Duchenne Muscular Dystrophy- Where Genetic Testing is Inevitable and Vital!

Ambika Gupta¹ · Madhulika Kabra¹ · Neerja Gupta¹

Received: 24 April 2020 / Accepted: 24 April 2020 / Published online: 16 May 2020
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Duchenne Muscular Dystrophy (DMD), an X-linked recessive disorder, is the most common and severe neuromuscular disorder affecting about 1 in 5000 males. The phenotype of dystrophinopathies depends on whether mutation leads to disruption of or maintenance of the “open reading frame (ORF)”, the former resulting in severe disease. The types of mutations in DMD include deletions (65%), duplications (6–10%), point mutations (25%), and complex mutations (<2%) [1]. Kohli S and colleagues have described a similar mutation spectrum of 1660 Indian DMD/ Becker muscular dystrophy (BMD) patients [2]. They identified exonic deletions and duplications in 1090 (65.7%) and 98 (5.9%) respectively. Among the 68 nondeletion/duplication cases tested, 50% had a nonsense mutation.

Use of steroids by the age of 5 y with multidisciplinary musculoskeletal care including respiratory support, scoliosis surgery; cardiac care using beta-blockers and angiotensin-converting enzyme inhibitors are the usual standard of care modalities. In the last decade, research in the field of precision medicine has led to the development of novel therapies for DMD, primarily aimed at mitigation of the underlying molecular defect. These include exon skipping and read through therapy. About 13% of DMD/BMD patients with deletions of exons 45–50, 47–50, 48–50, 50, 52, and 52–63 are likely to benefit with Exon 51 skipping therapy using Eteplirsen [3]. It restores the open reading frame and results in the production of small but functional dystrophin in these patients. Study on the longitudinal effect of Eteplirsen at 36 mo of treatment showed that patients receiving Eteplirsen showed a slower rate of decline in ambulation assessed using 6 min walk test (6MWT) compared to untreated patients [4]. Ataluren, a premature termination codon (PTC) read-through drug which is

likely to benefit 10–15% of DMD patients with non-sense variants is approved by the European Medicines Agency (EMA) [3]. Golodirsen, another exon 53 skipping drug has been recently approved by the United States Food and Drug Administration (US FDA) [5] which is likely to benefit 8% of DMD patients. Several other agents such as Casimersen for exon 45 skipping are being evaluated in clinical trials [6]. Clinical trials using Adeno associated vector (AAV) based micro-dystrophin gene replacement therapy and genome editing tools are also being conducted [3]. Kohli S et al., concluded that 647 of 1188 (54.5%) patients with deletion/duplication would benefit by skipping of any of 7 exons namely 43, 44, 45, 50, 51, 52 and 53 [2]. PTC therapy would be beneficial for 50% of patients with stop codon. Cumulatively, 681 out of 1256 (54.2%) of DMD patients are amenable to therapy, a figure similar to those reported in other studies [7] suggesting the importance of genetic testing.

It is important to remember that the efficacy of treatment is determined by the age at genetic diagnosis, presence of ambulation, and associated comorbidities (cardiomyopathy, pulmonary complications etc). There is an average delay of 2.5 y from symptom onset until definitive diagnosis [8]. Diagnostic delay, especially in the absence of family history occurs due to lack of adequate sensitization of the primary care physician, poor education, scanty resources and fear of social stigmatization among the families of those affected. Moreover, the unequivocal benefit of novel therapies in improving motor function in DMD patients' needs to be proven. Whether or not such therapies are able to target all muscle types including the cardiac muscle is yet another question [3]. To date, the biggest challenge is the exorbitant cost of these therapies that is prohibitive for most families. To combat such challenges, India needs to strengthen research and development for molecular genetic therapies for DMD using public-private partnerships.

Nevertheless, it is implicit from these futuristic therapies; mutation identification is essential in DMD patients. It also remains extremely pertinent in terms of prevention through prenatal testing in those who already have an affected family

✉ Neerja Gupta
neerja17@gmail.com

¹ Division of Genetics, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029, India

member. Where prenatal testing has been missed, younger male sibling should be offered testing as there is evidence that early treatment with a twice-weekly dosing regimen with steroids results in a measurable improvement in motor outcomes [9].

Till the time, personalized and novel genetic therapies are widely available, made affordable and have unquestionable benefit, prevention by prenatal diagnosis remains the best method to prevent the birth of affected children so that optimal care can be offered to the existing patients.

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Leigh F, Ferlini A, Biggar D, et al. Neurology care, diagnostics, and emerging therapies of the patient with duchenne muscular dystrophy. *Pediatrics*. 2018. <https://doi.org/10.1542/peds.2018-0333C>.
2. Kohli S, Saxena R, Thomas E, et al. Mutation spectrum of dystrophinopathies in India: implications for therapy. *Indian J Pediatr*. 2020. <https://doi.org/10.1007/s12098-020-03286-z>.
3. Salmaninejad A, Abarghan Y, Qomi S, et al. Common therapeutic advances for Duchenne muscular dystrophy (DMD). *Int J Neurosci*. 2020. <https://doi.org/10.1080/00207454.2020.1740218>.
4. Mendell JR, Goemans N, Lowes LP, et al. Eteplirsen Study Group and Telethon Foundation DMD Italian Network. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Ann Neurol*. 2016;79:257–71.
5. FDA grants accelerated approval to first targeted treatment for rare Duchenne muscular dystrophy mutation. Available at: <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation>. Accessed 10 April 2019.
6. Waldrop MA, Flanigan KM. Update in Duchenne and Becker muscular dystrophy. *Curr Opin Neurol*. 2019;32:722–7.
7. Bladen CL, Salgado D, Monges S, et al. The TREAT-NMD DMD global database: analysis of more than 7,000 duchenne muscular dystrophy mutations. *Hum Mutat*. 2015;36:395–402.
8. Ciafaloni E, Fox DJ, Pandya S, et al. Delayed diagnosis in duchenne muscular dystrophy: data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). *J Pediatr*. 2009;155:380–5.
9. Connolly AM, Zaidman CM, Golumbek PT, et al. MDA DMD Clinical Research Network. Twice-weekly glucocorticosteroids in infants and young boys with Duchenne muscular dystrophy. *Muscle Nerve*. 2019;59:650–7.

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