RESEARCH PAPER

MRI in sarcoglycanopathies: a large international cohort study

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ABSTRACT

Objectives To characterise the pattern and spectrum of involvement on muscle MRI in a large cohort of patients with sarcoglycanopathies, which are limb-girdle muscular dystrophies (LGMD2C–2F) caused by mutations in one of the four genes coding for muscle sarcoglycans.

Methods Lower limb MRI scans of patients with LGMD2C–2F, ranging from severe childhood variants to milder adult-onset forms, were collected in 17 neuromuscular referral centres in Europe and USA. Muscle involvement was evaluated semiquantitatively on T1-weighted images according to a visual score, and the global pattern was assessed as well.

Results Scans from 69 patients were examined (38 LGMD2D, 18 LGMD2C, 12 LGMD2E and 1 LGMD2F). A common pattern of involvement was found in all the analysed scans irrespective of the mutated gene. The most and earliest affected muscles were the thigh adductors, glutei and posterior thigh groups, while lower leg muscles were relatively spared even in advanced disease. A proximodistal gradient of involvement of vasti muscles was a consistent finding in these patients, including the most severe ones.

Conclusions Muscle involvement on MRI is consistent in patients with LGMD2C–F and can be helpful in distinguishing sarcoglycanopathies from other LGMDs or dystrophinopathies, which represent the most common differential diagnoses. Our data provide evidence about selective susceptibility or resistance to degeneration of specific muscles when one of the sarcoglycans is deficient, as well as preliminary information about progressive involvement of the different muscles over time.

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INTRODUCTION

Limb-girdle muscular dystrophies (LGMD) 2C, 2D, 2E and 2F are caused by mutations in the four genes coding for gamma, alpha, beta and delta sarcoglycans, and are therefore also referred to as sarcoglycanopathies. Sarcoglycans are a complex of glycopeptides associated with dystrophin and other proteins at the level of the sarcolemma, to form the so-called dystrophin-associated glycoprotein complex (DAGC).[1]

As for all the LGMDs, the correct molecular diagnosis is of great importance for adequate care management, planning the genetic counselling, scheduling the correct follow-up and allowing enrolment in ongoing and future gene therapy trials.[2] Sarcoglycanopathies can have a paediatric or adult age of onset and show overlapping features with other muscular dystrophies, for example, dystrophinopathies or alpha-dystroglycanopathies, being characterised by high creatine kinase (CK) level, a similar distribution of weakness, calf muscle hypertrophy and not infrequently cardiomyopathy.[1 3] The genetic diagnosis is addressed by muscle pathology that discloses an absence or reduction of one or more of the sarcoglycans. However, pathological diagnosis can occasionally be challenging since a defect in a protein of the DAGC can cause a secondary reduction of all the proteins of the complex, thus making it hard to identify the primary defect.[4] It is also known that a number of patients with partial sarcoglycan deficiency on muscle biopsy have no definite molecular genetic diagnosis.[5 6]

MRI has been increasingly exploited to identify muscle involvement and monitor disease progression in many inherited[7 8] and acquired myopathies.[9] However, only few patients with sarcoglycanopathy have been described with muscle imaging so far,[10 11] mostly LGMD2D[7 12 13] or LGMD2C.[14] A pattern of involvement in sarcoglycanopathies, proposed in a more recent study by ten Dam *et al*[15] as derived from a literature search (ie, predominant involvement of anterior thigh compartment, especially vastus intermedius; predominant involvement of soleus and peroneal group at the lower leg level; frequent hypertrophy of sartorius and gracilis), was proven to be quite specific but insensitive (22%) to distinguish 11 CT scans of sarcoglycanopathies from other dystrophies, and the authors advised assessments of larger groups.

The aim of our study is to describe the pattern and spectrum of muscle involvement in a multicentric cohort of sarcoglycanopathies assessed by MRI. This is expected to improve the distinction of sarcoglycanopathies from other muscular dystrophies and possibly from each other. We also intend to provide cross-sectional, baseline data on muscle imaging that are currently missing in these diseases.

