INVITED COMMENTARY

# Duchenne Muscular Dystrophy: Call to Action

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Duchenne Muscular Dystrophy (DMD) is the most common muscle disorder with onset in early childhood, characterized by progressive muscle degeneration due to dystrophin gene mutations. It is a significant public health challenge worldwide, with a prevalence of approximately 10 cases per 10,000 males. With established guidelines for multidisciplinary care [1,2] and many promising emerging therapies for this rare, albeit disabling, disorder [3], publication by Singh et al in the current issue of *Indian Pediatrics* is a timely reminder to consider the regional differences and to advocate for this devastating condition [4].

The symptoms of DMD typically start around the age of 2 years, wheelchair dependence is by age 12 and the need for assisted ventilation is around age 20. The usual lifespan is 20-40 years with death secondary to cardiac and/or respiratory failure [2]. Timely diagnosis and multidisciplinary care are the keys to limiting morbidity [2]. Glucocorticoids (prednisone or deflazacort) are usually started around age 4 or 5 years and are known to help delay or limit the decline in ambulation, pulmonary function, cardiomyopathy and scoliosis. Interestingly, the current study by Singh et al documents later onset of symptoms (60 months) for this patient population in eastern Uttar Pradesh (UP), India. This is not typical and might need some further studies in the future. Lack of public awareness might be contributory.

The paper by Singh et al highlights disparity in clinical care in resource limited settings. According to the US based Muscle Dystrophy Association, cardiac screening is recommended early with a baseline echocardiogram (before age 7 years) or MRI (after age 7 years) in all patients with DMD. However, in the population from UP, due to resource constraints, only an echocardiogram was performed (35/112 patients). With a timely diagnosis of cardiomyopathy, early use of angiotensin-converting-enzyme inhibitors (ACE inhibitors) (around age 10) can be cardioprotective [5].

Carrier testing of proband related females is important as they can be symptomatic with muscle weakness (up to 19%) and cardiomyopathy (up to 17%) [6]**.** Further, genetic counselling should be offered to all the families as a carrier female has 50% chance of having an affected son or a carrier daughter [2]. Unfortunately, it was offered to only 10 families in the study from UP, India.

The molecular profile detailed in the UP, India, analysis reveals deletions in a remarkably high percentage (95%) of participants vs the global trend of 60-70% deletions, 5-15% duplications and 20% other mutations [7]. Genetic variations specific to regional populations may provide valuable information for targeted therapies. Although the advent of next-generation sequencing has transformed our understanding of DMD, allowing for more precise genetic diagnoses and the potential for tailored therapies [8], however, this is not a universal cost-effective option. The current study highlights the value of multiplex polymerase chain reaction (mPCR) (Hot spot exons) and multiplex ligation dependent probe amplification (MLPA) as an alternative tool in these areas.

Although thousands of mutations are known in DMD, up to 50% of those (deletions and duplications only) are found in the hot spot regions at exons 45-55 and 3-9. This fact has made the advent of newer therapies that help restore functional dystrophin protein to some extent, a reality. Exon skipping with Antisense Oligonucleotides (ASOs) is now available in certain countries for exons 51, 45, 43 and 44 [3]. Study by Singh et al highlights patients that could potentially benefit from available exon skipping therapies (22/112) although cost would be a challenge. In fact, this number would be even higher (35/112) if exon 44 is included which has recently been given a rare pediatric disease status by US Food and Drug Administration (FDA). FDA has now also approved (June 2024) gene therapy "Delandistrogene-moxeparvovec-rokl" for children with DMD who are at least 4 years old. However, making these treatments available to people world over is still a distant dream.

The case-record analysis from UP provides an important perspective on DMD management in a specific

socio-cultural context, but it also serves as a reminder that our understanding of the disorder must be enriched by diverse experiences. International collaborations can lead to innovative solutions that address the needs of patients globally [9]. As gene therapies for DMD advance, it is crucial to ensure that clinical trials include diverse populations. This inclusivity will enhance the efficacy and safety of treatments and ensure equitable access to innovative therapies.

An essential aspect of improving DMD care globally is increasing awareness and advocacy. The insights gained from the current study can inform educational campaigns to raise awareness about DMD among healthcare providers and the public. Advocacy efforts should also focus on policy changes that support rare disease research and improve access to healthcare resources. In the US advocacy organizations play a vital role in funding research, supporting families, and promoting awareness. Similar initiatives in India and other countries could greatly enhance the landscape of DMD care and provide a voice for affected families.

By fostering awareness, enhancing healthcare infrastructure, and prioritizing research collaboration, we can significantly improve outcomes for DMD patients worldwide. By embracing a collective responsibility to advance knowledge, care, and treatment for DMD, we can create a more equitable future for all affected individuals and their families.

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