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282nd ENMC international workshop - standards of diagnosis and care for the sarcoglycanopathies. 8-10 November 2024, Amsterdam, Netherlands

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ABSTRACT

Sarcoglycanopathies are rare autosomal recessive limb-girdle muscular dystrophies (LGMD R3–R6) caused by pathogenic variants in SGCA, SGCB, SGCG, or SGCD genes. They present predominantly in childhood with progressive proximal muscle weakness, frequently leading to loss of ambulation in adolescence or early adulthood, and may involve cardiac and respiratory complications. Despite their severity and multisystem impact, no internationally agreed standards of care (SoC) currently exist, contributing to diagnostic delays, inconsistent management, and inequitable access to multidisciplinary expertise. The 282nd ENMC International Workshop (Amsterdam, November 2024) convened 29 global stakeholders including clinicians, researchers, industry, and patient representatives to harmonize literature evidence with international clinical experience. Key outputs included: consensus on the clinical spectrum and diagnostic algorithm (with and without genetic testing); recommendations for multidisciplinary management covering neurology, cardiology, respiratory care, rehabilitation, and psychosocial support; and identification of outcome measures for clinical monitoring and trials. Natural history data were reviewed to define prognostic factors, and emerging therapeutic avenues including gene therapy, small-molecule correctors, and antifibrotic strategies were discussed. The workshop concluded with a mandate to develop and disseminate comprehensive, accessible SoC guidelines tailored to sarcoglycanopathies to improve care delivery and readiness for forthcoming disease-modifying therapies.

1. Introduction

The 282nd ENMC International Workshop on "Standards of Diagnosis and Care for the Sarcoglycanopathies" was convened in Amsterdam 8th-10th November 2024 as in-person meeting, following three virtual preparatory sessions on 25th July 2024, 4th September 2024 and 16th September 2024 [1] The meeting brought together a total of 29 stakeholders including multidisciplinary experts in the fields of basic science, translational research, clinical care, industry representatives, patients and patient advocacy organization representatives, and two early career researchers supported by the ENMC Early-Career Program.

1.1. Background

The sarcoglycanopathies are a type of limb-girdle muscular dystrophy (LGMD) that result in muscular weakness and wasting progressing across the lifespan [2] There are four genes (*SGCA, SGCB, SGCG*, and *SGCD*) that make up the sarcoglycan complex. Pathogenic variants in any of these four genes result in an autosomal recessive LGMD (R3 / alphasarcoglycan-related; R4 / betasarcoglycan-related; R5 /

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gammasarcoglycan-related; and R6 / deltasarcoglycan-related). The prevalence of each sarcoglycanopathy varies depending on the region and population studied [2–5]

The sarcoglycanopathies are characterized by early onset muscle weakness, typically in childhood and predominantly affecting muscles of the pelvic and scapular girdle. The trajectory of muscle involvement typically follows a proximal to distal pattern of weakness, with an expected loss of ambulation during adolescence or early adulthood [6] Due to the heterogenous presentation of these diseases however milder phenotypes, later symptom onset, and slower progressive courses have been described, including symptoms limited solely to exercise intolerance [7–10] Clinical manifestations of the sarcoglycanopathies also include reports of varying degrees of cardiac and pulmonary involvement [2,6,11,12] As a result, the diagnosis and clinical care of these individuals include a variety of subspecialties such as neurologists, neuropediatricians, geneticists and genetic counselors, cardiologists, pulmonologists, physical and occupational therapists, nutritionists, and others [13–15]

There are currently no consensus standard of care (SoC) documents developed for the diagnosis and clinical management of individuals diagnosed with a sarcoglycanopathy. Evidence for the necessity of these types of documents was exemplified during presentations throughout the workshop.

The overarching goal of this workshop was to harmonize data from existing literature with the clinical and personal experiences of multidisciplinary experts around the world, to establish a consensus guideline for the diagnosis and clinical management of individuals diagnosed with a sarcoglycanopathy.

We aim to achieve this goal through:

1. A review of the clinical spectrum of the sarcoglycanopathies via literature review and regional experience of international experts.
2. Developing a diagnostic algorithm with and without the availability of genetic testing, including differential diagnoses, common symptoms related and not related to the sarcoglycanopathies, and discussion of screening tools for higher risk populations.
3. Discussing multidisciplinary clinical management of individuals following a diagnosis of sarcoglycanopathy.
4. Reviewing new perspectives to therapeutic treatments of the sarcoglycanopathies.

2. Establishing need for standard of care guidelines in LGMD

The workshop began with Linda Lowes, who reported the results of two international LGMD SoC surveys completed by Dr. Lindsay Alfano in collaboration with TREAT NMD. This two-part project included a patient/patient caregiver survey with 1285 respondents (87 with a sarcoglycanopathy) from 68 countries and a clinic-based survey with 146 clinics responding from 30 countries.

On average, it took 6.4 years from the first visit to a medical professional until a diagnosis was obtained with 31 % of the individuals being misdiagnosed before LGMD was confirmed. When asked where the patient received their care, only thirty three percent of the respondents reported attending a multidisciplinary clinic while 13 % reported they were not seeking care for their LGMD. The remainder of the respondents received care either locally or at a regional specialist. Of those not attending a multidisciplinary clinic, 39 % reported the reason for not attending was that they had never been referred. The remainder of the reasons for not attending were: no clinic in their area; travel was too difficult; or that they did not find value in attending. During the visit the clinics reported performing the following tests: strength testing (83 %), pulmonary function (68 %), functional (63 %) and patient reported outcomes (33 %). Further, when asked what is missing from their current care the most common responses were: assistance for living with LGMD, the lack of expertise and knowledge about LGMD and, reports that specialists are too far away and too difficult to travel to. These standard of care surveys provide justification of the need to establish standard of care recommendations that can be easily accessed by providers and patients everywhere.

3. The clinical spectrum of sarcoglycanopathies

The first session of this workshop, chaired by Elena Pegoraro and Lea Leonardis, was dedicated to reviewing the clinical spectrum of LGMDs R3–6, which included presentations comprised of literature reviews and multi-national clinical experience.

