

Muscular Dystrophy – A Review

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Abstract :**Aim:**

To review on muscular dystrophy affecting an individual.

Objective:

To study all the features related to muscular dystrophy and providing a conclusion on its effects to the muscle tissues.

Background:

Muscular dystrophy (MD) is a condition caused by genetic mutations leading to defects in the synthesis of muscle proteins required in the formation and maintenance of healthy muscles. It is characterized by the weakening of muscle tissues, which hinder bodily movements and may involve the breakdown of nerve tissues. Generally, there are nine types of muscular dystrophy, each related to the reduction in strength, difficulty in movements and potential distortion. Duchenne muscular dystrophy (DMD) is the most common in India compared to the others such as Becker muscular dystrophy. In 1997, about 22,000 cases related to DMD were reported and more than 2500 cases are added every year. The overall conservative estimation of MD is 29 per 100,000 population (0.029%).

Reason:

The present study targets on the true facts of muscular dystrophy, along with the effects of genetic mutations and gene therapy on the disease.

Keywords: Weakness, muscles, gene

INTRODUCTION

Muscular dystrophy (MD) is a condition caused by genetic mutations leading to defects in the synthesis of muscle proteins required in the formation and maintenance of healthy muscles. It is characterized by the weakening of muscle tissues, which hinder bodily movements and may involve the breakdown of nerve tissues. Generally, there are nine types of muscular dystrophy, each related to the reduction in strength, difficulty in movements and potential distortion. Duchenne muscular dystrophy (DMD) is the most common in India compared to the others such as Becker muscular dystrophy. In 1997, about 22000 cases related to DMD were reported and more than 2500 cases are added every year.

Muscle dystrophy (MD) refers to a condition in which a group of non-inflammatory and progressive muscle disorders are inherited without the presence of an abnormal central or peripheral nerve. MD causes defect to the muscles with specific fiber degeneration without undergoing morphological changes. MD results in a progressive weakness of the muscles responsible for movement and loss of muscle mass. Muscle dystrophy occurs due to the disruption in protein synthesis required for the formation of healthy muscles. This is due to the presence of abnormal genes caused by mutations.

The genetic basis of all types of MD is the defects in the genetic code for dystrophin, which was discovered through the advancement of molecular biology techniques. Dystrophin is a 427-kd skeletal muscle protein (Dp427) that can be found in cardiac smooth muscles and in the brain, which contributes to a slight mental retardation resulting from the disorder.^[1] Defects to dystrophin may lead to a wide range of problems related to MD such as muscle weakness, musculoskeletal injuries and pseudohypertrophy.

All types of MD have a common characteristics of developing muscle weakness, which normally takes place from the proximal part to distal part of the body and in certain cases of rare distal myopathies, muscle weakness occurs mainly in the distal portion. The progressive muscle weakness may affect an individual's ambulation ability and cardiopulmonary function. Patients who are diagnosed with MD usually have poor postures due to the developing muscle weakness and disproportion of the body, leading to soft tissue contractures and spinal abnormality. For example, Equinovarus contracture involves the shrinking and hardening of muscles, tendons or other tissues, which results in the abnormality and rigidity of joints and decrease in flexibility. MD patients with wheelchair dependence are at a higher risk of developing severe contractures and scoliosis. Normally, the force of vital capacity (FVC) decreases by 4% for each 10° of thoracic scoliosis curvature.^[2]

Hoffman and his colleagues reported the Xp21 region as the locus of defect with about 2 million base pairs.^[2] Dystrophin is present in skeletal, smooth and cardiac muscles, along with the brain. Alterations in the gene may be due to its large size, which makes it easier for spontaneous mutations and defects in protein synthesis to take place at various parts of the gene. The translation reading frame and promoter sequence in the synthesis of dystrophin may be affected in cases of Duchenne MD, leading to irregular and ineffective proteins. Defects present during translation process as seen in Becker MD may result in the synthesis of proteins with lower molecular weight, making them less efficient.

