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Establishing prevalence in rare neuromuscular diseases

A lesson from congenital myopathies

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Congenital myopathies (CMs) are a heterogeneous group of early-onset muscle disorders with weakness, distinct histopathologic features, and normal to slightly elevated creatine kinase (CK).¹ The age at onset and clinical severity can be variable, ranging from severely affected at birth to a milder later-onset disease.² Cardiac involvement has been reported.^{3,4} CMs are generally considered nonprogressive disorders. Three main categories are recognized within the classical CMs based on their typical histopathology: nemaline myopathy (NM), core myopathy, and centronuclear myopathy (CNM). Inheritance in CMs may be dominant, recessive, or X-linked. Greater than 25 unique genetic causes of CM have been identified and different types of mutations within the same gene (e.g., deletions, duplications, missense, nonsense, splice-site, and frameshift mutations) have been identified, as well as de novo dominant mutations.⁵

In this issue of *Neurology® Genetics*, Witting et al.⁶ report a comprehensive analysis of the prevalence, genotype, and phenotype of CM in patients 5 years and older in Denmark. The study was conducted at the Copenhagen neuromuscular center, Rigshospitalet, Denmark, in collaboration with the Danish National Rehabilitation Center for Neuromuscular Diseases. After identifying all registered Danish patients with a diagnosis of CM aged older than 5 years, comprehensive clinical, histopathologic, and genetic investigations were performed. This approach allowed for a unique prospective assessment of this patient group that has not been studied previously in CMs.

The study found that the prevalence of CM in Danish patients older than 5 years (age range 5–69 years with a mean of ~28 years) was 2:100,000; significantly lower than previous studies that estimated the prevalence at ~4:100,000.^{7,8} This may be due to the exclusion of pediatric patients who have succumbed to their illness prior to age 5. This limitation, although acknowledged by the authors, underrepresents an entire group of early-onset CMs with

high mortality in the first few years of life. This may also account for the lower prevalence of *MTM1* mutations—carrying patients in this study.^{9,10}

The prevalence did not include patients who phenotypically and pathologically fulfilled criteria for CM yet were found to have a genetic etiology considered not to be associated with CM. Whether this patient group was included in other studies is not entirely clear. However, 10 patients had mutations in *DES*, *COLVI*, *COLXII*, *DOK7*, and *RAPSN*. These patients are interesting because some had pathologic features of NM, core myopathy, and CNM. Notably, *DES* mutations were identified in one patient with NM and another with core myopathy. Whether these genes explain undiagnosed causes of CM in the global patient population remains to be determined. Notably, *DES* and genes associated with congenital myasthenic syndrome are not routinely included in CM gene panels. Therefore, neurologists should consider these etiologies in patients with CM and an unknown genetic cause.

A genetic etiology was reached in 56% of Danish CM patients. This is somewhat lower than in other similar studies in which a genetic cause was found in 67%–79% of patients.^{11,12} This may relate to the inclusion of patients without distinctive features on biopsy, but a phenotype consistent with CM. For example, in patients with histopathologic features consistent with NM, CNM, or core myopathy, a genetic diagnosis was identified in 83% of patients. By contrast, in patients with unspecific histopathologic features, the genetic diagnosis was achieved in only 21% of patients.

Another unique aspect of this study was the inclusion of patients with CM regardless of age. Indeed, the oldest patient was a 69-year-old woman with a *DNM2* mutation. Although difficult to ascertain from the small cohort size, in general, older and younger patients with CM demonstrated a consistent phenotypic pattern of weakness depending on their gene mutation. Moreover, older patients with CM

See article

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continued being active in their education or work life. This supports the prevailing theory that CM is a non-progressive disorder.

Studies such as that performed by Witting et al., which define the prevalence and genetic heterogeneity of a defined patient population, are the next step in neuromuscular patient care. How the composition of Danish CM patients relates to other countries or even individual academic centers remains to be determined. Research initiatives focused on the identification of novel genetic etiologies are important, but reporting the genetic makeup of existing patient populations is absolutely essential, as we enter a new and exciting era of personalized neuromuscular therapeutics.

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