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SCIENTIFIC LETTER

The Performance of Upper Limb (PUL) module in limb-girdle muscular dystrophy

Eleonora Diella[1*], Antonella LoMauro[2*], Morena Delle Fave[1], Rossella Cima[1], Maria Grazie D'Angelo[1]

[1] Neuro Rehabilitation of Rare Diseases of Central and Pheripheral Nervous System Unit Scientific Institute IRCCS E. Medea, Bosisio Parini (LC), Italy; [2] Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy

[*]Equal contribution

Limb-girdle muscular dystrophy (LGMD) is a genetic muscle disorder causing weakness and wasting of the proximal limb musculature. When ambulation is lost, the attention must be shifted to the upper limb muscles' function. We studied the upper limb muscle strength and the corresponding function in 15 LGMDR1/LGMD2A and 13 LGMDR2/LGMD2B, through the Performance of Upper Limb scale and the MRC score of upper limbs. The proximal item K and the distal items N and R were lower in LGMD2B/R2. The mean MRC score of all the muscles involved linearly correlated (r2 = 0.922) for item K in LGMD2B/R2. The functional worsening paralleled the muscles weakness in LGMD2B/R2. By contrast, at proximal level the function of LGMD2A/R1 was preserved despite muscle weakness was present, presumably due to compensatory strategies. Sometimes the combination of parameters might be more informative than considering them separately. PUL scale and MRC might be interesting outcome measures in non-ambulant patients.

Key words: Performance of Upper Limb (PUL version 1.2) scale, limb-girdle muscular dystrophy, LGMD2A/R1, LGMD2B/R2, MRC score

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Correspondence
Maria Grazia D'Angelo
Central and Peripheral Nervous System Rare Diseases Unit, Scientific Institute IRCCS E. Medea, via Don Luigi Monza 20, 23842 Bosisio Parini (LC), Italy. Tel.: +39 031877870. E-mail: grazia.dangelo@lanostrafamiglia.it

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Limb-girdle muscular dystrophy (LGMD) is a heterogeneous group of genetic muscle disorders with variable age of onset, primarily causing weakness and wasting of the proximal limb (i.e., the hip/shoulder girdle) musculature. Based on inheritance, LGMD was initially divided into two main subgroups: autosomal dominant and autosomal recessive (LGMD1 and LGMD2) [1].

The two most common forms of LGMD2/R in Italy are LGMDR1/LGMD2A and LGMDR2/LGMD2B [2]. Calpainopathy or LGMDR1/LGMD2A is an autosomal recessive LGMD characterised by progressive, symmetric proximal muscle weakness contractures, scapular winging without cardiac manifestations and sparing of pulmonary function [3]. The onset of weakness begins in early childhood or as late as 20 years of age. Severity varies, worse with earlier onset and with null mutations at both alleles.

Dysferlinopathy is caused by mutations in the *DYSF* gene, which encodes the skeletal muscle protein dysferlin [3]. The most common clinical diagnoses associated with dysferlinopathy are limb girdle muscular dystro-

phy type 2B (LGMDR2/LGMD2B) and a distal posterior myopathy (Miyoshi myopathy 1 MM1)[2]. Onset typically occurs during young adulthood, and clinical presentation is inconsistent, with a wide range of ages of onset, patterns of muscle weakness, and severity. Disease progression is variable, with loss of ambulation occurring 5 to 35 years after the onset of muscle weakness, while a small number of patients remain only mildly affected for decades [3,4].

Due to the promising ongoing preclinical studies, there is a high need to obtain natural history data in order to reach trial readiness. Very few studies focused on the natural history of LGMD2A/R1 and 2B/R2 have been reported [5-7]. Most studies in LGMD focused their attention on different aspect of the diseases such as motor, cardiac and respiratory function [8] but the authors' attention was mainly focused on lower limb and loss of ambulation.

The need also for non-ambulant patients to access to clinical trial is essential in these days. In this case, the attention must be necessarily shifted and dedicated to upper limb muscles' function.

According to the pathology, upper limb residual abilities are clinically assessed with a variety of outcome measures. These include the Fugl-Meyer Motor Scale, the Action Research Arm Test (ARAT), the Barthel Index, the Brooke scale and the Motor Function Measure (MFM). However, these scales do not allow the identification of functional changes in short time-lapse.