3.1. The French experience

Highlighting the experience of a multicenter French cohort, Tanya Stojkovic presented a retrospective study of the sarcoglycanopathies that was conducted at neuromuscular disease reference centers in the Paris area. Data from 100 individuals were included (R5, $N = 54$; R3, $N = 41$; R4, $N = 5$). Average disease onset by subtype was variable, with R3 and R5 presenting earlier than R4. Symptoms at onset were mostly represented by lower limb weakness and Achille's contractures, however a smaller subgroup of individuals presented with exercise intolerance and/or hyperCKemia. Common clinical features at last follow up were predominant proximal weakness of the four limbs, axial weakness, contractures, scoliosis and scapular winging. More than half of those included (65 %) were non-ambulatory at last follow-up. Dilated cardiomyopathy was present across all subtypes (R3, R4, and R5), and in this cohort was especially concerning in patients with R5. Seventy-four percent of patients had some degree of respiratory insufficiency and assistive ventilation was necessary in 30 % of patients (mostly non-invasive ventilation). Absent sarcoglycan protein expression on muscle biopsy and age at onset before ten years were significantly associated with earlier time to loss of ambulation. Genetic heterogeneity was observed for R3, although the c.229C>*T* variant predominated. Further, the c.525del variant was found in >90 % of R5 patients. No obvious genotype-phenotype correlations were observed. Finally, loss of ambulation was significantly associated with low FVC while the occurrence of cardiomyopathy was independent of loss of ambulation.

3.2. The Italian experience

Claudio Bruno presented an analysis of data collected from 12 specialized centers in Italy, including the clinical data from 115 individuals diagnosed with a sarcoglycanopathy. Each center employed a dedicated proforma, providing valuable information on the natural history, clinical manifestations, and management outcomes of this rare subset of LGMDs. Age at onset varied among subtypes, averaging between 4–8 years of age. Initial presentation was predominantly symptomatic, with muscular symptoms being the primary manifestation in >64 % of individuals, however, up to 23 % of patients were identified through asymptomatic hyperCKemia. The most common presenting symptoms included proximal lower limb weakness and gait disturbances. Loss of ambulation (LOA) was found at variable ages across subtypes, with averages ages of LOA between 17–22 years of age. Cardiac involvement was observed across all subtypes, however, at a greater frequency in individuals with R4 (38 %) and R6 (50 %). Respiratory insufficiency requiring non-invasive ventilation was also documented in all subtypes, however, was most prevalent in non-ambulatory individuals with R5 and R6 diagnoses. Bone mineral density (BMD) analysis, while available in only 19 % of patients, revealed a critical pattern: ambulant patients maintained normal BMD Z-scores (>−2 SD), while non-ambulant patients showed pathologic scores (−2 SD) at total body less head (TBLH) and femur sites; this emphasized the need for systematic monitoring. Steroid therapy was uncommon and variable across subtypes.

3.3. The Brazilian experience

The sarcoglycanopathies are the third most common LGMD in Brazil, although in some reference centers it is the second most prevalent, reported Filipe Di Pace. In this cohort, it was documented that females were more frequently affected compared to males, with symptoms presenting in the first decade of life and most patients losing ambulation by the age of eighteen [16] In the experience of the Neuromuscular Center at the University of São Paulo, R3 was the most common subtype (6 patients) with a disease onset after 10 years of age along with a less severe course compared to other subtypes. Other subtypes are represented in an equal frequency (5 patients each), which Dr. Pace suggested, could reflect a sampling bias of his center. The Brazilian population seemed to have a higher prevalence of R6 compared to other countries; this subtype had an earlier onset of distal weakness progressing over time a leading eventually to foot deformities, preceding loss of ambulation (LOA), which also occurred earlier than other subtypes [2] Cardiac evaluation revealed rhythm or structural involvement, but not typically at the onset of the disease. Interestingly, R3 patients revealed only rhythm problems, and no cardiac involvement was observed in R5 patients in his center. Regarding genetic testing, missense variants were the most common type, particularly in R3 and R4. In R5, however, only one frameshift variant was identified among all patients (c.525del), and for R6, nearly all patients shared the same frameshift variant (c.657del), suggesting a possible founder effect.

3.4. The North African experience

Najoua Miladi then reported on the history of sarcoglycanopathies in North Africa followed by her personal relevant experience. In 1980, Mongi Ben Hamida first reported a study of 31 children presenting a severe form of progressive muscular dystrophy that appeared to be inherited as an autosomal recessive monogenic trait, with equal distribution among sexes and the absence of clinical manifestations in the two parents. Frequent in Tunisia, this was seemingly related to the high degree of consanguinity in the country, however, there was marked variability in age of onset, intensity of symptoms, and severity of disease course from within and between families. In 1995, Satoru Noguchi et al. showed that a variant in *SGCG*, mapped to chromosome 13q12, was likely to be the primary genetic defect in this disorder. These variants not only affected gamma-sarcoglycan but also disrupted the integrity of the entire sarcoglycan complex. The clinical pattern was similar in all the patients with symmetric involvement of trunk and limb muscles, calf hypertrophy and absence of cardiac dysfunction. A high allelic diversity was found in the endogamic populations of North Africa, where in unrelated families the patients were homozygous for different variants in *SGCA*. Therefore, North African sarcoglycanopathies are genetically heterogeneous and not solely the result of defects in *SGCG*. In 1995, Najoua Miladi conducted a cognitive and psychological profile study and demonstrated that this population of R3 and R5 was functioning well within normal limits of cognitive abilities: IQ of 102 ± 3 mean ± SEM but had low self-esteem with feelings of sadness and internalized culpability.

From January 2014 to September 2024, Najoua diagnosed R3 ($N = 3$) and R5 ($N = 20$) at her pediatric neurology consultation in Maghreb Medical Center-Tunis. Three individuals had a *SGCA* gene (R3) variant c157 G > *A* and 15 had a *SGCG* gene (R5) small deletion c525 del T « Hot Spot mutation » (65 %) and 5 Libyan patients with a variant c581 $T > C$ including a compound heterozygous (c525delT and c581 $T > C$). All individuals received prednisone 0.75 mg/kg/d, 10 days on & 10 days off and daily ACE inhibitor, rehabilitation, and psychological support. The clinical presentation was similar but heterogenous in the same siblings and from one family to another; some ambulatory individuals presented with decreased forced vital capacity (FVC), and none had developed cardiac involvement. Similar results were found in Morocco, Algiers and Egypt.

3.5. European joint group experience

During this communication, Jorge Alonso-Pérez presented the findings obtained in two multinational collaborative studies that have allowed us to increase our knowledge about the clinical and genetic spectrum of the 4 types of sarcoglycanopathies. In the first study, a total of 33 neuromuscular centers from a total of 16 European countries participated, managing to recruit information from a total of 439 patients with sarcoglycanopathies (159 SGCA patients, 73 SGCB patients, 157 SGCG patients and 7 patients with SGCD) which is the largest cohort of patients described to date[2]. Data from patients with SGCA, SGCB and SGCG were analyzed. Clinical differences and severity progression were observed between the different types of OS, with SGCA presenting a later onset and a milder phenotype than patients with SCGB and SCGG. The second study focused on patients with SGCD, 128 centers around the world were contacted and a total of 23 patients with SCGD were recruited, confirming that it is an ultra-rare disease[11]. This study showed that these patients have a very severe disease with an early onset and a very early loss of ambulation compared to the rest of the types of sarcoglycanopathies.

