CO158

Loss of Ambulation in Patients with Limb-Girdle Muscular Dystrophy Sarcoglycanopathy Subtypes: A Systematic Review

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Background

- Limb girdle muscular dystrophies (LGMD) are a group of rare genetic disorders characterized by progressive weakness and degeneration of the voluntary muscles in the hip and shoulder regions[1]
- Sarcoglycanopathies (LGMD2C/R5, LGMD2D/R3, LGMD2E/R4, LGMD2F/R6) comprise autosomal recessive LGMD subtypes caused by mutations in sarcoglycan proteins (α-, β-, γ- or δ-), which are essential for maintaining muscle membrane integrity and supporting critical signaling during muscle contraction[2]
  - Affected individuals may experience loss of ambulation (LOA) and/or other serious clinical complications[2]
- The clinical course of LGMDs is highly variable;[2] consequently, designing clinical and real-world studies is challenging
- A clearer understanding of the natural history of patients with sarcoglycanopathies would be valuable to help inform prospective study designs

Objective

- To summarize contemporary data on LOA among patients diagnosed with sarcoglycanopathies, overall and by subtype

Methods

- An existing systematic literature review (SLR)[3,4] was refreshed to identify published data on ambulatory status for patients with autosomal recessive LGMD subtypes; the present analysis focuses on sarcoglycanopathies
- The search strategy comprising key terms for LGMD (i.e., "limb girdle", "muscular dystrophy") was re-run in May 2023 in MEDLINE, Embase, and the Cochrane Library
- Observational studies, case series, and case reports reporting individual patient-level data on ambulatory status or predictors of LGMD progression were included
  - Findings from studies reporting on the correlation between protein expression and age at LOA were also summarized
- Descriptions of ambulatory status (as defined by original investigators) were extracted for each patient, and categorized as ambulant or non-ambulant (**Figure 1**)
  - In sensitivity analyses, patients with unclear descriptions of ambulatory status were excluded
- Outcomes of interest by subtype were:
  - Mean (standard deviation [SD]) age at LGMD onset
  - Mean (SD) age at LOA
  - Potential predictors of earlier LGMD onset or LOA, as described by the original investigators

Figure 1: *Definitions applied to categorize patients as ambulant or nonambulant*

Ambulant

- Able to walk
- Remains ambulant
- Asymptomatic
- Asymptomatic hyperCKemia with / without exercise-induced myalgia
- Not yet lost ambulation

- Running with difficulties
- Does not require assistive devices but crawls up the stairs
- Able to run

- Ambulant with knee-ankle-foot orthoses*
- Waddling gait
- Ambulant with support*

- Imminent LOA*
- Not wheelchair bound

Nonambulant

- LOA
- Non-ambulant
- Wheelchair bound
- Loss of independent ambulation
- Inability to ambulate >1 block

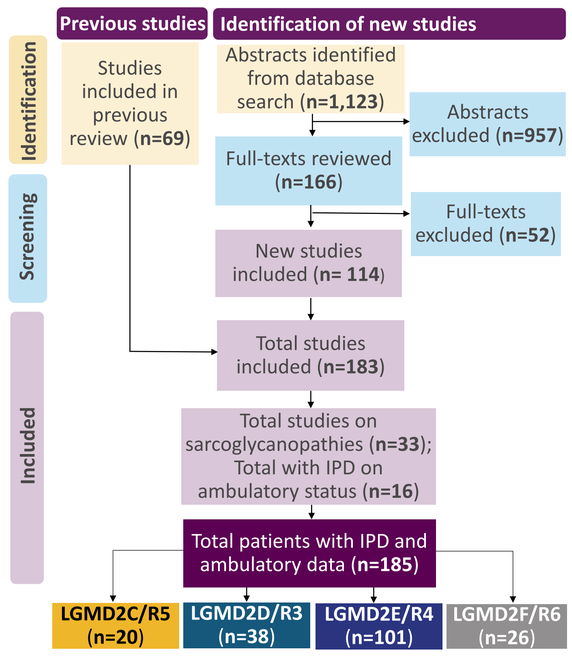
Notes: *Excluded from category of ambulant patients in sensitivity analyses