The Performance of Upper Limb (PUL) scale was designed specifically to measure the upper limb motor performance of Duchenne muscular dystrophy (DMD) [9]. The spectrum of DMD severity ranges from weak ambulant male children to non-ambulant patients with limited residual finger movements. The PUL scale testes the proximal to distal progression of muscle weakness in DMD through three levels: high (shoulder domain), mid (elbow domain), and distal (wrist and finger domain). The PUL score (version 1.2) includes 22 items related to functional tasks that patients and clinicians identified as relevant. Nine items are dedicated to proximal (i.e., mid-level elbow) level. These comprise bringing hand(s) to mouth and to table from lap, moving weight on table, lifting light and heavy cans, stacking light and heavy cans, removing lid from container and tearing paper. Eight items are dedicated to distal (i.e., wrist and fingers) level. These comprise: tracing a path, push on the light, turning light, picking up coins, placing fingers on number diagram, lifting with finger pinch grip, lifting with 3 point grip and lifting with thumb (key) grip [9].

Reliability of PUL in non-ambulant DMD patient and in different muscular dystrophies such as LGMD and BMD has been shown [10].

For this reason, we evaluated the PUL score in 28 LGMD patients: 15 LGMD2A/R1 (8 females, 3 ambulant) and 13 LGMD2B/R2 (6 females, 3 ambulant). As expected, the disease onset was earlier in LGMD2A/R1 (median age: 10 years) compared to LGMD2B/R2 (median age: 20 years, $p < 0.001$); while median disease duration at time of evaluation was similar (respectively 24 and 29 years, $p = 0.106$). Consequently, LGMD2A/R1 patients were younger than LGMD2B/R2 patients were (median age: 33.4 *vs* 51.2 years, $p < 0.001$).

Table I reports all the items that were not significantly different between the two groups. Of note, all items related to the shoulder (from B to E) were zero for both dystrophies. The shoulder girdle was completely compromised as almost all patients were not able to perform shoulder abduction or flexion, neither to or above shoulder height. Figure 1 reports the items (namely, K, N and R) that significantly differed between the two groups of patients, being lower in LGMD2B/R2. More in detail, item K corresponds to a function involving proximal muscles (stacking light cans) whereas item N and R to functions depending on distal muscles (tearing paper and picking up coins, respectively).

In all these patients, the MRC score of upper limbs was also administrated to assess muscles strength. For items K, N and R, the mean MRC score of all the muscles involved in the required function was calculated. Trapezius, deltoids and biceps brachialis muscles were pooled for item K, being lower in LGMD2A/R1 (Fig. 1). Biceps brachialis, triceps brachialis, wrist extensor and flexor, opponent of the thumb and hand grip muscles were pooled for item N. Wrist extensor, opponent of the thumb, interosseous and hand grip muscles were pooled for item R. Figure 2 shows the correlations between muscular strength (i.e.: mean MRC score) and the function (i.e.: item) for item K, N and R. The dystrophies showed two well distinct patterns for item K. While reduced muscular strength corresponded to reduced function in LGMD2B/R2 with a strong linear regression ($r2 = 0.922$), the function of LGMD2A/R1 was independent on the muscles strength (Figure 2, left panel). Although the upper limb girdle muscles in all but one LGMD2A/R1 patients were weaker (i.e.: MRC < 3), the function of stacking light cans was almost preserved presumably due to compensation mechanisms/strategies.

Similarly, all but two LGMD2A/R1 patients were able to fully tear paper even in presence of weakness (MRC < 3) of the muscles specifically involved in the function. On the other hand, only LGMD2B/R2 patients whose upper limb muscles were relatively strong (i.e.: MRC > 3) fully achieved the task of item N; while LGMD2B/R2 patients with moderate to severe muscular weakness showed impaired function (Figure 2, middle panel).

Finally, the distal muscles of the hand were preserved in the majority of patients, independently of the type of dystrophy so that they were able to pick up coins, therefore accomplishing the task required by item R (Figure 2, right panel).

Table I. Items and times of the PUL that were not significantly different between the LGMD2A/R1 and LGMD2B/R2 patients. Data are expressed as median, 25th percentile (25th p) and 75th percentile (75th p).