3.6. Pediatric considerations

Claudio Bruno followed by asserting that the clinical spectrum of sarcoglycanopathies poses a significant challenge in pediatric neuromuscular disorders and therefore requires knowledge by the general pediatrician [17] Highlighting this need, he reported that the sarcoglycanopathies constitute the third most common form of autosomal recessive LGMD worldwide, with a global prevalence ranging from 0.27 to 0.56 per 100,000 individuals, and higher prevalence rates observed in consanguineous populations, where they account for 44 % of cases [18, 19] Characterized by early onset of symptoms, clinical manifestations progress from initial motor difficulties to significant functional impairment). Common complications include joint contractures (81.2 %), scoliosis (63.3 %), respiratory involvement (74.2 %), and cardiac manifestations (25 %), with R4 and R5 carrying the highest cardiac risk (40 % and 37.2 %, respectively) [2,11] Diagnostic approaches require systematic evaluation, beginning with recognition of early signs by primary care physicians and general pediatricians and progressing through specialized neuromuscular assessment. Further, there is critical importance of early diagnosis and intervention within the first five years after symptom onset [20] Management strategies emphasize multidisciplinary care, incorporating preventive measures, therapeutic interventions, and emergency protocols [5] Family support, including genetic counseling, psychological support, and resource access, forms an integral component of comprehensive care. The transition planning from pediatric to adult care requires careful coordination, which usually begins between the ages of 12 and 14, where the role of the pediatrician again becomes crucial [21] Finally, Claudio reported that understanding the current research landscape is crucial to the pediatrician, including awareness of current research focuses on novel therapeutic approaches, including gene therapy and protein recovery strategies, and future directions in therapeutic development which will emphasize age-appropriate endpoints, safety monitoring, and outcome measures specific to pediatric populations [22]

This session was concluded with a group discussion focusing on common clinical features associated with a diagnosis of a sarcoglycanopathy, those that are not, and a collection of differential diagnoses. These clinical features can be seen in Fig. 1.

4. Diagnosis of the Sarcoglycanopathies

The second session of this workshop was chaired by Tanya Stojkovic and was dedicated to the experiences of the diagnostic process across subtypes and regions. Those presenting made an effort to consider disparities in access to, and cost of, diagnostic measures across the world.

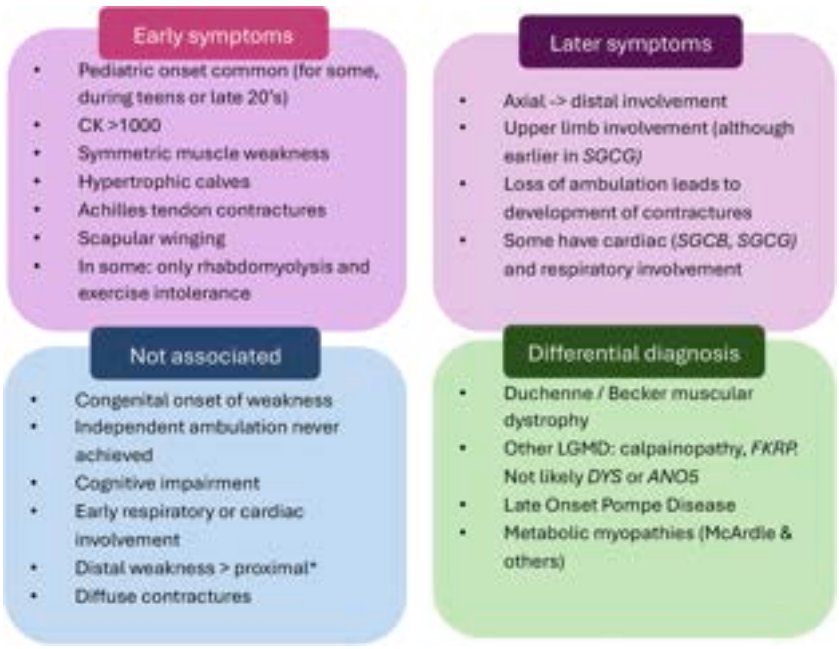

Fig. 1. Clinical symptoms and signs that can help in the diagnosis process of patients with sarcoglycanopathies. *Patients with delta-sarcoglycanopathy can develop early distal contractures, especially in the lower limbs.

4.1. Lab results and muscle biospy

Beril Talim described findings of 109 muscle biopsies of individuals with a sarcoglycanopathy at her hospital in Turkey, from 1999 to 2019. The age at biopsy ranged between 1–20 years and muscle weakness was the main presenting symptom (72 %), followed by elevated CK only (25 %). CK was elevated in all cases; >2500 IU/L in all but five. The histopathological pattern was dystrophic in 94 % and mild myopathic in 6 %. Inflammatory infiltrates were observed in 9 %. An immunohistochemistry (IHC) panel including four sarcoglycan (SG) and three dystrophin antibodies revealed deficiency of all four SGs in 60 %, deficiency of two or three SGs in 25 % and isolated gamma SG deficiency in 15 %. Reduction in dystrophin staining was present in 41 %, mostly in cases with deficiency of all SGs. Although molecular confirmation was not available in most cases, IHC did not always predict genotype reliably. There were three cases with normal immunolabeling for SGs but variations in *SGCA*. She revealed that mild protein deficiency might not be detected by IHC, and Western blot analysis and molecular studies would be helpful on such occasions. Since SG deficiency can also be secondary to dystrophin deficiency, a panel of antibodies for all SGs and dystrophins were suggested and need for molecular confirmation was emphasized. Literature reports about correlation between SG expression and clinical severity/loss of ambulation were also discussed.

