries or observational studies that follow patients over time would be valuable to better characterize the natural history of LGMD2. Given the present lack of such data, this SLR provides useful insights through the synthesis of available data on clinical progression for a rare disease with a limited evidence base.

CONCLUSIONS

- This study characterized the timing of LOA among patients with the most common LGMD2 subtypes, with variability observed across subtypes both in terms of proportion experiencing LOA and age at LOA.

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