PATIENTS AND METHODS

Patients

Patients with a diagnosis of LGMD2C–2F followed in the 17 participating neuromuscular centres in Europe (Italy, Finland, UK, Spain, France, Germany, Denmark, the Netherlands, Czech Republic, Russia) and USA, in the framework of the MYO-MRI COST Action (www.myo-mri.eu), were enrolled if they already had or were available for a new lower limb MRI scan.

MRI scans and evaluation

MRI studies were performed using different 1.5T scanners according to standard protocols.[16] T1-weighted sequences were acquired covering the body length from proximal lumbar spine to the ankles for the majority of the scans. Few scans were acquired only from the femur heads to the ankles.

All the scans were independently evaluated by two observers, neurologists with experience in muscle imaging (GT and MM), blinded to the molecular diagnosis, using a 5-point scale estimating the extent of fatty replacement of single muscles as in previous studies,[16 17] with scores ranging from 0 (normal appearance) to 4 (complete fatty replacement). In case of discordance between the observers, agreement was reached by consultation. A cumulative score per patient (T1-MRI score) as well as a median score per muscle were calculated. If the pelvic region was not covered, the scores of the muscles not entirely visualised were considered as missing values. Hierarchical analysis was performed using R V.3.1.3 software (The R Foundation for Statistical Computing; http://www.r-project.org) as previously described.[18] The Gower's distance was used for clustering of patients and muscles. Scans were also judged to assess the overall pattern of involvement.

This study was approved by the ethics committees of the involved institutions. All involved subjects or their legal guardians gave their written informed consent.

RESULTS

Patients

Sixty-nine patients were enrolled in the study. Thirty-eight were LGMD2D, 18 were LGMD2C, 12 were LGMD2E and 1 was LGMD2F. The age at scan ranged between 4 and 59 years, and patients were almost equally distributed between paediatric (age ≤18 years: 36 patients) and adult age (age >18 years: 33 patients). Thirty-four patients were male and 35 were female. Sixty-six patients had a complete molecular diagnosis with two mutations in one of the sarcoglycan genes, while three had only one pathogenic mutation and a clear reduction of staining of one or more sarcoglycans on muscle biopsy. In these three patients deletions/duplications or deep intronic mutations on the other allele had not been ruled out.

Clinical severity ranged from asymptomatic or mildly affected to severe patients who are wheelchair users (both children and adults). A summary of clinical and genetic features is reported in online supplementary table 1.

Muscle imaging

Six patients, five LGMD2D and one LGMD2C, had normal lower limb MRI at age 9–26 years. Five patients (age at scan 4–7 years, 2 LGMD2D, 2 LGMD2C, 1 LGMD2E) showed only minor changes and had a T1-MRI score <8. In these mildly affected patients, initial abnormalities were mostly in the adductor magnus and glutei muscles. The overall involvement was symmetrical (side-to-side differences of at least two points in the scores were found only in 4 couples of muscles out of 2448). The complete set of data is shown in online supplementary table 2.