4.2. Magnetic resonance imaging (MRI)

The diagnostic use of muscle MRI was presented by Giorgio Tasca. He reported the pattern of muscle involvement in the pelvis and lower limbs in sarcoglycanopathies has been well established, characterized by fatty changes in adductor magnus, hamstrings, and glutei muscles, with relative or complete sparing of other leg muscles [23] Additional common features included the gradient of fatty replacement of the vastus lateralis, preserved in the distal portion even in severely affected individuals, and the relative sparing of iliopsoas among pelvis muscles. These features were shared among the different sarcoglycanopathies and helped to distinguish them from the most common muscular dystrophies with overlapping phenotypes, such as dystrophinopathies and alpha-dystroglycanopathies [24,25] Current studies are addressing the distribution and degree of muscle of involvement in other body regions, showing that latissimus dorsi and subscapularis are key affected muscles in the upper girdle. Sparing of the tongue was particularly helpful to distinguish sarcoglycanopathies from Late Onset Pompe disease. Interestingly, peculiar gradients of vulnerability were identified in the upper body muscles as well. Giorgio also suggested to add AI algorithms, such as the one described in Myo-Guide (www.myoguide.org) to the diagnosis algorithm of the disease[26].

4.3. Genetics

Leonela Luce presented a proposal of a three-tier genetic diagnostic algorithm for the sarcoglycanopathies. The full strategy should be implemented in cases of clear suspicion of sarcoglycan-related muscular dystrophy, based on clinical presentation, MRI patterns consistent with the disease, absent or reduced SGCs in the biopsy immunohistochemistry staining, family history of the disease and/or family tree compatible with an autosomal recessive inheritance pattern [23] Given the high prevalence of small variants (point substitutions and indels) across individuals with a sarcoglycanopathy, the first-tier entailed sequencing the SGC genes linked to the development of limb-girdle muscular dystrophy (*SGCA, SGCB, SGCG* and *SGCD;* R3–6, respectively) by Sanger sequencing or next-generation sequencing (NGS) technologies. Yet, pre-screening of locally recurrent or founder variants could be implemented as a starting point in some ethnic cohorts. The second level consisted of the analysis of copy number variants (CNVs), which can be done by multiplex ligation-dependent probe amplification (MLPA) or the application of a CNV pipeline to the NGS data. The last level of testing included the screening of non-coding variants altering splicing or the expression levels, which could be pursued non-invasively by whole gene or genome sequencing, and/or by the analysis of mRNA from muscle biopsy. The identified variants should be classified according to the guidelines of the American College of Medical Genetics and Genomics (ACMG), a process that might require further studies such as familial segregation and functional tests [27] The presumptive clinical diagnosis of a sarcoglycanopathy will be considered genetically confirmed if two pathogenic or likely pathogenic variants in *trans* are identified. Still, candidate variants of unknown significance and single heterozygous hits should also be systematically reported and curated to promote their re-analysis, interpretation, and further genetic

investigation in cases with strong clinical suspicion. As part of the genetic counselling, Luce emphasized the importance of offering carrier testing to at-risk unaffected family members, to allow informed family planning by prenatal or preimplantation genetic testing. Finally, she encouraged conducting genetic studies in the partner of carrier individuals, especially in cohorts with high endogamy or increased carrier rate.

4.4. Interpretation of variants

Conrad Weihl then discussed the challenges of validating variants of unknown significance (VUS) in sarcoglycan genes following genetic sequencing. The burden of VUS in LGMDs and the sarcoglycanopathies is a barrier to establishing a firm diagnosis, family planning, enrollment in clinical studies and ultimately therapeutic interventions [28] Resolving VUS in the sarcoglycan genes requires collaboration between clinicians, basic scientists, and geneticists. Variant-specific rules for their classification were discussed, and the improved performance of these rules in establishing a definitive diagnosis was presented. In particular, the inclusion of skeletal muscle biopsy features improved phenotype specific rules for classification. Using deep mutational scanning and high throughput screens, all 6340 possible missense variants in *SGCB* were screened for their ability to localize to the plasma membrane serving as a proxy for gene function. This approach accurately identified pathogenic variants previously reported in ClinVar and correlated with disease onset [29] Future studies will screen small molecules proposed to increase *SGCB* membrane localization using the mutational library. To avoid the need for performing a large-scale screen, other approaches of variant resolution utilize artificial intelligence and deep learning to predict pathogenic variants in the other sarcoglycans.

A graphic of a recommended diagnostic algorithm can be found in Fig. 2.

5. Natural history studies in Sarcoglycanopathies

The following session was chaired by linda lowes and focused on reviewing current published literature, and lessons learned from ongoing studies, to better define the current knowledge of disease experience across sarcoglycanopathies.

5.1. The nationwide children's hospital experience

Linda Lowes presented a prospective longitudinal observational study of individuals with R4 recruited through both Nationwide Children's Hospital neuromuscular clinics and through outreach events held in an area with a high incidence of a Founder variant (c.452C>*G*)[6]. Forty individuals were enrolled between the ages of 3 and 55 years, with the c.452C>*G* group being significantly older (average age 27.6 compared to 13.1 years, $p > 0.01$). Twenty-two subjects (55 %) were ambulant as defined by the ability to walk 10 m without support in 30 s. All individuals completed the Performance of Upper Limb (PUL), 9-hole peg test, North Star Assessment for limb girdle-type muscular dystrophies (NSAD) which includes timed function tests (10-meter walk/run [10 m] and time to rise from floor [TTR]), and 100-meter timed test (100 m) as appropriate for their abilities. Except for the 9-hole peg test, all outcome assessments were able to quantify change over time. The NSAD was the only measure that showed a statistically significant decline (median change = 2 points, $p < 0.05$) at Year 1; in a 24-month period the NSAD, 100 m, 10 m and PUL all had a statistically significant change. A small ceiling effect was seen on the PUL among the younger, ambulant individuals. Over the course of the study, only one subject obtained a perfect score on the NSAD at age 6.2 years. Three subjects scored within three points of the max of the scale (> 51 points; ages 5, 9, and 11 years) which could suggest a small ceiling effect in some younger children. The ability to rise from the floor was the first milestone to be lost, with only 15 subjects (33 %) able to complete and the average age of those was 10.8 years (range 3.0 - 24.6 years); all subjects who independently rose from the floor had a 10 $m < 7.8$ s. There was a great deal of heterogeneity of functional abilities at all ages. In general, performance improved until around age 7, albeit at a lower level than age-matched peers and was followed by a plateau until around age 10–12 years. Respiratory concerns were not always present, but if they were, not until the