Emery-Dreifuss MD refers to a sex-linked disorder characterized by the localization of defect in the long arm of X chromosome at the q28 locus.^[3] Limb-girdle MD, facioscapulohumeral MD and distal MD occur with the defects localized at 13q12 locus, 4q35 locus and 2q12-14 locus respectively.^[4]

HISTORY

Muscular dystrophy (MD) was first reported in 1836 by Conte and Gioja.^[5] In the study, two brothers were observed with developing weakness starting from the age of 10 years old. Later, the two boys were diagnosed with generalized weakness and multiple muscle hypertrophy, which are the characteristics of Becker MD. However, the study was not acknowledged since many thought that it was a study on tuberculosis.

In 1852, Meryon did a study by examining four brothers at necropsy or autopsy.^[6] The result indicated that each of the four boys developed muscle changes with no significant abnormality in the central nervous system. The report was written as a comprehensive monograph on MD including suggestions on sarcolemmal defect being the source of the disorder and how it is genetically transmitted through females but only males are affected.

In 1868, a study was done by a French neurologist named Guillaume Duchenne, who was well known for faradism, which is the stimulation of muscles and nerves by electric current in treating patients with neurologic disorders.^[7] The study involved 13 patients with the same disorder, which he called as "paralysie musculaire pseudo-hypertrophique". Duchenne muscular dystrophy was derived from his name due to his contributions in the study of muscle diseases.

MECHANISM OF ACTION

The complex interaction between muscle membrane and extracellular environment requires the presence of multiple proteins. Dystrophin and dystrophin-associated glycoproteins (DAGs) are required to maintain sarcolemmal stability. The dystrophin gene, which codes for large proteins such as Dp427 can be found on the short arm of chromosome X close to the p21 locus and it contains 3685 amino acids. Dystrophin contributes to about 0.002% but it has significant effects on maintaining the integrity of muscle membrane.^[2] Aggregation of dystrophin leads to the formation of homotetramer at the costomeres in skeletal muscles. It is associated with actin at N-terminus and DAG complex at the C-terminus to form a stable complex, which undergoes interaction with laminin in the extracellular environment.

Dystrophin deficiency in patients of Duchenne MD may cause cellular irregularity at the links, along with developing leakage of intracellular elements which leads to an increased level of creatine phosphokinase (CPK) in blood. Patients of Becker MD have less-active form of dystrophin, which can still act as a sarcolemmal anchor but less efficient as they allow the leakage of intracellular components. Both Duchenne and Becker MD involve the death of muscle-cell unit, allowing macrophages to invade. The muscles of MD patients have a higher susceptibility to T-cell mediated infections due to the presence of class I human leukocyte antigens on the muscle membrane. Fibrofatty infiltrate are then present as muscle pseudohypertrophy to replace the dead muscle shell, resulting in muscle weakness and contractures due to the lack of functioning muscle units.

Other types of MD such as facioscapulohumeral are normally caused by variation in coding a DAG complex

protein. The gene loci for each DAG complex protein is located outside the X chromosomes and defects to the gene may cause changes in cellular permeability. Other effects may be seen in certain types of MD such as ocular and limb-girdle form depending on the mechanism of action and position of gene products in the body.

TYPES OF MUSCULAR DYSTROPHY

The major source of MD is a defect in the genetic code for specific muscle proteins.^[8] Different types of MD are classified based on the clinical phenotype, pathology and mode of inheritance. According to its inheritance pattern, MDs can be classified into sex-linked MDs, autosomal dominant MDs and autosomal recessive MDs. Each class of MD can be further divided into certain disorders, which are characterized by their clinical presentation and pathology.

Classifications of heritable MD:

- 1) Sex-linked MDs
 - Duchenne muscle dystrophy
 - Becker muscle dystrophy
 - Emery-Dreifuss muscle dystrophy
- 2) Autosomal Dominant MDs
 - Facioscapulohumeral muscle dystrophy
 - Distal muscle dystrophy
 - Ocular muscle dystrophy
 - Oculopharyngeal muscle dystrophy
- 3) Autosomal Recessive MDs
 - Limb-girdle muscle dystrophy

MAJOR TYPES OF MUSCULAR DYSTROPHY^[9]

1) Myotonic or Steinert's disease (MMD)

Myotonic MD (MMD) normally occurs mainly in adults. The term "myotonic" refers to its common symptom called myotonia, which is a prolonged spasm or hardening of muscles after an activity. MMD may affect various parts of the body, which include the central nervous system, gastrointestinal tract, heart, eyes and glands.

