International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 04, 2020
ISSN: 1475-7192

Muscular Dystrophy – Review

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Abstract--- *Muscular dystrophy is a group of genetic disorders that result in progressive loss of muscle mass and weakness. This condition results from mutation in dystrophin gene that results in synthesis of abnormal dystrophin protein leading to formation of damaged muscles. Duchenne muscular dystrophy is the most common form of Muscular Dystrophy. Most people end up in wheelchair as the muscles become weaker progressively. At present there is no treatment for this inherited diseased condition. Medications available are generally prescribed to give symptomatic relief. However, with the advancement in technology, scientists all over the world are researching for a therapy that might help people suffering from this disease by either reversing the disease or completely curing it. Of the approaches available, exon skipping, stem cell transplant are some of the areas that are being explored. This article gives a brief about the condition of muscular dystrophy, its types, causes, treatment and research area along with clinical trials that are being run for the condition.*

Keywords--- *Muscular Dystrophy, Duchenne Muscular Dystrophy, Exondys 51.*

I. INTRODUCTION

It is a group of over 30 conditions that are characterized by muscle weakness and loss of muscle mass. As the condition progresses, it becomes difficult to move. In some cases, it can affect breathing and cardiac functions, which lead to life-threatening complications.

Based on the type and severity, the effects are classified into

- Mild
- Gradual progression
- Moderate disability, and
- Fatal

There is no prophylaxis for muscular dystrophy. However, available treatment methods can be used to control disease progression and help to improve overall quality of life [1].

Symptoms

Most common symptoms are listed below (These symptoms are associated with Duchenne type, the most common form of muscular dystrophy)

Early Symptoms Include

- A waddling gait
- Stiff and painful muscles
- Trouble running and jumping
- Walking on the toes

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DOI: 10.37200/IJPR/V24I4/PR2020464
Received: 12 Mar 2020 | Revised: 25 Mar 2020 | Accepted: 10 Apr 2020

- Difficulty in sitting up or standing
- Learning disabilities, such as developing speech later than usual
- Frequent falls

As time goes on, the following become more likely:

- Trouble walking
- Restricted movement due to shortening of muscles and tendons
- Difficulty in breathing can become so severe that assisted breathing is necessary
- Curvature of the spine.
- Cardiac disorders due to weakening of myocardium.
- Trouble swallowing, which may lead to aspiration pneumonia. A feeding tube is sometimes necessary.(Fig. 1 and Fig. 2)

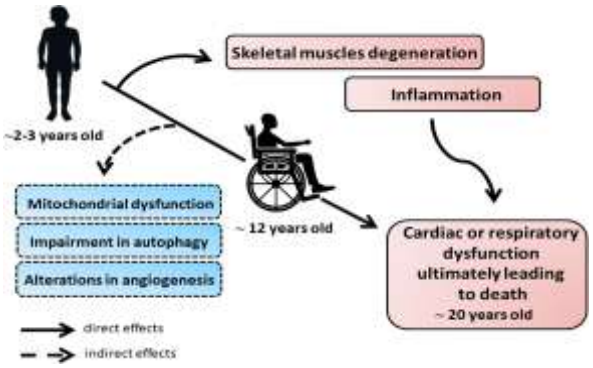

Figure 1: Symptoms of Duchenne Muscular Dystrophy

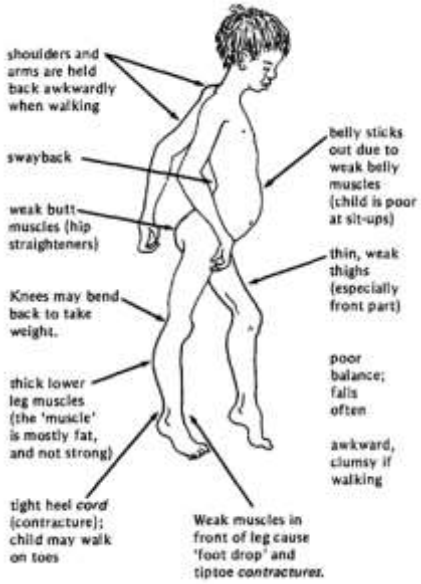

Figure 2: Pictorial Representation of MD Symptoms

DOI: 10.37200/IJPR/V24I4/PR2020464
Received: 12 Mar 2020 | Revised: 25 Mar 2020 | Accepted: 10 Apr 2020