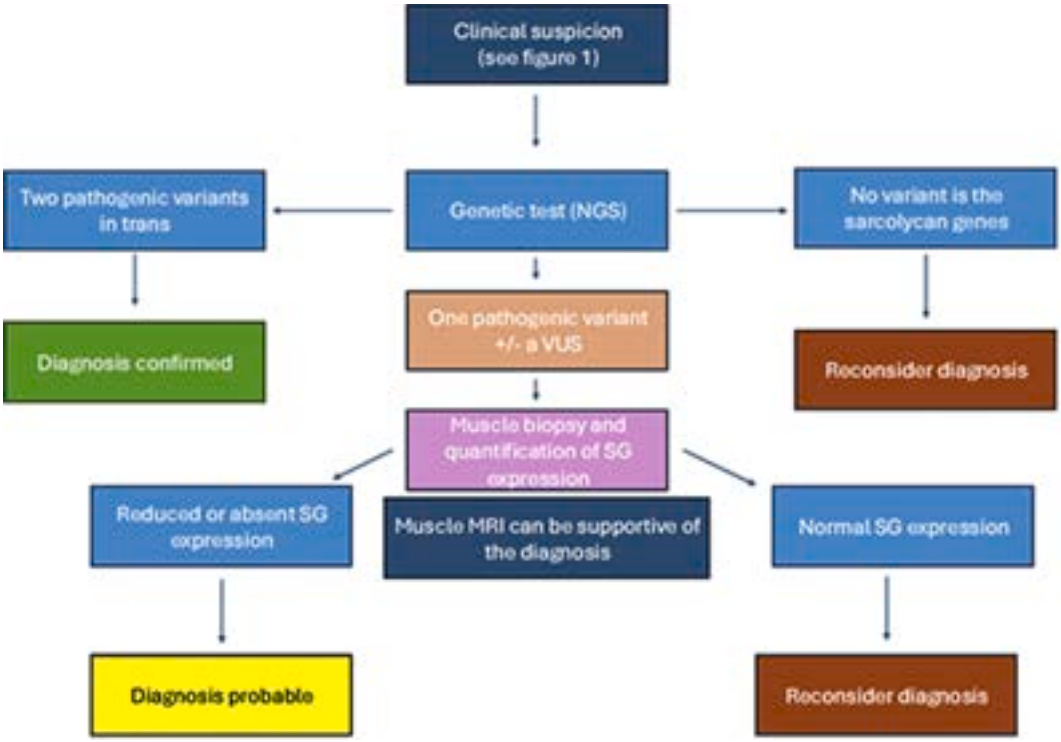

Fig. 2. Diagnosis algorithm of patients with sarcoglycanopathies.

individual became non-ambulatory.

5.2. The European experience

During this communication, Jorge Alonso-Pérez showed the findings obtained from the two retrospective multi-national studies carried out with a cohort of >400 individuals with sarcoglycanopathy. In the first study, at the European level, it was observed age of symptom onset as an independent risk factor for disease progression in individuals with R3, R4 or R5, so that those who start the disease before 10 years of age have a worse prognosis and lose ambulation earlier than those with a later onset of disease [2] Further, those who began the disease after 18 years of age remained ambulatory even until 50–60 years of age. Furthermore, this study showed that the residual amount of protein expression is also an independent risk factor for progression, as those with an absence or <30 % protein expression had more severe disease trajectory with an earlier loss of ambulation [2] The percentage of residual protein has a more important influence in patients with R3, where only an expression of <30 % is enough to change the prognosis of the disease significantly. In the case of *SGCD*, in the second multi-national study carried out, it was also shown that residual protein expression is a risk factor that is associated with a later onset of the disease and a milder phenotype [11]

5.3. The GRASP experience

As the lead Principal Investigator of The Genetic Resolution and Solving Phenotypes (GRASP)-LGMD consortium, Nicholas Johnson presented data from the 12-month observational natural history study in children and adults with LGMD R3–6. The goal of this study was to characterize disease presentation and progression in individuals diagnosed with a sarcoglycanopathy, using standardized clinical outcome assessments (COAs), patient-reported outcomes (PROs), and common clinical biomarkers. In 30 individuals with a sarcoglycanopathy, 73 % were ambulatory and the vast majority were diagnosed with R4. The COAs were demonstrated high inter-day reliability, with an ICC>0.99. Total NSAD score was able to distinguish those who reported that they have 'no difficulty', 'moderate difficulty', or 'severe difficulty' with ambulation on the LGMD-HI, a disease-specific PRO. Overall, there was a 5 % decline on the NSAD and PUL over the course of 12 months. When anchored to patient reported change, there was an approximate 3-point difference on between those who reported 'no change' in quality of life or that their quality of life got 'a little worse'. As a sub-study, the authors analyzed the level of alpha-sarcoglycan expression in individuals with a single pathogenic variant in *SGCA* (i.e., carriers). In these individuals the degree of alpha-sarcoglycan expression was approximately 30 % of healthy individuals.

5.4. Muscle function outcomes for trials

To further appreciate the documentation of the heterogeneity of trajectories of motor function in individuals with sarcoglycanopathy, Meredith James presented on standardized COAs specific to the LGMDs. She reported that clinical outcome measures, including clinician-rated and patient-reported, should reflect the lived experience of an individual with sarcoglycanopathy. Patient-centered, standardized assessments, appropriate to age, ability, and disease stage, should be utilized within clinic and clinical trial settings[30] Standardized outcomes identify the patient's location on the disease trajectory and are used to guide individualized care discussions and prepare the individual for future needs. Potential outcomes include gross-motor function measures, timed tests, respiratory function, strength, patient-reported outcome measures and health- related quality of life instruments. These measures should align with the International Classification of Functioning, Disability and Health (ICF) framework, addressing body structures, activity, and participation, while ensuring reliability, validity, and sensitivity to change (https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health).

International, collaborative efforts alongside single-center studies are underway to explore and validate appropriate outcome measures for individuals with sarcoglycanopathies (NCT03492346, NCT04475926, NCT03981289). Currently the NSAD, 100-meter timed test, 4-stair climb, timed up and go, pulmonary function tests, and PUL, are common elements being utilized in global natural history studies of the sarcoglycanopathies after validation in other LGMD subtypes[20,31–33] The Egen-Klassifikation scale is a clinical management tool that can be used to evaluate general function in non-ambulant individuals[34] ACTIVLIM can be utilized in children and adults to review abilities in daily tasks and quality of life for slowly progression neuromuscular conditions (QoLGNMD) is a health-related questionnaire validated in adults with neuromuscular disease[35,36] Other patient reported outcomes could include the PROMIS toolkit of scales. A proposed list of outcome measures by type and level of functional ability can be found in Fig. 3.

Within the clinical setting, as staffing and time allocated has significant global variation, a proposed minimal data set could include 10 m, ability to rise from a chair, ability to rise from the floor, and PUL entry item (Table 3 or Fig. 3). This would allow for continued monitoring of individuals for clinical management in addition to continued documentation of functional trajectories.