Results

Data availability

- From 1,123 abstracts, 33 eligible studies were identified for the present analysis (**Figure 2**)
- Patient-level data on ambulatory status were identified for 185 patients with sarcoglycanopathies, from 16 studies
- Overall, 114/185 (62%) patients with sarcoglycanopathies had LOA:
  - LGMD2C/R5: 11/20, 55%[5-11]
  - LGMD2D/R3: 17/38, 45%[5-7,10-13]
  - LGMD2E/R4: 70/101, 69%[5,6,8,10,11,14-19]
  - LGMD2F/R6: 16/26, 62%[5,20]
- Three studies described the relationship between level of sarcoglycan protein expression and age at LOA[18,21,22]
- Included studies spanned multiple decades, with publication years ranging from 1996 to 2022
- Geographic regions varied widely, and specific countries from which results were derived included:
  - Brazil[14]
  - China[11]
  - Iran[5]
  - Italy[16]
  - The Netherlands[6,10]
- Moreover, individual ethnic groups were represented, such as Magdalen Islands Acadian[13], Pakhtun[19], and Taiwanese[12]

Figure 2: *PRISMA diagram*

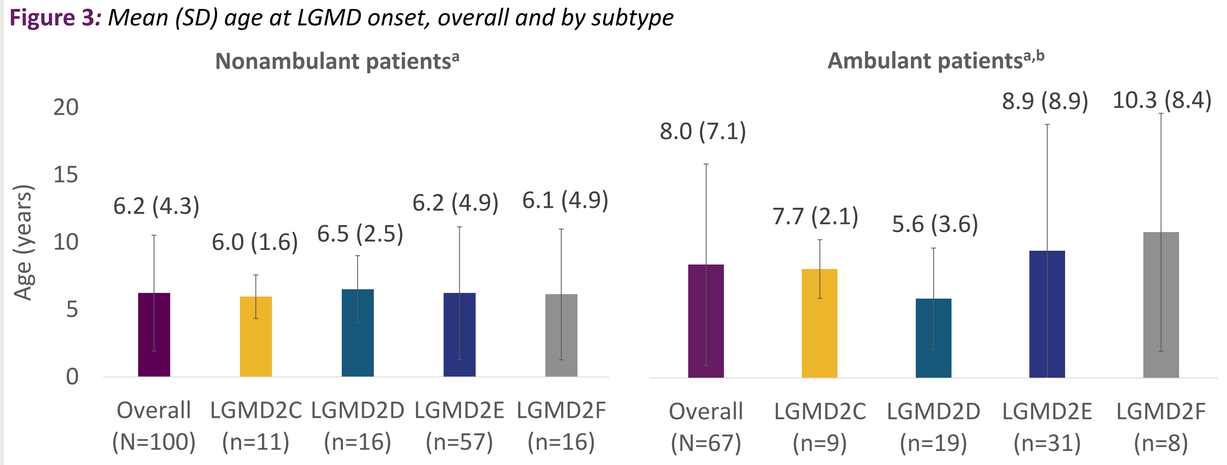


Abbreviations: IPD, individual patient data; **LGMD,** limb girdle muscular dystrophy

Age at LGMD onset

- Mean (SD) age at LGMD onset among sarcoglycanopathy patients with LOA was 6.2 (4.3) years, and 8.0 (7.1) years among those who remained ambulant during the study (**Figure 3**)
- In the sensitivity analyses excluding patients with uncertain ambulatory status (n=6), mean (SD) age at LGMD onset was generally consistent with the main analysis
- Sample sizes across subtypes limited the ability to draw reliable conclusions regarding differences in age at onset by LOA