II. TYPES OF MUSCULAR DYSTROPHY

Different types of muscular dystrophy include (Alan E H Emery et al):

- ***Duchenne Muscular Dystrophy (DMD):*** This is the most common type. Symptoms usually occur by the age of 3 and by the age of 12, children are generally wheelchair-bound. Death usually occurs due to respiratory failure by their early-to-mid-twenties [2].
- ***Becker Muscular Dystrophy:*** Similar symptoms to DMD but with a later onset and slower progression; death usually occurs in the mid-forties [2].
- ***Myotonic (Steinert's Disease):*** Most common in adults, this type is characterized by an inability to relax a muscle once it has contracted. Facial and neck muscles are the initial targets. Symptoms also include cataracts, sleepiness, and arrhythmia.
- ***Congenital:*** This occurs from birth or by the age of 2 years. It occurs in both the genders. Some forms progress slowly whereas others can move swiftly and cause significant impairment.
- ***Facioscapulohumeral (FSHD):*** Symptoms can occur almost in any age group but is mostly seen in the teens. It begins with weakening of facial and shoulder muscles. People with FSHD, when they raise their arms, their shoulder blades are protruded like wings. Affected individuals may sleep with their eyes slightly open and have trouble fully closing their eyelids.
- ***Limb-Girdle:*** This variant begins in childhood or teenage years and first effects the shoulder and hip muscles. Individuals with the limb-girdle muscular dystrophy might have trouble raising the front part of the foot, making tripping a common problem.
- ***Oculopharyngeal Muscular Dystrophy:*** Symptoms occur between 40 to 70 years of age. Prior to shoulder and pelvis, this form initially affects the muscles of eyelids, throat, and face.

Causes of Muscular Dystrophy

Dystrophin is a part of a large protein complex that is useful in muscle building and repair. This is primarily located in skeletal and cardiac muscles. It acts as a connection between centre of the muscle cell to the cell membrane (sarcolemma). Complete or partial absence of dystrophin alters this process and causes disruptions in the outer membrane. This eventually leads to muscle weakens and can also actively damage the myocytes.

In muscular dystrophy, a mutation on the short arm of X-chromosome prevents the body from making enough dystrophin for normal functioning of the muscles.

When mutations occur in dystrophin gene, due to which it fails to make dystrophin protein, it causes DMD. A different mutation in the same gene, does not prevent the production of dystrophin, but the produced protein is compromised in either quantity of quality. This causes Becker muscular dystrophy.

DMD is caused by specific mutations in the gene that encodes dystrophin. The percentage of dystrophin in total proteins in striated muscle is just 0.002 percent, however, it is necessary protein for the general functioning of muscles [3].

DOI: 10.37200/IJPR/V24I4/PR2020464
Received: 12 Mar 2020 | Revised: 25 Mar 2020 | Accepted: 10 Apr 2020

General Aspects of Muscular Dystrophies

MD is a collective group of primary inherited myopathies which have a chronic and continuous progressive course. The term dystrophy means "deficient nutrition". It was popularized by the end of the nineteenth century, when the pathogenesis of MD was mysterious. The recent advances in molecular genetics made us understand the pathogenesis of some of these conditions. We now know that all types of MDs are genetic. While some forms are inherited, others are previously unknown mutations. These mutations are commonly found in genes encoding proteins of the dystrophin- associated glycoprotein (DAG) complex at the outer membrane of the muscle cell (sarcolemma). The mutations finally cause either partial of complete absence of DAG complex. These structural proteins are responsible in forming a support network which connects inner myofilament proteins to the outer sarcolemma. Without DAG complex, forces generated by myofibers lead to tears of the sarcolemma and finally result in muscle damage. The regenerative ability in muscle cannot balance the increased susceptibility for structural damage. Moreover, a dystrophic muscle cannot sufficiently repair itself from the damage. This imbalance between muscle damage and muscle repair causes loss of myofibers which in turn increases the level of fibrosis. This occurs until the operative capacity of the muscle reduces to a point below the required force output. MD is caused not only by the abnormality of sarcolemma proteins, but also caused by the abnormalities in the proteins of nuclear envelope or their post-translational glycosylation [4]