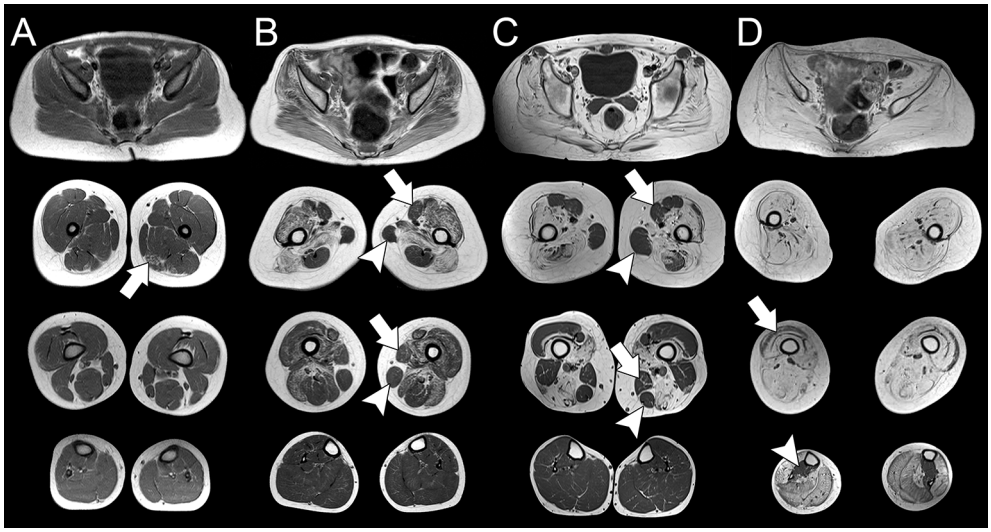

Figure 1 Progressive muscle involvement in sarcoglycanopathies. (A) Early involvement is noticeable in adductor magnus (arrow), with milder concomitant changes in gluteus maximus and minimus. (B,C) At later stages, glutei muscles become involved, as well as proximal quadriceps and posterior thigh. Lower leg remains spared even when the thigh and pelvis are significantly affected, and sartorius and gracilis (arrow and arrowhead) may show relative hypertrophy. (D) In most advanced patients, there is severe diffuse muscle involvement with selective sparing of flexor digitorum longus and tibialis posterior (arrowhead), and of a rim of the distal vastus lateralis (arrow). (A) ES2_3 (age 4, LGMD2C), (B) IT3_9 (age 11, LGMD2D), (C) IT1_1 (age 34, LGMD2D) and (D) FI1_3 (age 35, LGMD2D). LGMD, limb-girdle muscular dystrophies.

Pelvis

Gluteus minimus and medius, quadratus femoris, adductor minimus and brevis, obturator internus and pectineus were the most severely affected muscles (median score 4). Glutei and adductors were also among the most frequently affected muscles together with piriformis (score ≥1 in >82% of the patients). Recti abdominis were never more affected than obliqui, except in one patient. Gluteus maximus was more involved than gluteus minimus only in five patients. Iliopsoas (median score 1) and tensor fasciae latae (median score 2) were among the relatively spared muscles, at least in the mild or moderately affected patients (figures 1 and 2).