			LGMD2A/R1			LGMD2B/R2		
		Description	*Median*	*25th p*	*75th p*	*Median*	*25th p*	*75th p*
High level shoulder dimension	Item A	Entry item	3.0	2.0	3.0	2.5	1.8	3.0
	Item B	Shoulder abduction to shoulder height	0.0	0.0	0.0	0.0	0.0	0.0
	Item C	Shoulder abduction above shoulder height	0.0	0.0	0.0	0.0	0.0	0.0
	Item D	Shoulder flexion to shoulder height	0.0	0.0	0.0	0.0	0.0	0.0
	Item E	Shoulder flexion above shoulder height	0.0	0.0	0.0	0.0	0.0	0.0
Mid level elbow dimension	Item F	Hand(s) to mouth	2.0	1.5	3.0	1.5	0.0	2.3
	Item G	Hand(s) to table from lap	3.0	3.0	3.0	3.0	2.0	3.0
	Item H	Move weight on table	2.0	1.0	4.0	1.5	1.0	4.3
	Item I	Lifting light cans	5.0	0.0	5.0	5.0	0.0	5.0
	Time I		5.2	3.4	7.0	5.7	5.0	6.0
	Item J	Lifting heavy cans	3.0	0.0	5.0	3.0	0.0	5.0
	Time J		2.4	0.0	4.3	5.2	3.1	6.5
	Time K	Stacking light cans	8.6	6.4	11.3	8.8	5.3	9.8
	Item L	Stacking heavy cans	4.0	3.5	4.0	3.0	0.0	4.0
	Time L		9.8	6.1	12.8	7.4	5.2	9.9
	Item M	Remove lid from container	1.0	1.0	1.0	1.0	0.8	1.0
Distal wrist and hand dimension	Item O	Tracing path	4.0	4.0	4.0	4.0	3.0	4.0
	Item P	Push on the light	3.0	3.0	3.0	3.0	2.8	3.0
	Item Q	Turning light	2.0	2.0	3.0	2.0	2.0	3.0
	Item S	Placing finger on number diagram	3.0	3.0	3.0	3.0	3.0	3.0
	Item T	Lifting with finger pinch grip	2.0	2.0	2.0	2.0	2.0	2.0
	Item U	Lifting with 3 point grip	2.0	2.0	2.0	2.0	2.0	2.0
	Item V	Lifting with Thumb (key) grip	3.0	3.0	3.0	3.0	3.0	3.0
	TOT		50.5	41.0	54.5	50.0	28.5	53.0

Several authors suggest that understanding the impact of muscular weakness on daily activity and function is essential for the quality of life of these patients as well as for prompting clinical (pharmacological and/or rehabilitative) interventions. Taken together, the results of this pilot study showed that the performance of the upper limb of the two considered forms of LGMD2/R differed for only three items (one proximal and two distal), being all lower in LGMD2B/R2. In addition, different patterns were found in the function-strength relationship. The functional worsening paralleled the muscles weakness in LGMD2B/R2. At proximal level (item K), the correlation between function and muscular strength was very strong, while it was apparently weaker at distal level. However, the two distal functions were preserved in the majority of LGMD2B/R2 corresponding also to acceptable muscle strength. A part for a couple of outliers, the other patients showing muscular weakness had also lower functions. Only for item R, this function-strength correspondence was found in LGMD2A/R1 whose function and muscle strength almost reached their maximum scores. By contrast, at proximal level the function was preserved despite muscle weakness was present and similar to LGMD2B/R1. Muscular weakness, therefore, did not correspond to impaired function, presumably due to compensatory strategies commonly adopted in this dystrophy.