6. Cardiac and respiratory assessments in the Sarcoglycanopathies

The cardiac and respiratory session, chaired by Tanya Stojkovic, included cardiac and respiratory care considerations, as well as other considerations for adolescent and young adult individuals living with a sarcoglycanopathy.

6.1. Cardiac assessment and management

Marta de Antonio Ferrer reported that cardiac involvement in the sarcoglycanopathies is a progressive feature, affecting 21 % of patients, with a higher prevalence in R4 and R5[2,11] Dilated cardiomyopathy is the most common cardiac disease, followed by rhythm abnormalities. Early detection and consistent monitoring are critical for timely treatment. Cardiac evaluations, including clinical examination, electrocardiogram (ECG), and echocardiography, should begin at diagnosis, with yearly follow-ups for R4 and R5 and every 1–2 years for other phenotypes. For patients with abnormal findings, heart failure, or loss of ambulation, annual follow-ups and a cardiologist referral is recommended.

Cardiac MRI (CMR) is valuable for assessing ventricular function and tissue characteristics. Treatment for heart failure with reduced ejection fraction should align with clinical guidelines, involving sacubitril-valsartan/ACE inhibitors/Angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists (MRA), and SGLT2 inhibitors [37] Early initiation of ACEI/ARB, beta-blockers, and MRA in asymptomatic patients with left ventricular dysfunction may help delay progression. Preventive ACEI/ARB therapy after age 10 is reasonable, though evidence is lacking. In patients with sarcoglycanopathies and reduced left ventricular ejection fraction, the indication for implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death should follow the same criteria as those established for other etiologies of heart failure. Cardiac transplantation or mechanical support is considered only for select cases without respiratory issues after multidisciplinary evaluation.

6.2. Respiratory assessment and management

Respiratory assessment and management in the sarcoglycanopathies were then discussed by Stephan Wenniger. Respiratory involvement in

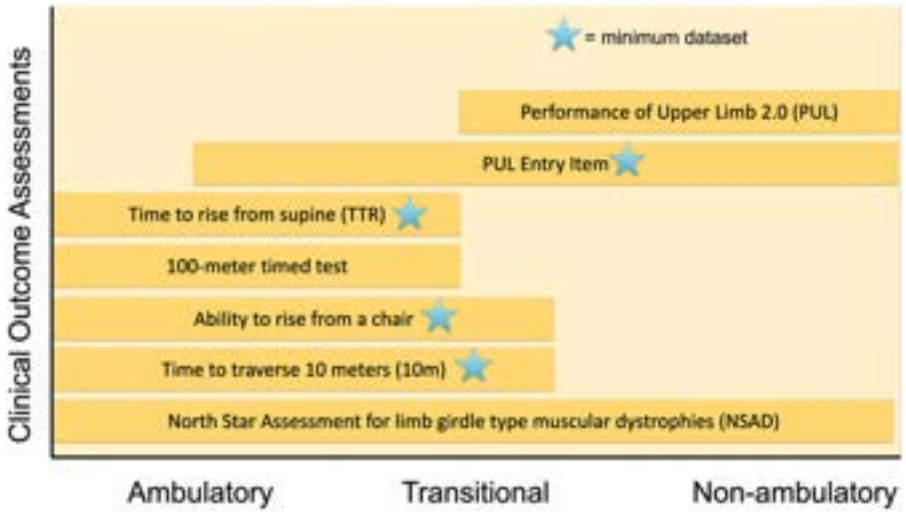

Fig. 3. Recommended motor function COAs by ambulatory phase. A minimum dataset of motor function assessments includes the 10 m, time to rise from floor, ability to stand from sitting, and PUL entry item.

sarcoglycanopathies may develop during the disease course in a variable degree[2,4,5,12,38] Clinical observational studies on respiratory function in this group of LGMDs are rare, but, according to published data, an annual decline in forced vital capacity (FVC) of −1.45 % can be estimated[38] Regular monitoring of pulmonary function should include at least core assessments by spirometry (sitting and lying forced vital capacity [FVC], forced expiratory volume in the first second [FEV1]), peak cough flow (PCF) and blood gas analysis (BGA)[39,40] They are crucial for the early detection of respiratory muscle involvement and initiation of treatment at the proper time, as chronic hypoventilation is associated with significantly reduced quality of life and increased morbidity and mortality[40].

For ambulatory patients, core diagnostic assessments, depending on the clinical progression, are recommended every 12 months with longer intervals acceptable in individual cases of long-term clinical stability and maintained ambulatory function. In patients who are on the verge of losing their ambulation or in non-ambulatory patients, involvement of the respiratory muscles can be presumed, warranting follow-up visits every 6 months. Nocturnal capnometry ($tcCO_2$) is particularly indicated for patients showing clinical signs of nocturnal hypoventilation but with normal or borderline spirometry results. Clinical signs of hypoventilation should be routinely assessed, but specific validated patient questionnaires for LGMDs or are lacking. However, alternatives such as the "Respicheck" (validated in myotonic dystrophy type 1) could serve as a good screening tool for this group[41] Although no clinical studies specifically address inspiratory muscle training for the sarcoglycanopathies, findings from other forms of neuromuscular disorders with chronic-progressive involvement of respiratory muscles suggest that inspiratory muscle training strengthens respiratory muscles and improves thoracic compliance and alveolar recruitment, which may help mitigate disease progression[42–44] Non-invasive ventilation should be recommended for patients with clinical signs of nocturnal hypoventilation, significantly reduced FVC, and elevated CO_2 levels[45–48] A PCF <270ml/min indicates the need for review of airway clearance ability and referral to respiratory team for appropriate provision of airway clearance support such as cough augmentation in the form of breath stacking, lung volume recruitment or mechanical insufflation-exsufflation devices . Severe impairment of cough strength is associated with reduced airway clearance and a high risk of respiratory infections[49]