Diagnosis of Muscular Dystrophy

Various methods used to diagnose muscular dystrophy include [5]

- ***Enzyme Assay:*** The level of the creatine kinase (CK) enzymes rises when there is a damage to muscle cells in the body. Enzyme assays are used to measure elevated CK levels.
- ***Genetic Testing:*** As genetic mutations are the known cause of muscular dystrophy, genetic testing checks for any mutations that would prevent the production of dystrophin.
- ***Heart Monitoring:*** Mainly useful in the diagnosis of myotonic muscular dystrophy. Techniques like electrocardiography and echocardiography can detect changes in the myocardium.
- ***Lung Monitoring:*** Checking lung function can give additional evidence.
- ***Electromyography:*** A diagnostic procedure used to evaluate the health condition of the muscles by measuring the electrical activity.
- ***Biopsy:*** Muscle sample is taken from the body and is analysed under microscope.

Treatment of Muscular Dystrophy

At present, no cure exists for muscular dystrophy; but there are treatments that can slow the disease progression thus maintaining the mobility of the person for maximum possible time. The treatments are aimed to manage different problems arising from MD resulting in an improvement in quality of life of the diseased person. Treatment of MD are aimed for prevention of complications resulting from [6].

Within different types of MDs, distinction is sorted by the difference in age of onset, severity, modes of inheritance and clinical course. A clear knowledge of disease profile is helpful in differential diagnosis of MDs. In

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general, the initial onset of symptoms is presented during childhood or young adulthood; however, neonatal or late adult onset cases are not uncommon. Early onset is the main characteristic of many MDs and this must be considered for differentiating them with infantile denervation, metabolic or mitochondrial diseases. The primary symptom is muscular weakness that progresses steadily and unremittingly, however, the severity is different. Each MD affects a particular set of skeletal muscles, suggesting that biological differences exist between individual muscles that predispose them to specific pathological aetiologies. For instance, limb girdle muscular dystrophy (LGMD) is an umbrella name given for a set of diseases that show proximal weakness of the shoulder and pelvic girdles [7]. Similarly, facioscapulohumeral dystrophy (FSHD) symptoms show progressive weakness of facial muscles, along with muscles of shoulder and upper arms. Specific symptoms such as myotonia, dysphagia or ptosis may be useful for a specific diagnosis.

Drug Therapy of Muscular Dystrophy

Following classes of the drugs prescribed in MD can either slow the progression disease or help in management of the symptoms arising from MD [8].

- ***Corticosteroids:*** there are reports wherein treatment by glucocorticoids like prednisone has shown to enhance strength and ability of the muscle in addition to respiratory function; thus, reducing the weakness progression. However this treatment is accompanied by side effects like weight gain, brittle bones, increase in blood pressure and cataract formation on long term use.
- ***Anticonvulsants:*** These drugs help to control muscle spasms and seizures. Phenytoin has been used in MMD for management of delayed relaxation of muscles.
- ***Immunosuppresants:*** generally prescribed to for treatment of autoimmune disorders, this class might help to prolong the damage to the muscle cells that are in dying stage.
- ***Antibiotics:*** For treatment of respiratory infections.
- ***Heart Medications:*** Beta blockers and angiotensin-converting enzyme (ACE) inhibitors can be used if the condition effects heart.
- ***Physical Therapy:*** A variety of stretching and motion can aid in battling of unavoidable inward limbs movement on shortening of muscles and tendons. This helps in keeping the limbs mobile for prolonged duration. Such exercises include standard low-impact aerobic exercises like walking and swimming.
- ***Respiratory Therapy:*** MD results in weakening of muscles that aid in respiratory function; in such cases devices that aid in enhancement of oxygen delivery throughout the night might help. In severe cases, a ventilator s used for breathing.
- ***Physical Aids:*** Shortening of muscles and tendons can be slowed down by use of braces that in addition can also provide support while moving. Other aids are wheel chair or crutches.
- Occupational therapy helps one to maximise or enhance his/her independence by use of different techniques like using assistive devices like utensils and wheelchairs; thus helping them relearn their abilities and movement.

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- ***Speech Therapy:*** MD subjects experiencing throat and facial muscles weakness might get benefited from learning to slow down their speech pace by taking short breathes and by use of special communication equipment.
- ***Corrective Surgery:*** Some subjects might require surgery for treatment of conditions resulting from MD. For example those suffering from myotonic MD, might need a pacemaker for heart conditions or else surgery for removal of cataract.