2) Duchenne Muscular Dystrophy (DMD)

Duchenne MD (DMD) is present mainly in children and affects only males. It usually begins at the age of 2 to 6 years old. In DMD, the muscles gradually decrease in size and become weaker. DMD patients normally require the use of wheelchair at a young age as the arms, legs and spine become gradually distorted. The condition progresses by affecting the heart and respiratory system of the patients, resulting in severe breathing and heart diseases.

3) Becker Muscular Dystrophy (BMD)

Becker MD (BMD) occurs only in males. It normally begins around the age of 2 or 16 and may appear as late as the age of 25. BMD shows similar symptoms as those of Duchenne MD but occur at a slower rate and less severe compared to DMD. The disease may lead to certain heart problems.

4) Limb-girdle Muscular Dystrophy

Limb-girdle MD mainly appears in teenagers up to early adulthood, for both males and females. Limb-girdle MD begins by affecting the hips and continues to the shoulders, arms and legs. As the disease progresses, movements such as walking become difficult.

5) Facioscapulohumeral Muscular Dystrophy

The term “facioscapulohumeral” refers to the muscles responsible for the movement of face, shoulder blade and upper arm. It begins in teens to early adulthood, for both males and females. It develops at a slow rate, along with progressive muscle weakness. Simple actions such as chewing, swallowing, speaking and walking become difficult for the patients. Compared to other types of MD, individuals with facioscapulohumeral MD are still capable of walking on daily basis and have average life span.

6) Congenital Muscular Dystrophy

The term “congenital” refers to the condition that occurs at birth. The condition is present in both males and females. Congenital MD can be further divided into 2 types, Fukuyama and congenital MD with myosin deficiency. Fukuyama congenital MD causes defects in the brain, while congenital MD caused by myosin deficiency leads to muscle weakness and reduction in muscle size, causing joint problems that may begin at birth or in the early months of life.

7) Oculopharyngeal Muscular Dystrophy

The term “oculopharyngeal” refers to the eyes and throat. It occurs in both men and women (40 and above). Oculopharyngeal MD develops at a slow rate and causes muscle weakness in the eye and face, which makes it difficult for the patient to swallow. Choking and repeated pneumonia are common. It may also affect the pelvic and shoulder muscles.

8) Distal Muscular Dystrophy

Distal MD leads to weakness in distal muscles of hands, forearms, lower legs and feet, which are situated away from the centre. The condition is less severe with a slow rate of proliferation as fewer muscles are affected by it compared to other types of muscular dystrophy.

9) Emery – Dreifuss Muscular Dystrophy

Emery – Dreifuss MD affects on males and normally begins from childhood to early teens. It may result in muscle weakness in the shoulders, upper arms and lower legs. Shrinking of muscles normally begins during the early stages of Emery – Dreifuss MD. Weakness of muscles may affect the chest and pelvic regions. Emery – Dreifus MD develops at a slow rate and its effects on muscle weakness are less severe compared to other types of muscular dystrophy. Severe heart problems are common in individuals with Emery – Dreifuss MD.

SYMPTOMS

Muscular dystrophy is normally associated with progressive muscle weakness. Different types of muscular dystrophy show specific signs and symptoms depending on the age and muscle groups.

1) Duchenne muscular dystrophy

- ✓ Muscle pain
- ✓ Difficulty in running and jumping
- ✓ Waddling gait
- ✓ Learning difficulty
- ✓ Enlarged calf muscles
- ✓ Inability to walk properly such as walking on toes
- ✓ Frequent falls

2) Becker muscular dystrophy

Becker MD possess similar signs and symptoms to those of Duchenne MD but occur at a slower rate and less severe.

