The Quest for the Prediction of Steroid Responsiveness in Duchenne Muscular Dystrophy

Renu Suthar¹ • Jitendra Kumar Sahu¹

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Duchenne muscular dystrophy (DMD), first described in 1834, is a progressive and crippling muscle disease. With an improvement in supportive care, the life span of boys with DMD has increased significantly, but the quality of life remains suboptimal. Glucocorticoids, an approved therapy for boys with DMD, improve muscle strength, lengthen the duration of independent ambulation, postpone the onset of cardiomyopathy, improve pulmonary function, and decrease the incidence of scoliosis [1]. The mechanism of action of glucocorticoid therapy in DMD is not fully elucidated, and there are several proposed mechanisms like anti-inflammatory, membrane stabilization, differentiation of epigenetic regulators in muscle fibers etc. Long term steroid use is associated with significant adverse effects [2]. The concern for adverse effects among the parents and physicians is so much that more than 50% of boys with DMD do not receive optimum steroids therapy despite being the standard of care.

Pradhan and colleagues studied the levels of histone deacetylase-2 (HDAC-2) in boys with DMD receiving prednisolone at 0.75 mg/kg/d for six months and reported that high baseline HDAC-2 levels correlated with good steroid response [3]. The results of this study are interesting and relevant in elucidating the mechanism of steroid responsiveness in boys with DMD.

The variable response to steroid therapy is well known in boys with DMD. The most important predictor of disease course is the nature of the genetic defect in the dystrophin gene. The most plausible explanation is the reading frame rule, whereas the deletions causing disruption of reading frame and premature truncation of dystrophin protein are often associated with a more severe phenotype. Another predictor for steroid responsiveness is the baseline functional abilities of

the child. Six-minute walk test (6MWT), a global muscle and cardiorespiratory functions indicator, is a reliable and universally accepted outcome measure in boys with DMD. The trajectories of 6-min walk distance at baseline predict future course of the disease in boys with DMD; <350 m 6MWD is associated with rapid decline and predicts non-ambulation in next 1–2 y.

Increased HDAC-2 expression in skeletal muscles has been observed, and HDAC inhibitors are currently being explored as a novel therapeutic option for DMD. Dystrophin-deficient muscles of Mdx mouse display an aberrant, constitutive activation of HDAC-2 [4]. HDAC-2 serves as an epigenetic regulator in muscle satellite cells and fibro-adipogenic progenitors in the skeletal muscles. Down-regulation of HDAC-2 leads to enhancement in the ability of muscle satellite cells to form multinucleated myotubes. Givinostat, an HDAC inhibitor, is found to reduce fibrosis and increase muscle tissue expression in skeletal muscle biopsy of boys with DMD [5].

Pradhan et al. suggested that HDAC-2 value of >4.4 at baseline in boys with DMD can predict good steroid responsiveness [3]. Limitations in the clinical application of HDAC-2 assessment at baseline in boys with DMD are obvious, with the availability of the testing facility and increase in the cost of the care. The other interesting application of increased HDAC-2 expression in peripheral blood leucocytes in boys with DMD, as observed by Pradhan and colleagues, could serve as a surrogate marker of HDAC-2 expression in skeletal muscles.

Compliance with Ethical Standards

Conflict of Interest None.

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✉ Jitendra Kumar Sahu
jsh2003@gmail.com

¹ Pediatric Neurology Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India

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