Rare disease clinical trials
Power in numbers

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The limb-girdle muscular dystrophies (LGMDs) encompass a collection of genetic muscle diseases with proximal-predominant weakness of the limbs. Thirty-two of these disorders are named via the common nomenclature, including 8 autosomal-dominant (LGMD1A-H) and 24 autosomal-recessive (LGMD2A-X) disorders.[1] In addition, numerous other genetic muscle diseases, including Bethlem myopathy, dystrophinopathies, ryanodine receptor–associated myopathies, and many more, may clinically present with similar proximal-predominant weakness.[2] Therefore, current genetic testing panels targeting neuromuscular weakness frequently encompass >75 genes. These disorders are quite rare, each with minimum prevalence estimates of 0.01–0.60 cases per 100,000 persons.[3] LGMD2A (attributable to mutations in the gene for calpain-3) and LGMD2B (attributable to mutations in the gene for dysferlin) consistently are the 2 most prevalent LGMD subtypes in a variety of ethnic cohorts.

In this issue of *Neurology® Genetics*, Harris et al.[4] describe baseline clinical and functional features in a large cohort of 193 patients participating in the international Clinical Outcome Study, a 3-year observational trial of dysferlinopathies. Criteria for inclusion required ≥2 pathogenic mutations in *DYSF*, the gene for dysferlin, or 1 pathogenic mutation plus evidence for significant quantitative deficiency of dysferlin protein. The investigators delineated 175 mutations, with no distinct hotspot along the gene, and 112 of these mutations were present in just 1 participant. Thus, many isolated, individual, unique mutations were selectively seen in a single person. On muscle immunohistochemistry or immunoblot, most patients had absent or diminished dysferlin expression. It is noteworthy, however, that dysferlin actually expressed normally in 3 patients with moderate to severe disease, reiterating the fact that protein-based assays may miss a portion of dysferlinopathy cases.[5]

In this large, rare disease cohort, the clinical features reinforce findings in the literature. Harris et al. report onset at 3–60 years of age (median 19 years). Interestingly, 24% of patients serendipitously obtained their diagnosis after evaluation for hyper-CKemia, whereas 13% were discovered after diagnosis in a family member. Dramatic improvement has occurred in the timeframe from symptom onset to diagnosis, reducing from 20.5 years in the 1970s to 3.1 years since the year 2000. Of the patients, 16% were misdiagnosed as polymyositis, and 25% received corticosteroid treatment, an ineffective treatment strategy in dysferlinopathies.[6] Leg weakness was the common initial symptom and presented roughly equally in a proximal, distal, or proximodistal pattern. At all stages of disease, lower extremities were nearly uniformly more affected than upper extremities. And, in terms of pattern of weakness, hip extensors were statistically significantly weaker than hip flexors, while hip abductors were relatively spared, with hip adductors definitely weaker. Calf atrophy manifested in 71%; however, muscle hypertrophy actually occurred in 11%. Mean serum CK was 4,562 U/L (range, 209–23,124 U/L) with lower values seen over time. Similar to earlier publications of athletic prowess before disease onset, participation in sports was very common (80%), with 19% contending at regional or national levels.

One crucial reason to pursue a definitive, genetic diagnosis remains determination of the involvement of other organs in muscle diseases. In LGMDs, some subtypes have significant, early, or disproportionate cardiopulmonary dysfunction leading to greater morbidity and early mortality. LGMD1B (laminopathies), 2C-F (sarcoglycanopathies), and 2I (Fukutin-related protein and α-dystroglycanopathies) have significant risk of cardiac and/or pulmonary dysfunction requiring pacemaker/defibrillator placement, management of congestive heart failure, and/or noninvasive ventilatory support. Conversely, LGMD2A (calpainopathies), 2B (dysferlinopathies), and 2L (anoctaminopathies) have been thought to be virtually without cardiopulmonary dysfunction. In this study, no patients had frank heart failure, only 6 patients had a forced vital capacity <50% (all with moderate to severe skeletal muscle weakness), and

only 4 patients used nocturnal noninvasive ventilation (all for the diagnosis of obstructive sleep apnea). This reemphasizes the paucity of clinically relevant cardiac and respiratory dysfunction in dysferlinopathies. Moreover, these data support published guideline recommendations that clinicians need not refer LGMD2A and LGMD2B patients for cardiopulmonary surveillance unless symptoms arise.[7]

Treatment trials in rare diseases pose significant challenges. They require large, multicenter, collaborative efforts to identify, recruit, and retain sizable pools of patients for statistically meaningful results in studies with adequate power. Yet, understandably, most trial participants prefer not to go untreated. This creates an honest conundrum for clinical trial design. If rare disease populations could be well defined, those populations could theoretically be used to chart disease trajectories as historical control groups. However, this concept has not been generally accepted. So, of late, trials disproportionately divide cohorts into treated:untreated ratios of 2:1 or 3:1. As we move through to the era of genetic therapies,[8] impeccable descriptions of disease manifestations and progression in large populations, as in the Clinical Outcome Study for Dysferlinopathies, will prove imperative for successful trial design, accomplishment, and analysis.

In rare diseases, the power in numbers will be the big deal propelling us forward! The efforts of Harris et al. reflect a noble step in that direction.

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DISCLOSURE

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