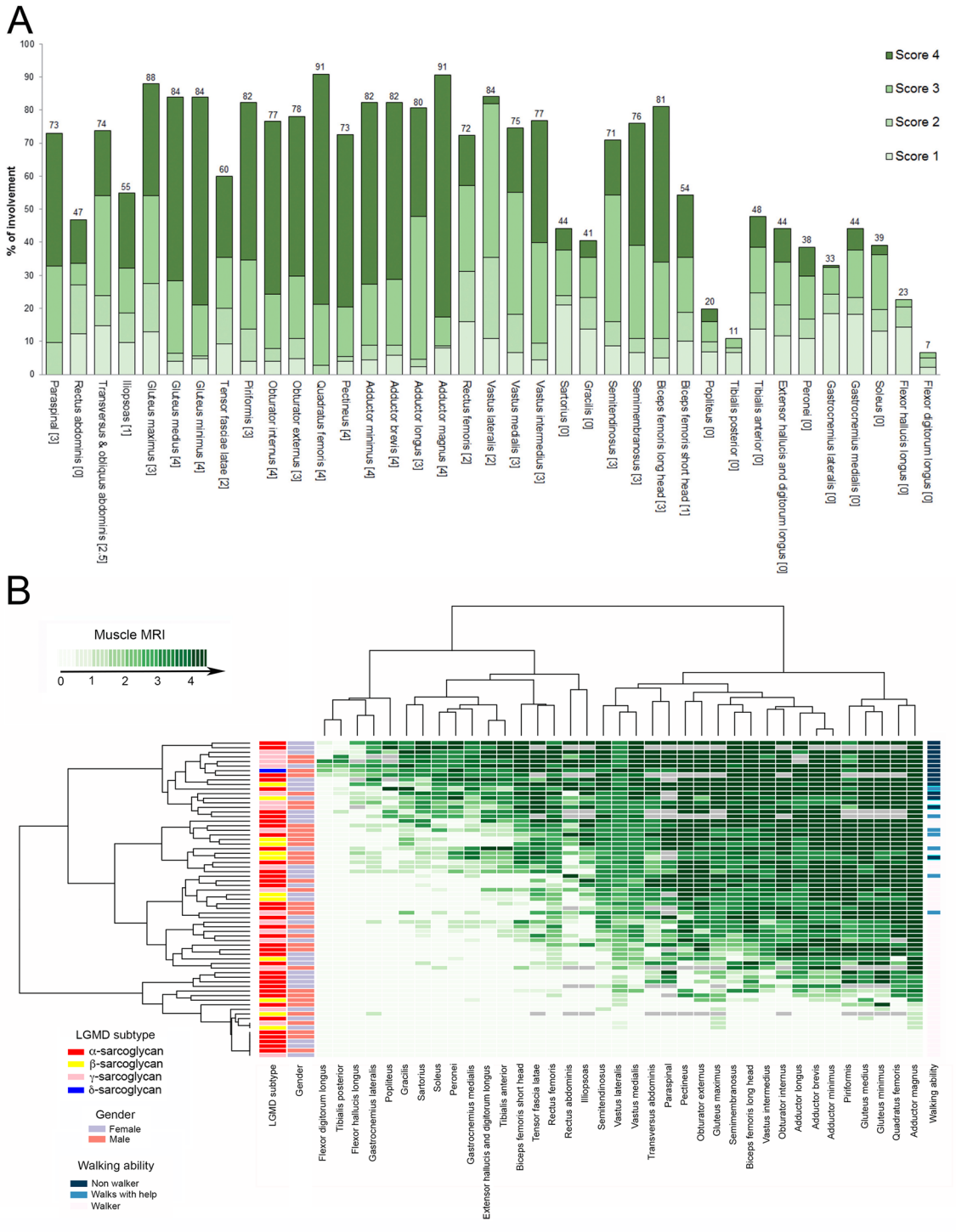

Figure 2 Summary of pelvic and lower limb muscle involvement in sarcoglycanopathy patients. (A) Frequency of involvement of the different muscles, grouped by body region, is expressed as a percentage of the total. Green bars indicate the percentage of muscles affected with each specified score. The numbers in square brackets represent the median score for each muscle. (B) Heatmap showing the hierarchical clustering of patients and muscles according to the scores given to the single muscles. Patients do not cluster according to their molecular diagnosis but rather to the severity of involvement. LGMD, limb-girdle muscular dystrophies.

Thigh

Adductor magnus was the most frequently and severely affected muscle in these disorders (figure 2). With the exception of the mildest patients, all the others (56/69) had a complete or almost complete fatty replacement (score 3–4) of both adductor magnus muscles. The other most severely affected muscles were adductor longus, vastus intermedius, biceps femoris long head and semimembranosus (median score 3). In the posterior thigh, semitendinosus was more affected than semimembranosus only in two patients. Among the vasti muscles, vastus intermedius was the most severely involved, followed by vastus medialis and lateralis (figure 2). Vastus lateralis showed areas of sparing in the distal part close to the knee even in the most affected patients (score of 4 only in 3/138 muscles). Sartorius and gracilis were the most spared muscles of the thigh: 34 and 39/69 patients, respectively, had a complete bilateral sparing (figure 1).

Lower leg

Lower leg was completely or almost completely spared in the majority of patients. If affected, the anterior compartment was more involved than the posterior, with tibialis anterior and extensor hallucis/digitorum longus being the most affected muscles. Tibialis posterior and flexor digitorum longus were typically completely spared even in advanced disease (score of 0 of both muscles in 60 and 61/69 patients, respectively) (figure 1).

