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Duchenne Muscular Dystrophy

Udhaya H Kotecha

Center of Medical Genetics, Sir Ganga Ram Hospital, Old Rajinder Nagar, New Delhi - 110 060

Email: druhkotecha@gmail.com

Abstract

With an incidence of 1 in 3500 affected males, Duchenne Muscular Dystrophy (DMD) is the most common muscular dystrophy and is inherited in an X-linked recessive pattern. Though this disorder has been known for two centuries, delays in its diagnosis and non-uniform practice of care exist even to date. Decades of research has led to better understanding of the pathophysiology of DMD which in turn has resulted in newer therapeutic advances. While these treatment strategies are yet to reach the clinic, they surely have placed an added responsibility on the treating physician to ensure early diagnosis and appropriate management so that maximum benefit can be ensured when these therapies are available. This review aims at bridging diagnostic gaps by describing various signs and symptoms of DMD followed by the currently utilized diagnostic approaches. Also discussed is the staged use of glucocorticoids, the need of multidisciplinary management and the current arenas which are being explored for the cure of this devastating disease.

Introduction

Duchenne muscular dystrophy is recognized as the most common muscular dystrophy with an incidence of 1 in 3500-5000 males.[1] Though still incurable, light seems to be emerging at the end of this long dark tunnel with many new therapies in the making.[2] While these treatment strategies are yet to reach the clinic, they have placed an added responsibility on the treating physician to ensure early diagnosis and appropriate management so that maximum benefit can be ensured when these therapies are available. Delayed diagnosis and inconsistent care in DMD has been reported and this review attempts to bridge these gaps by

a) Describing various clinical presentations – recognizing this will prevent delays in the diagnosis.

b) Discussing the available diagnostic methodologies and importantly their differences, limitations and utility.

c) Providing a brief outline on the management –which will enable uniform care to all thus helping improve quality of life.

d) Outlining the genetic basis, recurrence risks and prenatal diagnosis.

e) Providing an overview of the current novel approaches for treatment.

Clinical Phenotypes

A boy less than 5 years of age presenting with proximal muscle weakness and bilateral calf hypertrophy and 'who is one amongst many affected males' on the maternal side embodies the textbook description of DMD. This typical scenario is encountered only in 70% of the cases. A high index of clinical suspicion is necessary to diagnose the other atypical though not uncommon presentations which include:

a) Sporadic cases of DMD that account for one third of the patients affected with DMD and are usually recognized after onset of clinical symptoms.

b) Asymptomatic elevation of CPK that could be i) noted when investigations are performed for an unrelated reason ii) when an asymptomatic child is investigated due to a positive family history or iii) as a part of newborn screening.

c) Unexplained elevation of serum transaminases – consideration of muscular dystrophy is important as this could prevent unnecessary evaluation for liver dysfunction.

d) Impaired cognition or seizures in patients with symptoms suggestive of DMD- a particular behavior spectrum abnormality ranging from low IQ to an autism spectrum disorder and attention deficit can occur in 20% of Duchenne patients. Epilepsy is observed in 10% of cases.

e) Manifesting carrier females. While females are typically unaffected, mild proximal muscle weakness has been reported in 8-10% of cases.

Inclusive of the above scenarios, the term *dystrophinopathy* also includes the allelic milder disorder Becker Muscular Dystrophy as well as dystrophin-related cardiomyopathy.

When to suspect the disorder?

Proximal muscle weakness brings the disorder to parental notice. This is commonly evident as

- Difficulty in getting up from sitting or squatting position (patient gets up by supporting himself on his legs and thighs, a maneuver named as Gower's sign)
- Difficulty in climbing stairs
- Development of a waddling gait
- An inability to jump or hop or
- Tripping while running
- Other observations include a delay in walking, tip-toe walking, presence of muscle stiffness or cramps or prominent calf muscles.

Disease course

After its onset at 3-5 years of age, the disease follows a relentlessly progressive course culminating in wheelchair dependency by the age of 13 years. While the skeletal muscles bear the major brunt of the disorder, cardiac, respiratory and smooth muscles are also affected albeit at a later stage. Death occurs in the early teens due to respiratory failure which is accentuated by development of scoliosis.[3] The inclusion of glucocorticoids along with multidisciplinary care has gone a long way in changing this natural history and prolonging the life expectancy. Along with increments in life span, available evidence concludes that usage of steroids leads to better quality of life due to delay in wheelchair dependency, scoliosis and hypertrophic cardiomyopathy and better preservation of pulmonary function.[4]

Becker muscular dystrophy is a milder allelic version of DMD with a slower rate of progression, preserved ambulation till the second decade and survival into the fourth decade.

Investigations and diagnosis

1) *Creatine kinase levels (CK):* The first test to be performed on clinical suspicion of DMD is a serum CK level. An elevated serum CK (up to 100-200 times normal) is commonly observed in patients with DMD. Elevation is maximum in the initial stages of DMD followed by a decline later due to fibrous replacement of muscle. Also an increased CK is only present in approximately 30% of carrier females thus making it an unsuitable test for carrier detection.[5]

2) *Molecular diagnosis:* Molecular testing for confirmation is often provided as a two or three tier testing.

   a) **Detection of deletions and duplications:** Deletions in the dystrophin gene are responsible for 65-70% of the cases while duplications are seen in 5-10%. Evaluation for these is possible via multiplex-probe-dependent-amplification (MLPA). However this requires expertise to judge results and is currently available only in limited centers in India. Many laboratories offer multiplex PCR assay. This can be used for studying deletions in only the 'hot spot' regions (within exons 1-20 and 45-50) and cannot detect duplications. Hence MLPA is recommended as the second step if multiplex- PCR results are normal.