III. CURRENT RESEARCH

Vast amount of information is available on muscular dystrophy mechanism (muscular and genetic). Although a full curable treatment might be some period away, lots of research is being carried out that might help in achieving the goal of perfect treatment that might either slow down, reverse or stop the ravaging disease effects.

Gene Transfer

One approach is replacing the dystrophin gene responsible for MD by another new gene in treatment of DMD; but however this complicated process faces two major hurdles. One being the chances of the immune system to resist the new protein and the other being the large size of the dystrophin gene that needs to be replaced. Other problems include direct targeting of the viral vectors to skeletal muscles. There is a ray of hope by scientists that delivering replacement copies of the mutated gene might slow down the disease progression [9].

Protection against Muscle Damage

Targeting utrophin production is another approach. A protein similar to dystrophin, utrophin is not altered by MD. There are chances of disease being halted or slowed down if utrophin production is upregulated thus safeguarding the muscles from damage done at initial stages due to decreased levels of dystrophin ([10].

Exon Skipping

Generally, the protein synthesis machinery of the biological system reads the dystrophin gene for protein production. However the production of protein is not completed in cases the gene is mutated that results the machinery to stop reading the gene code. Such sections of DNA containing information for proteins are called ‘exons’. In DMD and BMD, the missing or duplicated exons result in interfere with the production of dystrophin protein. Research is going on for search of drugs that might cause skipping of the mutated content or the exons by the protein-making equipment thus still continuing to create more dystrophin and reducing the disease severity [4].

IV. DRUGS TO DELAY MUSCLE WASTING

Use of myostatin inhibitors is another area that is being investigated apart from gene related research. Myostatin inhibitors are drugs that enhance muscle strength thus improving symptoms and slowing down disease progression [11].

Stem Cell Research

Researchers are also investigating the probability of insertion of muscle stem cells that have the ability to produce the lacking dystrophin protein. In this regard, the type of cells to transfuse and their way of delivery to

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skeletal muscles are being inspected [12].

Myoblast Transplantation

Table 1: Treatments for MD

Program	Sponsor	MOA	Product type
Exondys 51 (eteplirsen)	Sarepta Therap	Dystrophin expression stimulant, Gene silencing	Nucleic acids, nucleotides & nucleosides
Vyondys 53 (golodirsen)	Sarepta Therap	Dystrophin expression stimulant	Nucleic acids, nucleotides & nucleosides
Vyondys 53 (golodirsen)	Sarepta Therap	Dystrophin expression stimulant	Nucleic acids, nucleotides & nucleosides
Translarna (ataluren)	PTC Therapeutics, Sanofi	CFTR-G542X nonsense allele inhibitor	Biologics
Viltepso (viltolarsen)	Nippon Shinyaku	Dystrophin expression stimulant	Nucleic acids, nucleotides & nucleosides
Emflaza (deflazacort)	Marathon, PTC Therapeutics	Anti-inflammatory agent, Immunosuppressant	Small Molecule
Puldysa (idebenone)	Santhera, Chiesi	Mitochondrial protein stimulant	Small Molecule
givinostat (ITF2357)	Italfarmaco	HDAC inhibitor	Small Molecule
SRP-5051	Sarepta Therap	Dystrophin expression stimulant	Gene Therapy
SRP-9001	Nationwide Children's, Sarepta Therap, Roche	Gene transference	Gene Therapy
Galgt2 gene therapy	Sarepta Therap, Nationwide Children's	GALGT2 stimulant	Gene Therapy
SRP-9003	Sarepta Therap	Gene transference	Gene Therapy
SRP-9004	Sarepta Therap	Gene transference	Gene Therapy
allogeneic cardiosphere-derived cells (CAP-1002)	Capricor	Stem cell stimulant, Immunomodulator	Cell Therapy
givinostat (ITF2357)	Italfarmaco	HDAC inhibitor	Small Molecule
autologous bone marrow-derived mesenchymal stem cells	Stem Cells Arabia	Stem cell stimulant	Cell Therapy
NT0200	NeuBase Therap	RNA interference	Nucleic acids, nucleotides & nucleosides
Exon 43	Sarepta Therap	RNA interference	Nucleic acids, nucleotides & nucleosides
Exon 52	Sarepta Therap	RNA interference	Nucleic acids, nucleotides & nucleosides
Exon 44	Sarepta Therap	RNA interference	Nucleic acids, nucleotides & nucleosides
Exon 50	Sarepta Therap	RNA interference	Nucleic acids, nucleotides & nucleosides
Exon 55	Sarepta Therap	RNA interference	Nucleic acids, nucleotides & nucleosides
SRP-5052	Sarepta Therap	RNA interference	Gene Therapy
SRP-5053	Sarepta Therap	RNA interference	Gene Therapy
SRP-5045	Sarepta Therap	RNA interference	Gene Therapy
SRP-5050	Sarepta Therap	RNA interference	Gene Therapy
SRP-5044	Sarepta Therap	RNA interference	Gene Therapy
GNT0004	Genethon, Sarepta Therap	Gene transference, Dystrophin replacement	Gene Therapy
SRP-9005	Sarepta Therap	Gene transference	Gene Therapy
SRP-9006	Sarepta Therap	Gene transference	Gene Therapy
Emery-Dreifuss muscular dystrophy Type 1	Sarepta Therap	Gene transference	Gene Therapy
CRISPR/Cas9 gene editing therapeutic	Sarepta Therap, Duke University	Gene transference	Gene Therapy
RNA targeting gene therapeutic	Locana	Gene transference	Gene Therapy
CRISPR-Cas9 gene editing technology-based therapeutic	Vertex, CRISPR Therap	CFTR modulator	Gene Therapy