TREATMENT

The specific treatment for MD has yet to be found despite the current advances in gene therapy and molecular biology. Certain treatments such as medications, surgery and physical therapy help in the movements of MD patients by overcoming the problems related to the joints and spine. MD patients are normally provided with proper care and attention to ensure a better living. The disorder may lead to death if not treated properly due to cardiopulmonary failure. In terms of medications, MD patients are normally prescribed with corticosteroids such as prednisone and heart medications such as angiotensin-converting enzyme (ACE) inhibitors or beta blockers if the heart is affected. Prednisone helps to enhance muscle strength and slows down the development of muscular dystrophy but it needs to be taken under control as over consumption of prednisone may lead to weight gain and bone fractures. MD therapy includes a wide range of activities and assistive devices to help MD patients in their daily lives. This include range-of-motion and stretching exercises, regular exercises such as walking and swimming, breathing assistance such as ventilator and sleep apnea device, braces and mobility aids such as walkers and wheelchairs. Surgery may be required for correcting spinal curvature that can cause difficulty in breathing.

Advantages of MD Therapy

- 1) Range-of-motion and stretching exercises – maintain flexibility and mobility of patients.
- 2) Regular exercises – provide strength and maintain mobility and good health.
- 3) Braces – support the weakened muscles.
- 4) Mobility aids – maintain mobility and provide independence.
- 5) Breathing assistance –provide adequate oxygen during the night as the respiratory muscles are weakened.

COMPLICATIONS

Muscular dystrophy (MD) patients with minor musculoskeletal injuries or disabled patients may experience early wheelchair dependence. Other complications include a high tendency of non-ambulatory state or incapable of walking without the help of a device such as walker in patients who undergo prolonged immobilization.

DIAGNOSIS

Muscular dystrophy (MD) can be diagnosed by conducting a test on creatine phosphokinase (CPK) levels. Increase in the level of CPK during the active phase of the disease indicates muscle diseases, in which enzymes are discharged from the muscle cells. CPK levels of MD patients increase about 50 to 300 times more than the normal levels. However, the values decrease as the muscle mass decreases. CPK levels increase to the highest point in Duchenne MD patients while the least can be seen in patients with Becker MD.

Multiplex polymerase chain reaction (PCR) assay can also be used to test for MD. PCR test was first introduced by Chamberlain et al.,^[10] and it helps to detect the deletions of dystrophin gene at exons 3-30 and exons 44-55, which are called as the hot-spot regions.^[11] Screening of deletion of dystrophin gene is done by increasing DNA in the hot spot regions or by subsequently using primers to enclose the hot-spot regions.

Screening of MD patients is normally done by ultrasonography, in which it shows the increase in echogenicity in the muscles and reduces the underlying bone echo. Ultrasonography is mainly preferred due to its advantages, which include non-invasiveness and ability to provide a continued observation on the disease for a period of time.

Electrocardiography (ECG) can be used to test for MD. The results are normally demonstrated as a right ventricular strain, deep Q waves, tall R waves and inverted T waves. The patients should be referred to a cardiologist as cardiac management may be required for post-operative care. Pulmonary function test (PFTs) is also a test for MD, in which it includes an evaluation of arterial blood gases and hematologic workup. A pulmonologist needs to be present in order to maintain the patient's airway during the post-operative stage.

Muscle biopsy had been used as a definitive test for diagnosis and confirmation of muscular disease before the advent of molecular biology techniques. Histologic changes are affected by the stage of disease and the selected muscle. Muscle biopsy is normally done at the vastus lateralis through a small lateral thigh incision.

HISTOLOGIC SPECIMENS

Histologic specimens obtained from muscle biopsy of MD patients indicate differences in the sizes of muscle fibers with focal areas of degenerating and regenerating fibers during the early stages of MD. As the patients enter the later stages of MD, significant changes can be observed, in which the variations in muscle fiber sizes are more prominent. In addition, rounded opaque fibres, internal nuclei, separation of fibers and proliferation of connective and adipose tissues can be seen. In the final stage of MD, the muscles are replaced by adipose tissue, along with residual islets of muscle fibers in fat. Histochemical staining of the muscle fibers can be done by adenosine triphosphatase (ATPase) reaction, which displays a large amount of type I muscle fibers without its distinctive features. Other techniques that can be used include electron microscopy that shows the non-specific degeneration of muscle fibers and immunocytochemical technique, which displays fetal persistency and slow myosin in most of the muscle fibers.

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