   b) **DMD Gene sequencing:** As elucidated above, MLPA results would be normal in 30% of affected individuals, thus necessitating further gene sequencing for detecting point mutations and small genomic rearrangements.[6]

3) *Muscle biopsy:* With current advances in genetic testing the need for muscle biopsy is decreasing. It has been an important practice parameter till recently and is still availed to in atypical situations and hence is briefly discussed here. It is important that the biopsy be performed at centers where facilities are available for immunohistochemistry (IHC) or immunoblotting (IB). If not, then a part of the muscle biopsy sample should be preserved in liquid nitro-

gen and shipped on dry ice. While routine histopathology will demonstrate dystrophy, it is only through IHC/IB that the type of dystrophy can be ascertained. Thus IHC/ IB are central to the diagnosis and need to be performed on every patient undergoing biopsy.[7] Being invasive, it is now reserved for only those cases that do not show a mutation in dystrophin or the pathogenicity of a mutation is not proven. This test helps in differentiating several other dystrophies.

The need for molecular diagnosis is often questioned. The utility is multifold including i) definitive management - allows confident discussion for use of corticosteroids in the treatment ii) carrier detection iii) prenatal testing iv) genotype-phenotype correlation v) application of newer treatment strategies like exon skipping and nonsense mutation read-through.

Management

There are two intertwined branches of dystrophinopathy management: Pharmacological management and Multidisciplinary care.

- Pharmacological management: Corticosteroids are currently the only class of drugs with proven clinical benefit. Both prednisolone/prednisone and deflazacort have been used with equal success, the former being used in nations where deflazacort is not available. While the adverse effect profiles are essentially similar, weight gain is more common with prednisolone/prednisone while cataracts occur more frequently with deflazacort. Both medications have been tested at different doses and the recommended initiating dose for ambulatory patients is 0.75 mg/kg for prednisone and 0.9 mg/kg for deflazacort.

The next pertinent issue is when to start pharmacological management – to make decision making easier, motor performance has been divided into three stages: making progress, plateau and decline. The commonest practice is to wait for the 'plateau phase' usually around 4-6 years of age when the child has stopped making any progress but not yet started to fall downhill. Parental observations, routine follow up visits and timed performance tests help recognition of this stage which in some cases is very short lasting. With loss of ambulation the dose of steroids needs to be scaled down. If however a patient presents for the first time in the non-ambulatory stage, it is still worthwhile considering glucorticoids so as to reduce the need of scoliosis surgery and preserving pulmonary function. An updated immunization schedule with special emphasis on varicella vaccine is essential before starting steroids. Principles for investigating adverse events are similar to other diseases where long term steroids are utilized.[8]

- Multidisciplinary care: Though disease progression is curtailed with steroids, it cannot be avoided and a careful modus operandi to discern involvement of other organ systems should be in place. The cardiac and respiratory muscles are the two major systems whose involvement is fatal and screening via ECG, echocardiography and pulmonary function tests should begin after 6-8 years of age. Similarly wheel chair dependency accelerates development of scoliosis which increases pulmonary burden and careful management for the same is important. A close association with experts in above fields will allow for comprehensive patient care. In addition to physical limitations, the disorder has a major psychosocial impact on the patient as well as the entire family – constant encouragement, discussing options to keep the child as independent as possible (includes rearrangements at home, wheelchair options, splints and orthosis, home tutoring, use of electronic devices) and interaction with other parents faced with the similar challenge play a major role in coping with the disorder.[9]

Genetic Counseling

The entire dystrophinopathy spectrum is an X linked recessive condition. This translates into males being preferentially affected, with females being carriers in a majority. In 1/3 cases there is no family history and the mother tests negative for the mutation detected in her affected son-implying that either it is due to a de novo mutation or germline mosaicism. The risk of recurrence varies according to the maternal carrier status. In obligate cases the risk of recurrence is 50% if the fetus is male. In sporadic cases even in the absence of a detectable genetic mutation in the mother, there exists a 8-20% recurrence risk due to germline mosaicism. Daughters have a 50% risk of being a carrier and the most sensitive method of detection is investigation for the mutation present in her family.

Prenatal diagnosis is possible in families where

mutations are known through chorionic villous sampling from 10 weeks onwards. In cases where genetic testing in the proband is pending, one can resort to linkage analysis provided the pedigree is informative and at least two affected members are available, Linkage involves detection of the high risk chromosome using Short Tandem Repeat markers and carries with itself a 5% risk of recombination which may lead to diagnostic errors.[10]

Newer drugs and emerging therapies

Research targeting various aspects of Duchenne muscular dystrophy is being explored and many compounds are currently in phase I or II clinical trials.[11] Current therapies in the pipeline include:

a) Inducing dystrophin expression – either through exon skipping using anti sense oligonucleotides, read through of stop codons, introducing a functional dystrophin molecule employing viral vectors or by upregulating utrophin expression.

b) Muscle regeneration and replacement- myoblast transfer, mesangioblast transfer and stem cell transfer are all probable modalities to achieve this. Besides this, pharmacological agents which can help muscle regeneration are also being explored and include myostatin inhibitors and IGF-1.

c) Modulation of signaling pathways- Modification of nitric oxide signaling pathways to augment its effect has shown to be beneficial in improving cardiac and skeletal performance in mouse models.

d) Inhibiting fibrosis- Fibrosed muscle signifies irreversible destruction and prevents transfer of effective therapy- hence inhibiting the same is an attractive and advantageous idea and is plausible through myostatin and transforming growth factor inhibition.[12]

Conclusion

Utilizing the above outlined diagnostic methodologies it is possible to detect cases of DMD earlier, thus making it possible to institute early management, detect carrier females and provide prenatal diagnosis. Ensuring uniform care with optimum usage of steroids and multidisciplinary care will contribute to improving the quality of life in affected patients.

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