6.3. *Transition of patients from pediatric to adult services*

To conclude this session, Kristl Claeys presented approaches to transitioning individuals from a pediatric to adult services, beginning with the clarification that 'transition' needs to be distinguished from 'transfer'. 'Transfer' refers to the *event* through which adolescents/young adults with chronic medical conditions move their care from a pediatric to an adult healthcare environment, which simply implies the change of facility (e.g. from comprehensive pediatric clinics to adult medical care). In contrast, 'transition' refers to the *process* by which adolescents/young adults with a chronic childhood illness are being prepared to take charge of their lives and their health in adulthood. This involves a purposeful planned movement during which young people acquire skills and access resources to ensure that their physical, psychosocial, educational, and vocational needs are met. Transition is the process from child patient/parent-centered care towards adult patient/self-centered care. Four models for transition have been proposed: joint clinic model, introductory model, pediatrician-in-adult-care model and the transition coordinator model[50] Particularly, the latter transition model is well-supported in the literature, but there is no evidence yet to prioritize it in the field of neuromuscular disease. Many potential barriers have been identified in the transition process, ranging from a lack of training, education, standardized programs, and guidelines to difficulties in accessing the medical records or adapted clinical settings for patients with special needs (e.g. autism, intellectual disabilities), up to emotionally driven reasons such as pediatricians being attached to their patients or patients themselves preferring to remain in the pediatric clinic. Other very important potential barriers include the lack of financial support for transition programs, as well as the lack of a dedicated transition coordinator (e.g. nurse, social worker)[50,51] Kristl supported the need for transition to start early in care, if possible already at age 12 years, and the transition process to continue after transfer to adult healthcare services. Empowerment of the patient is a key issue in the transition process. Several tools for transition have been developed such as the Ready Steady Go program, or the Transition Readiness Assessment Questionnaire (TRAQ)[52,53].

7. Therapeutic interventions

The final session of the workshop was chaired by Nicholas Johnson and focused on therapeutic interventions for individuals with a sarcoglycanopathy and protentional therapeutic strategies for disease-modifying agents in the future. This session included the experience of

both industry stakeholders and research scientists.

7.1. Physiotherapy and orthosis

Meredith James began the session by validating the vital role of a specialist neuromuscular physiotherapist (PT) and occupational therapist (OT) in the management of individuals with sarcoglycanopathies. Allied health professionals have an essential role to play in assessing muscle function, strength, and changes over time, as well as providing timely and anticipatory treatment, advice and support. PT and OT work with the individual to: develop specific exercise and stretching programs; identify and prescribe aids and equipment (e.g. orthoses, mobility aids, wheelchairs and standing frames); advise on moving and handling issues and fall management; review upper limb function; address home aids and adaptations, including modified vehicles and driving; and, depending on the location, monitor respiratory function and advise on techniques to assist with chest physiotherapy including breathing exercises and secretion clearance techniques and equipment. Although there are no currently approved treatments, acquired secondary co-morbidities can be anticipated, and functional abilities maximized with a multidisciplinary approach.

7.2. Exercise in neuromuscular diseases

Megan Iammarino followed with a review on exercise studies in neuromuscular disease, with recommendations for application in a clinical setting with individuals with a sarcoglycanopathy. Exercise studies have primarily focused on both safety, cardiovascular endurance, and strength training across neuromuscular diseases. These cohorts are typically small in number with mixed geno- and pheno-types, including LGMDs, Becker muscular dystrophy (BMD), and Duchenne muscular dystrophy (DMD). One study found that while high intensity training was not tolerated by individuals with LGMDs, resulting in elevated CKs and reports of muscle pain, low-intensity strength training was well tolerated in these individuals[54] When working at 40 % of maximum knee extension and biceps flexion strength, improvements in strength were found after 6 months without elevated CK[54] Many studies have focused on the impact of aerobic training on the cardiovascular system as well. Methods including the use of stationary bicycle and/or arm ergometer, and on average, working at 65 % $V0_2$ max, over 12–52-week periods have had promising outcomes including increased work capacity, increase in cardiac reserve, improved balance and walking ability, without safety concerns[55–59] Further, there is additional evidence that exercise may have positive psychological benefits in BMD and LGMDs, including a decrease in depression symptoms and anxiety, and an increase in self-esteem and self-worth[60].

In a clinical setting, exercise prescription has been generalized as a balance between pushing too hard (inciting muscle damage) and doing nothing at all (resulting in muscle atrophy). It is important that a physiotherapist specialized in muscle disease provide a patient-centered and patient-driven exercise program, including activities that these individuals enjoy. Commonly recommended is aquatic-based activities or therapies, as the buoyancy of the water allows the individual to safely walk and/or move in a way that they are unable to on land. However, before considering an aquatic program, if the individual has cardiac concerns it is recommended to get clearance from a cardiologist first, as the hydrostatic pressure of the water can push more fluid toward the heart. Overall, exercise can be fun, may be able to improve cardiovascular fitness and overall mobility, and reduce overall quality of life.

*7.3. Lessons learned from gene therapy*Andre Mueller-York from Sarepta Therapeutics then reported on the lessons learned from their gene-therapy programs. The development and clinical use knowledge can be transferred, to a certain extent, between Sarepta's gene therapy development pipelines for DMD and LGMD based on the AAVrh74 platform. Selecting the appropriate vector for targeted therapy is one important approach to minimize off-target effects due to diverse AAV serotypes and their tissue affinity[61–63] The clinical trials led by Sarepta in LGMD using this AAVrh74 platform to date have shown no complement-mediated adverse events (AEs). The functional endpoints for this program, including the NSAD and timed function tests, have indicated a higher level of function compared with an LGMD natural history cohort[22] Further, endpoints that were assessed by MRI and devices may aid in documenting the efficacy of gene therapies for muscular dystrophies. Due to the small prevalence of some LGMD subtypes, natural history cohorts may provide an adequate external control group for small-scale gene therapy trials without a placebo arm[22,64] In response to the need for a natural history cohort across LGMDs, Sarepta initiated a natural history study, JOURNEY (NCT04475926) for LGMD subtypes R3, R4, R5, R6, and R1 (calpain-related). Preliminary baseline results suggest that a higher proportion of participants in the younger age groups are ambulatory, however a substantial portion of participants over 8 years of age are already non-ambulatory. Cardiac abnormalities are more common in non-ambulatory participants aged $\geq$ 17 years and pulmonary function generally decreases with age, with a more substantial decline in non-ambulatory individuals in their late teens. Future longitudinal analysis of functional performance will help support a better interpretation of functional outcomes in clinical trials for LGMD subtypes.