Pattern recognition and 'gestaltic' criteria

Consistent features emerged from the assessment of muscle scans for pattern recognition. In the anterior thigh, while vasti were frequently involved in the proximal part, a clearly less prominent involvement in the distal portion could be noticed in most patients (figure 3). This proximodistal gradient was more evident in the vastus lateralis and present also in the most severely affected patients. Another muscle often showing small and symmetrical areas of sparing, although in the medial part, was adductor longus (figure 3). These features were typically combined with no or only minor changes in the lower leg, and with a complete or relative sparing of tibialis posterior and flexor digitorum longus. Less consistently there was also a sparing of tensor fasciae latae compared with the other pelvic muscles, and a relative hypertrophy of either sartorius or gracilis. No major differences could be found between men and women (figure 2B). A summary of these 'gestaltic' criteria is provided in table 1.

Table 1 'Gestaltic' criteria

Criteria	
Quadriceps gradient	58/58* (100%)
Relative sparing of tibialis posterior and flexor digitorum longus	66/69 (96%)
Adductor longus medial sparing	41/56* (73%)
Normal or almost normal leg	45/69 (65%)
Relative sparing of tensor fasciae latae	41/69 (59%)
Hypertrophy of either sartorius or gracilis	24/69 (35%)

*In the remaining patients the feature could not be assessed because of total muscle sparing or incomplete scans.

Differences between sarcoglycanopathies

No major differences among the sarcoglycanopathies could be found regarding the pattern of muscle involvement, in particular comparing LGMD2D and LGMD2C, which were the most prevalent forms. This inspective finding was confirmed by hierarchical analysis (figure 2B). The only studied patient with LGMD2F was more severe, but the affected and relatively spared muscles were similar to the other groups (figure 4). Three patients (IT1_11, ES1_5 and IT5_7) showed a mild phenotype and severity on MRI at older age, with a T1-MRI score of 73 at age 54, 65 at 47, and 18 at 55, respectively. Interestingly, all were LGMD2D and two had the same genotype (homozygous p.R284C mutation). Their pattern of involvement was consistent with the others.

DISCUSSION

To the best of our knowledge, in the present study we report the largest cohort of patients with LGMD2C–2F studied by muscle imaging so far, covering most of the spectrum of age and severity ranging from asymptomatic to patients who are wheelchair users.

Collectively, the sarcoglycanopathies are among the most common LGMDs worldwide,[3] representing the third most common form in Italy,[19] and definitely one of the most severe. LGMD2D is generally the most common, followed by LGMD2C,

