Duchenne Muscular Dystrophy

What is Duchenne muscular dystrophy?

Duchenne muscular dystrophy (DMD) is a genetic disorder which affects the muscles. It usually affects male children, but rarely female children may also be affected.

What are the symptoms of DMD?

The symptoms of DMD appear in early childhood, usually by 3 to 5 years of age, in the form of thigh muscle weakness, difficulty in getting up from sitting and squatting position, and difficulty in climbing stairs. Some affected children may have delayed milestones right from infancy such as delayed standing and walking. As the child grows older, the muscle weakness progresses, with gradually increasing difficulty in walking. Majority of the children lose their ability to stand or walk even with support and become wheelchair-dependent by the second decade.

How does DMD occur?

DMD results from a mutation (genetic defect) in the *DMD* gene which is present on the X-chromosome. The *DMD* gene is required for synthesis of a protein called dystrophin, which is important for normal muscle structure and function. Patients with the disease have an error in the *DMD* gene which leads to lack or deficiency of dystrophin in the body. This results in abnormal structure and breakdown of muscles.

Some patients with an error in the *DMD* gene have a less severe form of the disease called Becker muscular dystrophy, which has a slower progression compared to DMD.

How is DMD inherited?

DMD is inherited in an X-linked recessive manner, wherein a mother who is a carrier for the mutation (but usually unaffected) can pass on the mutation to her male child who develops the disease. About two-thirds of DMD patients inherit the mutation from a carrier mother, but in around one-thirds, the mutation may occur for the first time in the child (de novo).

How do we diagnose DMD?

Serum levels of creatine phosphokinase (CPK) are very high (more than 10 times above normal levels) in children with DMD. The diagnosis is confirmed by DNA testing of the blood sample, which identifies the error in the *DMD* gene.

What are the treatments available for DMD?

Management of children with DMD involves care by a multidisciplinary team consisting of a pediatric neurologist, clinical geneticist, cardiologist, and physiotherapist. Supportive care is given to all patients. Steroid therapy has some benefit. Some specific treatments have been recently approved for use in patients with DMD.

Supportive care:

- regular physiotherapy to prevent joint stiffness;
- orthotic support for spine deformity;
- vaccination against bacterial pneumonia and influenza to reduce the risk of lung infections;
- chest physiotherapy to improve lung functions;
- vitamin D and calcium supplements; and
- use of medications (such as angiotensin-converting enzyme (ACE) inhibitors or beta blockers) to support the heart when heart muscle weakness sets in.

Steroid therapy:

- Steroids such as prednisone or deflazacort are given to patients to delay the progression of the disease.
- They are usually started after 5 years of age and may be given till the child becomes wheelchair-dependent.
- Steroids may help to slow down the progression of the disease symptoms. They may help to prolong the patient's ability to walk by up to 2 to 3 years.
- Long term use with steroids is reported to cause side effects such as weight gain, cataract, behaviour changes, and increased risk of fractures.

DMD-specific therapies:

The following medications have been approved for use in patients with DMD and are available commercially. These are 'mutation-specific therapies' i.e., each of these are applicable for patients with specific types of errors in the *DMD* gene and not for all patients with DMD. Some studies have suggested use of steroids for at least 6 months prior to starting exon skipping therapy.

Name of the therapy	How does the therapy work	How is the treatment given
Eteplirsen (Exondys 51; Sarepta Therapeutics)	Exon 51-skipping therapy: bypasses and excludes the portion of the gene which	Once-a-week intravenous infusion, lifelong

	has the error, which helps to produce a shorter but functional form of the dystrophin protein	
Golodirsen (Vyondys 53; Sarepta Therapeutics)	Exon 53 -skipping therapy	Once-a-week intravenous infusion, lifelong
Viltolarsen (Viltepso; NS Pharma Inc., Nippon Shinyaku Co.)	Exon 53 -skipping therapy	Once-a-week intravenous infusion, lifelong
Casimersen (Amondys 45; Sarepta Therapeutics)	Exon 45-skipping therapy	Once-a-week intravenous infusion, lifelong
Ataluren (Translarna; PTC Therapeutics)	Stop–codon readthrough therapy: bypasses the gene defect and helps to produce functional form of the dystrophin protein	Daily oral doses (three doses per day); lifelong

What is the cost of therapy for DMD?

Based on the current price of these drugs and depending on the weight of the patient, the cost of treatment with the newer disease-specific therapies listed above, can range from around rupees 5 to 10 crores per year. There would be additional costs related to the supportive care and steroid therapy required for these patients.

What is the expected outcome in untreated patients with DMD?

Patients with DMD usually lose their ability to walk and become wheelchair-dependent by the beginning of the second decade of life. By the time they reach their teen years, the physical disability worsens, and heart muscle weakness and breathing problems develop. Due to life threatening complications related to the heart and the lungs, most affected patients do not survive beyond the second decade or early third decade.

What are the benefits of therapy in patients treated with new disease-specific treatments?

Data from clinical trials of the new disease-specific drugs suggest that they are safe and that they increase the dystrophin level in muscles. Some studies have suggested delay in progression of muscle weakness, and stabilization of lung

functions and cardiac functions of DMD patients treated with these drugs. Long term results in terms of definite benefits of these medications are awaited.

How can DMD be prevented?

Families having affected children are encouraged to consult a clinical geneticist for genetic counselling and prevention of recurrence in future pregnancies.

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