Our protocol allowed to study the upper limb more in detail. When we previously studied the clinical evolution of LGMDR we concluded that in both dystrophies, the impairment of the upper limbs seemed to be equally distributed

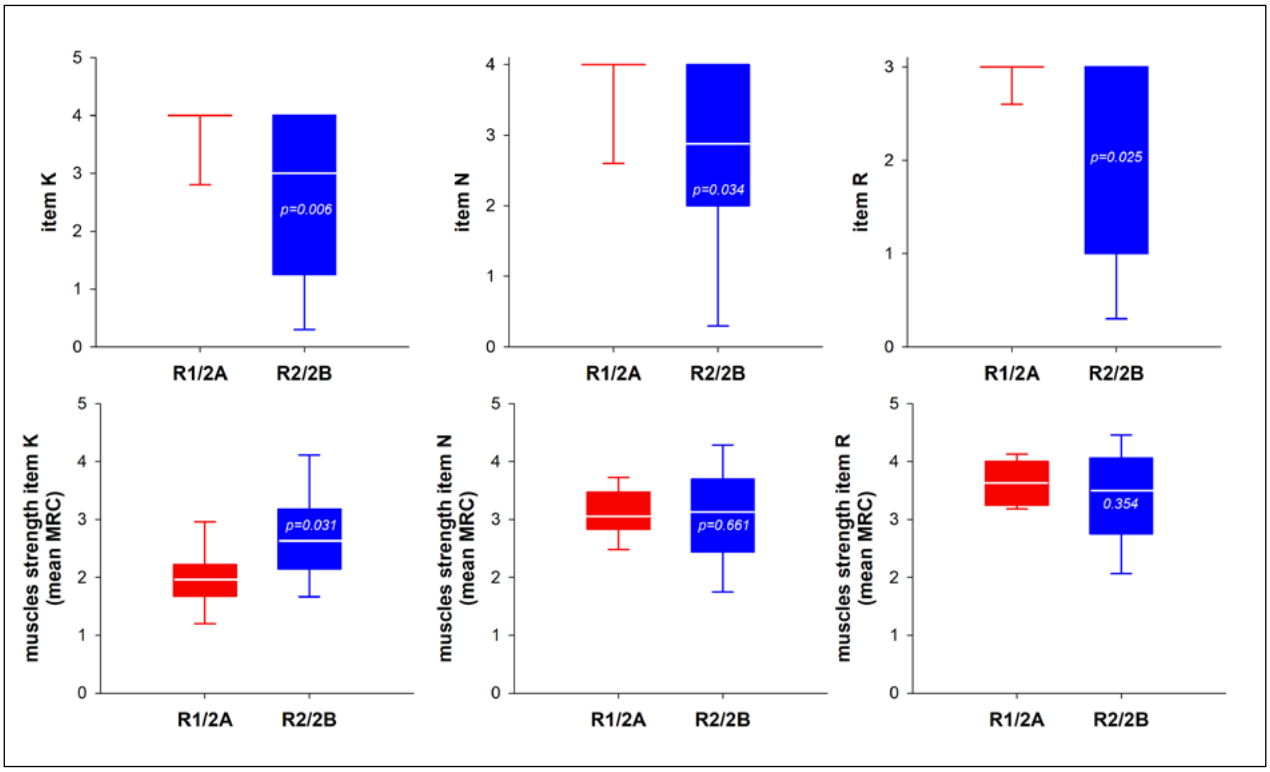

Figure 1. Box-and-whisker plot representing the median (white line within the box), the interquartile range (length of the box), the 90th and the 10th percentiles (whiskers above and below the box) of the item K (top left, i.e.: stacking light cans), N (top middle, i.e.: Tearing paper) and R (top right, i.e.: Picking up coins) of the PUL score measured on LGMD2A/R1 (R1/2A, red) and LGMD2B/R2 (R2/2B, blue) patients. Box-and-whisker plot representing the median (white line within the box), the interquartile range (length of the box), the 90th and the 10th percentiles (whiskers above and below the box) of the mean MRC score of all the muscles involved in item K (bottom left, i.e.: Biceps brachialis, triceps brachialis, wrist extensor and flexor, opponent of the thumb and hand grip muscles), N (bottom middle, i.e.: Biceps brachialis, triceps brachialis, wrist extensor and flexor, opponent of the thumb and hand grip muscles) and R (bottom right, i.e.: Wrist extensor, opponent of the thumb, interosseous and hand prehension muscles) of the PUL score measured on LGMD2A/R1 (R1/2A, red) and LGMD2B/R2 (R2/2B, blue) patients. The p-values are also reported in white.

between the shoulder girdles and the arms, with a relatively spared wrist. This conclusion came from the evaluation of only the muscular strength through MRC scale [6]. Future studies should investigate if the supposed different compensatory strategies explained the different pattern found by considering also the function in addition to the muscular strength. Indeed, LGMD2A/R1 were weaker but with almost preserved item K function. These results are relevant because they showed how the informational content of clinical test might change if its results were considered alone or in combination with others, as for the function-strength discrepancy found in LGMD2A/R1 for item K. Physicians should be aware that sometimes the combination of parameters might be more informative than considering them separately. More studies need to be undertaken either to collect natural history either to identify reliable outcome measures in non-ambulant patients with slowly progressive muscular dystrophies [6], with upper limb playing the major role.