The early stages of muscular dystrophy involves the replacement of faulty muscle fibres by myoblasts (also called satellite cells) that repair and replace them. However exhaustion of the myoblasts at later stages results in conversion of the muscles into connective tissue.

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Received: 12 Mar 2020 | Revised: 25 Mar 2020 | Accepted: 10 Apr 2020

Studies are being attempted to insert modified myoblast cells into muscles to take over the work of the exhausted natural myoblasts [13]

Some of the treatments that either in marketed or in clinical development for different types of MD are listed in table 1.

EXONDYS 51

This drug is indicated for specific group of patients with DMD (Duchenne Muscular Dystrophy). US FDA has approved this in 2016 to be indicated only on the patients with DMD.The therapy is aimed at internal production of Dystrophin protein. This drug usage clearly shows that there is a 2.8 times increase in Dystrophin over the baseline.

DMD causes muscle weakness majorly in legs, hips and pelvis and will cause all kinds of trouble for someone in walking, sitting and standing. This is majorly developed in people of ages 3-6.

Exondys 51 help increase in Dystrophin and makes it functional again.[14]

Currently, Exondys 51 is going through Clinical Trails on a large batch and results are still inconclusive. Whereas, FDA gave an approval for Indication of this drug under accelerated approval as it shows clear increase of Dystrophin.

The patients who got treated with this drug has observed some side effects pertaining to Hypersensitivity such as Flushing, Cough, Dyspnea, Brochospasm, hypertension, untricaria, rash, pyrexia etc.

Eteplirsen

Eteplirsen ,the active pharmaceutical ingredient of Exondys 51 is phosphoramidite morpholino sequence corresponding to a portion of exon 51 that exerts drug action by forcing the exclusion of exon 51 from the mature Duchenne muscular dystrophy (DMD mRNA)

V. MECHANISM OF ACTION

The characteristics of DMD include absence of dystrophin, an essential protein that maintains muscle cell membrane integrity which is caused by DMD gene mutation thus leading to disruption in translational reading frame, and a non-functional protein. Eteplirsen, causes exon skip of exon 51 and retains the translational reading frame which results in production of functional dystrophin protein. the clinical trials data indicate that patients confirmed mutation of the DMD gene vulnerable to exon 51 skipping. All patients treated with the drug generated messenger ribonucleic acid (mRNA) coding for truncated dystrophin protein. Post 48 weeks of treatment , the average dystrophin protein level was increase to 0.44% of that found in a healthy subject, compared to 0.16% prior to treatment.

The protein binding of the drug in humans is found to be 6-17% with a mean half life of 3.3 hours for dose of 30 mg/kg.[15,16]

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