7.4. Gene therapy strategies in sarcoglycanopathies

While there is no approved treatment for any of the sarcoglycanopathies to date, Isabelle Richard presented the current achievements of her group towards gene therapy in the sarcoglycanopathies. They are developing AAV-mediated gene transfer approach, focused on subtypes R3 and R5. For R5, a first clinical trial sponsored by Genethon to evaluate the safety of a recombinant AAV2/1 vector expressing the corresponding gene using an intramuscular route of administration showed limited expression of the transgene and good tolerance of the approach [65] Considering the evolution in the field, they switched the strategy to a systemic route of administration using an AAV8 vector. Therefore, they undertook a dose-effect study in mice to evaluate the efficiency of an AAV2/8 expressing gamma sarcoglycan under the control of a muscle-specific promoter by a systemic mode of administration. They observed a dose-related efficiency with a nearly complete restoration of gamma sarcoglycan protein expression, histological appearance, biomarker level and whole-body force with the highest dose tested. In addition, the data suggest that expression of the transgene should be achieved in virtually all the fibers for effective protection against mechanical stress[66] They then finalized the construct by performing a study for selection of the best promoter to lead to an expression profile as close as the endogenous expression. A dose study was performed and allowed the selection of the minimal efficacy dose (MED). Safety studies were performed: a GLP- toxicology study in rats and an exploratory non-GLP study in NHP, demonstrating a good safety profile. The development for the new vector was completed as well as the transfer to a manufacturing organization. This program has been licensed to Atamyo Therapeutics, a biotechnology company focusing on gene therapy for LGMDs and a clinical trial is planned for early 2025 (NCT05973630). A similar approach is being pursued for R3.

7.5. CRTF correctors as a therapeutic strategy for sarcoglycanopathies

Dorianna Sandona presented the work developed by her group aiming at developing novel therapeutic strategies for sarcoglycanopathies. The majority of genetic defects responsible for sarcoglycanopathies are missense variants, leading to the production of folding-defective sarcoglycans that are discarded by the cell's quality control system, despite their potential functionality[67,68]. Thanks to this knowledge, they have proposed the use of well-established molecules originally developed to correct type II variants of the cystic fibrosis transmembrane conductance regulator (CFTR), which, like the

sarcoglycans carrying missense variants, are folding-defective and thus prematurely degraded or unable to traffic properly to the plasma membrane[69,70].

Among the small molecules in the CFTR corrector family, several have shown success in rescuing various α-SG and β-SG mutants expressed in heterologous cell models, with C17 emerging as the most promising. C17 effectively restored the SG complex at the sarcolemma in primary myogenic cells derived from both LGMD2D/R3 and LGMD2E/R4 patients, enhancing plasma membrane stability and confirming functional rescue in vitro[71,72]. Additionally, chronic administration of C17 for 5 weeks in a humanized mouse model of LGMD2D/R3 successfully recovered the sarcoglycan complex and improved muscle strength[73]. The pharmacokinetic properties of this small molecule, along with preliminary toxicity studies, indicate a highly promising drug candidate profile[74].

7.6. Antifibrotic drugs for sarcoglycanopathies

Jordi Diaz-Manera presented the results of a interventional study done with nintedanib in a murine model of alpha-sarcoglycanopathy. Nintedanib is a second generation tyrosine kinase drug used for the treatment of patients with idiopathic pulmonary fibrosis since >10 years ago[75]. It is known to block the activation of the vascular endothelial growth factor receptor (VEGFR), the fibroblast growth factor (FGFR) receptor and the platelet derived growth factor receptor (PDGFR). Fibroadipogenic progenitor cells (FAPs) are muscle resident mesenchymal cell which are key in the process of muscle fibrosis and adipogenesis. Nintedanib, through its activity blocking the PDGFR, is known to reduce the proliferation and migration of human fibroadipogenic progenitor cells and also to reduce the expression of collagen and other components of the extracellular matrix by these cells[76,77]. In the paper presented, the group treated animals of 2 months of age for 8 weeks at a dose of 50 mg/12 h[78]. As a results, they observed an improvement in muscle function measured using the treadmill and the grip strength. Histological studies showed an improvement of the general architecture of the skeletal muscle associated to a reduction of the expression of collagen and other fibrotic markers in the muscles of the mice affected. Reduction in fibrosis was associated with a reduction in several inflammatory markers, FAPs muscle population and the number of regenerative fibers. These results suggest that nintedanib could be a therapeutic option for sarcoglycanopathies modulating FAP cell population and function.

8. Conclusion

The existence of a standardized guideline for the diagnosis, management of care, and clinical follow-up for individuals with a sarcoglycanopathy is currently of vital importance. In addition to a patient-reported global lack of specialists for the care of the LGMDs, there are several treatment proposals for the sarcoglycanopathies in the clinical trial pipeline. These include both clinical trials and advanced preclinical studies, such as gene therapy or the use of small molecules that restore the expression of residual protein; this suggests that in the coming years there will be one or more forms of effective treatment for these patients.

During the workshop, both existing knowledge and expert clinical opinion was presented on the clinical spectrum, diagnostic approach, and prognostic factors of the sarcoglycanopathies, harmonizing the experience of multidisciplinary stakeholders from various parts of the world. Additionally, the targeted tools for diagnosing these individuals were updated and data on the natural history of the disease was presented, as well as the cardiac or respiratory involvement that these patients may have. Subsequently, the different current and future treatment options for this disease were discussed.

While there appears to be quite a bit of heterogeneity in clinical presentation within and between the sub-types of the sarcoglycanopathies, their common features (e.g. younger age of onset and quicker rate of progression) set them apart from other subtypes of LGMD. Therefore, it is recommended that this group of LGMDs would benefit from diagnostic and care guidelines tailored directly for them, although not necessary for each individual subtype separately. So, based on workshop discussions, the group proposed to develop a specific diagnosis and care protocol for the sarcoglycanopathies.

Workshop organizers background in relation to the scope of the workshop

Tanya Stojkovic is an adult neurologist with long experience in the pathological and clinical classification of patients with sarcoglycanopathies.

Elena Pegoraro is a neurologist who has described clinical features of patients with different subtypes of sarcoglycanopathies

Linda Lowes is a specialized physiotherapist who has deeply characterized the muscle function of sarcoglycan patients in USA

Jordi Diaz Manera is an adult neurologist who has characterized the disease progression of patients with sarcoglycanopathies and has studied new therapies to stop disease progression.

Early career contributors

Megan Ianmarino is an early-career physio who has been particularly involved in developing new outcome measures for patients with sarcoglycanopathies.

Jorge Alonso-Pérez is an adult neurologist specializing in neuromuscular diseases who did his PhD on establishing phenotype-genotype correlations in sarcoglycanopathies.

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CRediT authorship contribution statement

M.A. Iammarino: Writing – review & editing, Writing – original draft, Conceptualization. **J. Alonso-Pérez:** Writing – review & editing, Writing – original draft, Conceptualization. **T. Stojkovic:** Writing – review & editing, Writing – original draft, Conceptualization. **E. Pegoraro:** Writing – review & editing, Writing – original draft, Conceptualization. **L. Lowes:** Writing – review & editing, Writing – original draft, Conceptualization. **J. Díaz-Manera:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

Authors of the workshop have no declaration of interest.

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