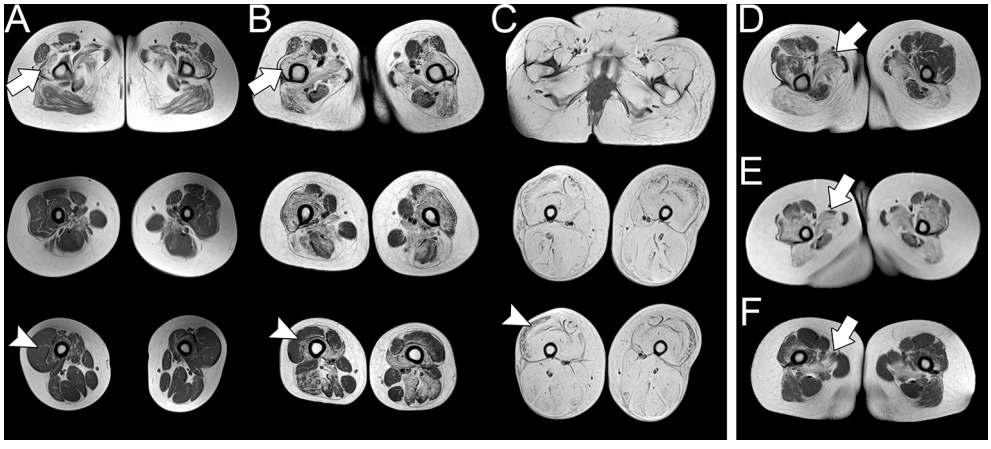

Figure 3 Pattern recognition and 'gestaltic' criteria. (A–C) Two consistent features are the proximodistal gradient of involvement of the vastus lateralis, with the typical proximal fatty replacement close to the femur head (arrow), and the distal sparing even in the most severely affected patients (arrowheads). (D–F) Adductor longus also shows peculiar involvement with sparing of the most medial fascicles (arrows). (A) US1_1 (age 9, LGMD2E), (B) IT3_5 (age 15, LGMD2E), (C) IT1_4 (age 50, LGMD2C), (D) CZ1_1 (age 8, LGMD2C), (E) IT1_2 (age 10, LGMD2) and (F) IT2_1 (age 29, LGMD2D). LGMD, limb-girdle muscular dystrophies.

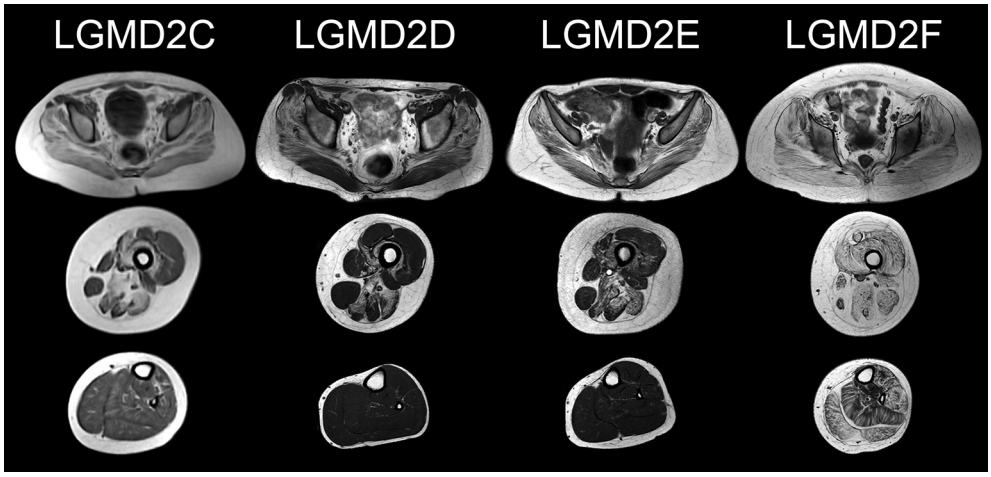

Figure 4 Examples of involvement at pelvis, thigh and lower leg level in the different sarcoglycanopathies. A similar pattern is shared by the different sarcoglycanopathies. IT1_2, LGMD2C; IT3_3, LGMD2D; IT3_4, LGMD2E; IT3_8, LGMD2F. LGMD, limb-girdle muscular dystrophies.

while LGMD2F is the rarest.[3] Our cohort mainly consisted of patients affected by LGMD2D and LGMD2C, which reflects the general prevalence of sarcoglycanopathies worldwide.

Although this is not a longitudinal study, the large cohort and broad clinical spectrum allow us to make some inferences also on disease progression. Adductor and glutei muscles seem to be the first affected in the disease course, followed by small pelvic and obturator muscles, biceps femoris long head, vastus intermedius, proximal vastus lateralis and medialis, and other posterior thigh muscles (figure 2). Iliopsoas is typically relatively spared early in the disease. Lower leg is not significantly involved until loss of ambulation occurs (figure 2B), and it is always less affected than pelvis and thigh. Tibialis posterior and flexor digitorum longus are particularly resistant to pathology even in advanced disease.