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Conflict of interest statement

The authors declare no conflict of interest.

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Author's contributions

DE, DAMG: study conception and design; DE, DFM, CR: data collection; ALM, DE, DAMG: analysis

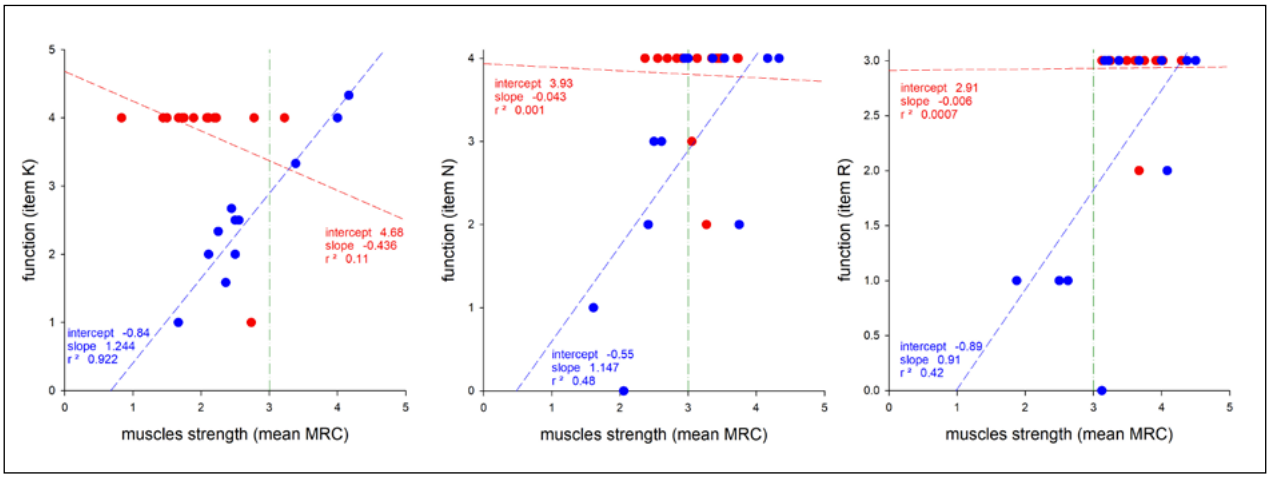

Figure 2. Scatter plot of the mean muscles MRC score (*x-axis*) and the corresponding function (*y-axis*) measured on LGMD2A/R1 (R1/2A, red) and LGMD2B/R2 (R2/2B, blue) patients. The mean muscles MRC score for item K (left, i.e.: stacking light cans) was computed by calculating the average of the MRC score of the trapezius, the deltoids and the biceps brachialis muscles. The mean muscles MRC score for item N (middle, i.e.: Tearing paper), was computed by calculating the average of the MRC score of the biceps brachialis, the triceps brachialis, the wrist extensor and flexor, the opponent of the thumb and the hand grip muscles. The mean muscles MRC score for item R (right, i.e.: Picking up coins) was computed by calculating the average of the MRC score of the wrist extensor, the opponent pollicis, the interosseous and the hand prehension muscles were pooled. The intercept and the slope of the linear regression lines (short-dashed lines) as well as the coefficient of determination (r^2) are also shown. The vertical dash-dotted green lines indicate the threshold when muscle contracts and moves with no resistance.

and interpretation of results; ALM, DAMG: draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

Ethical consideration

All the evaluations were performed following standard care guidelines for LGMD and all the retrospective data were anonymised. All patients or parents/legal tutors signed informed consent to anonymous data analysis, approved by the local ethics committee according to the declaration of Helsinki.

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