Figure 3: *Mean (SD) age at LGMD onset, overall and by subtype*



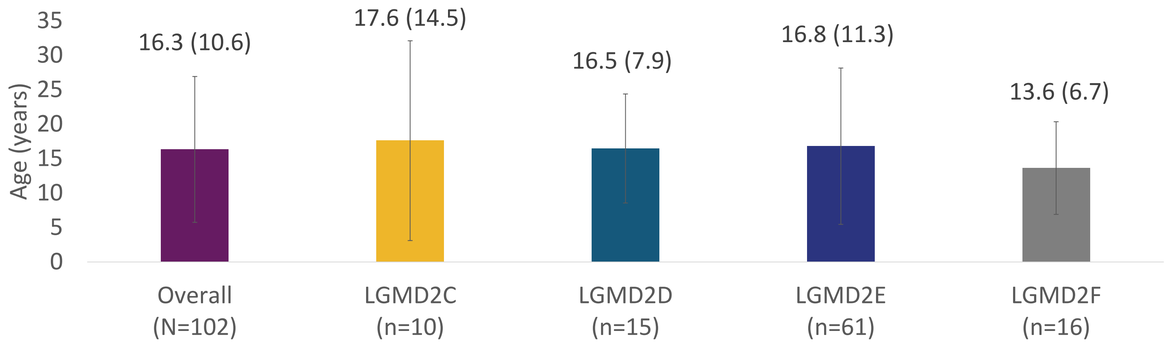
Abbreviations: LGMD, limb girdle muscular dystrophy; **LOA**, loss of ambulation; **SD**, standard deviation

Notes: [a]Among patients who had age at LGMD onset data, [b]Among patients who were ambulant at the time of study assessment

Age at LOA

- Among sarcoglycanopathy patients with available data, LOA typically occurred in adolescence, at 14-18 years of age across subtypes (**Figure 4**)
- Overall, the mean (SD) age at LOA among patients with sarcoglycanopathies was 16.3 (10.6) years

Figure 4: *Mean (SD) age at LOA, overall and by subtype**



Abbreviations: LGMD, limb girdle muscular dystrophy; **LOA**, loss of ambulation; **SD**, standard deviation

Notes: *Among patients who had age at LOA data

Protein expression as a predictor of age at LOA

- Among three studies describing the relationship between sarcoglycan protein expression and disease progression, patients with absent or reduced sarcoglycan expression were found to have earlier LOA ($p<0.05$) (**Table 1**)[18,21,22]

Table 1: *Studies reporting on sarcoglycan protein expression as a predictor of LOA*

Author, year	Subtype(s)	Outcome(s)	Findings
Guimarães-Costa, 2021[21]	LGMD2C/R5 (n=54) LGMD2D/R3 (n=41) LGMD2E/R4 (n=5)	Time to LOA (since birth and LGMD onset)	**Absent sarcoglycan protein expression and age at onset <10 years** were associated with significantly shorter times to LOA since birth (p=0.022 and p=0.000, respectively) or LGMD onset (p=0.021 and p=0.002, respectively)
Alonso-Pérez, 2020[22]	LGMD2C/R5 (n=157) LGMD2D/R3 (n=159) LGMD2E/R4 (n=73)	Age at LOA	In multivariate models, **having lower values of protein expression significantly increased the risk of LOA before age 18** (p=0.042)
Semplicini, 2015[18]	LGMD2E/R4 (n=32)	Age at LOA	**Absence of sarcoglycan expression** in muscle was a strong predictor of younger age at LOA (p=0.0005)

Abbreviations: LGMD, limb girdle muscular dystrophy; **LOA**, loss of ambulation

Key Findings

Patients with sarcoglycanopathies typically experience LOA during adolescence, with factors such as level of sarcoglycan expression potentially influencing the timing of LOA

Conclusions

Findings from this review suggest that patients with sarcoglycanopathies have LGMD onset in early childhood and commonly experience LOA

When LOA occurs, it typically occurs in adolescence, at 14-18 years of age

Absence or low levels of sarcoglycan protein expression may also be a predictor of earlier LOA

Considerations that may limit the generalizability of these findings include small sample sizes for some subtypes; variability in time periods as well as LOA definitions and classification across studies and countries; and potential reporting bias, particularly in case studies, as patients progressing to LOA may be preferentially described over those who were ambulant

Taken together, these findings could have implications for designing and interpreting clinical and real-world studies to characterize the clinical course of sarcoglycanopathy subtypes

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