Our findings are consistent with the previously reported minor involvement of the lower leg.[10 11] At variance with the pattern proposed by ten Dam *et al*,[15] we found that the adductor compartment of the thigh is more involved than the anterior one. We also add the following features to the previous descriptions: the sparing of the medial part of adductor longus, which in our experience is a rather peculiar, although not completely specific finding, and most importantly the relative sparing of the distal quadriceps, that, together with the sparing of the lower leg, collectively configure LGMD2C-2F as a 'typical' LGMD phenotype with an easily recognisable proximodistal gradient of involvement.

The most important differential diagnoses include muscular dystrophies with hypertrophic phenotype, mainly dystrophinopathies (Becker muscular dystrophy or forms with an intermediate severity between Duchenne and Becker muscular dystrophies) and alpha-dystroglycanopathies, especially LGMD2I. The complete or relative lower leg sparing has not been described in any of these conditions, with the exception of patients with the mildest Becker.[20] Moreover, in dystrophinopathies, LGMD2I and *ISPD*-mutated patients, the involvement is usually posterior more than anterior in the lower leg.[13 20–22] The sparing of the distal quadriceps also seems to be very specific for LGMD2C–2F and not reported elsewhere. In addition, one common feature of dystrophinopathies is that gluteus maximus is the most affected among the glutei,[20 21] at variance with LGMD2C–2F. The pattern we describe is also different from the other autosomal recessive[23] or dominant muscular dystrophies,[24 25] which are unlikely to display predominantly anterior and milder involvement at leg level compared with the thigh. Lower leg sparing may be a feature of late-onset Pompe disease,[26] but at variance with sarcoglycanopathies iliopsoas is usually involved early and it is not common to find anterior leg involvement in patients with Pompe disease. Conversely, the pattern of involvement seems to be homogeneous among the different sarcoglycan defects. This supports the idea of a common pathophysiology shared by these disorders: as sarcoglycans are tightly interacting proteins, their functions and target muscles in case of damage are likely similar. Although additional evidence coming from dedicated studies is needed to confirm these findings, it seems reasonable to speculate that, assuming the apparent absence of fatty replacement in calf muscles of the majority of patients with sarcoglycanopathy especially at early stages, a major contribution to calf hypertrophy in sarcoglycanopathies could be given by an increase in 'real' muscle tissue rather than by fat deposition, similar to what happens in Becker muscular dystrophy.[27]

Our study has some limitations. First of all, despite the consortium involving 17 neuromuscular centres, we were able to enrol only one patient with LGMD2F, given the rarity of this disease. Further patients with delta-sarcoglycanopathy studied with MRI are necessary to verify our findings. Another limitation is that quantitative measurements for intramuscular adipose tissue and T2 signal were not performed in our study. Collection of such data along with standard MRI sequences will be of particular importance in longitudinal, natural history studies.

In conclusion, MRI is a helpful tool to guide the differential diagnosis within muscular dystrophies with hypertrophic phenotype. It can be used to address genetic testing in the presence of a compatible phenotype and, in case of sarcoglycan reduction on biopsy, to support the decision to push forward the genetic screening, for example searching for deletions or intronic mutations, or instead to consider the sarcoglycan defect as secondary. In addition, results of muscle imaging may be helpful in the interpretation of variants of unknown clinical significance in the sarcoglycan genes. The selective sparing of some muscles can be an interesting clue to the understanding of the pathophysiology of these disorders. Imaging of other body segments is warranted to assess whether there are further selective patterns. Our study also provides a comprehensive overview of distribution and extent of muscle pathology in a large cohort of patients with LGMD2D–2F. This information can be used for designing clinical trials and to set the stage for longitudinal and quantitative

MRI studies, which are needed to reliably determine disease progression as well as to confirm the possible use of imaging as an outcome measure in these diseases.

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Contributors GT, ER and CB conceived and designed the study. All the authors acquired and analysed the data. GT, MM and JD-M drafted manuscript and figures. All the authors gave the final approval to the current version of the manuscript.

Competing interests None declared.

Ethics approval This study was approved by the ethics committees of all the involved Institutions.

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