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Editorial

Continued need for caution in the diagnosis of Duchenne muscular dystrophy

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The article by Schwartz et al. in this issue of *Neurology* emphasizes information important to the clinical and molecular diagnosis of limb-girdle (LGMD), Duchenne (DMD), and Becker (BMD) muscular dystrophies. They report that 13 out of their 102 patients previously diagnosed with sporadic DMD actually have one of the commoner forms of LGMD—LGMD type 2I—a disorder that is caused by mutations in the fukutin-related protein gene.[1] The implications of the report are that many if not most previous clinical articles on DMD and BMD where the molecular diagnosis was not confirmed will have included patients with this disease. While a DMD-like phenotype has been identified in other studies of LGMD2I,[2] the surprisingly large percentage of such cases in the current article has important implications for diagnosis, genetic counseling, and clinical trials.

The X-linked disorder DMD was once considered among the most stereotyped of inherited human diseases: boys with disease onset by age 5; pseudohypertrophic calf muscles; relentless progression to loss of ambulation by age 10 to 12; cardiomyopathy; respiratory muscle compromise by the end of the second decade; a creatine kinase level of 20 times above normal; and dystrophic features in the muscle biopsy. Few clinicians doubted their ability to make a diagnosis with 100% accuracy.

The discovery of the molecular defect in DMD seemed to justify this confidence. Patients with DMD often have out of frame deletions (60%) or duplications (10%) of the dystrophin gene that are readily detectable on routine molecular testing. These out of frame mutations result in the virtually complete absence of dystrophin in muscle, while mutations in the dystrophin gene causing partial loss of dystrophin were shown to account for the slightly milder "outlier" phenotype[3,4] and the often benign Becker dystrophy phenotype.[4] However, due to problems in detection of the point mutations that underlie the disease in up to 30% of patients, there remain patients in whom a precise molecular diagnosis has not been achieved. Recent improvements in molecular diagnosis mean that it is now possible to identify mutations in up to 90% of patients with a DMD phenotype,[5] but these techniques are not universally available. Given the technical difficulties of point mutation detection, biopsy evidence of total absence of dystrophin in DMD or reduced dystrophin in BMD has remained the gold standard for diagnosis.[6]

The publication of Schwartz et al. therefore reminds us that even 18 years after the cloning of the dystrophin gene we cannot afford to be complacent about the diagnosis. There are important clinical and research implications of knowing that patients with the clinical picture of DMD may have a form of LGMD. As noted, a definitive diagnosis of DMD requires muscle biopsy evidence of complete absence of dystrophin. A reduction in dystrophin does not always indicate that the patient has a dystrophinopathy. In the Schwartz et al. study, dystrophin was reduced in some of the patients with LGMD2I, and in sarcoglycanopathies there may also be DMD- or BMD-like phenotypes with a secondary reduction in dystrophin. The phenotypes of other LGMDs are still being characterized.[7] Without a definitive diagnosis of DMD, it is not possible to counsel families concerning the implications of an x-linked vs an autosomal disorder, and in the future, specific therapies for DMD may depend on the precise delineation of the mutation.

Past studies including clinical trials of DMD and BMD when the diagnosis was based on phenotype alone undoubtedly will have included patients with LGMD2I.[8-10] Future studies need to be based on patients fully characterized by biochemical and molec-

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ular analyses. At the same time, the virtually identical nature of the phenotype raises the possibility that patients with LGMD2I might respond similarly to corticosteroid treatment. It is also intriguing that the same clinical findings result from two widely differing gene abnormalities: one in the structural protein dystrophin that links α-actinin to the sarcolemma and the other in the fukutin-related protein that may act post-translationally to glycosylate α-dystroglycan and other proteins.

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