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Muscular Dystrophies: An Update Review

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Abstract:- A broad group of illnesses known as muscular dystrophies are defined by pathologic alterations found in muscle tissue following biopsy. A progressive weakening of the skeletal muscles characterises the clinical appearance of these disorders. The most common type of muscular dystrophy is Duchenne Muscular Dystrophy, an X-linked recessive disease. Distal muscular dystrophy is most common in people between the ages of 40 and 60 and primarily affects the lower limbs, such as the hands, feet, arms, and legs. The development of muscle weakness during infancy or early childhood, usually before the age of two, is a common symptom of congenital muscular dystrophy. The majority of MD types frequently result in respiratory issues that affect the diaphragm and other breathing muscles. Several MD subtypes are linked to cardiac arrhythmias or cardiomyopathy. This class of disorders is the main target of gene transfer and gene repair therapies.

Keywords:- Muscular Dystrophy, Immunosuppressant, Duchenne Muscular Dystrophy, Electrocardiogram, Facioscapulohumeral Muscular Dystrophy

I. INTRODUCTION

A broad group of illnesses known as muscular dystrophies are defined by pathologic alterations found in muscle tissue following biopsy. In its most pathogenic sense, the term "dystrophy" refers to notable and enduring myopathic changes in the muscle. Fibrosis and fatty replacement are pathologic hallmarks of most muscular dystrophies at the end of the illness progression.[1] Clinically speaking, these conditions are characterised by a progressive weakening of skeletal muscles; however, there is a great deal of variation in terms of genetic and biochemical characteristics, the location of the affected muscles, the degree of respiratory and cardiac compromise, and the involvement of other organ systems such as the eyes and central nervous system.[1,2] Prognosis, effective treatment, and the age at which the disease first manifests itself can differ significantly, even among individuals with the same genetic abnormalities. The pathological processes underlying various forms of muscular dystrophy differ significantly. Disease-causing mutations have been linked to changes in the genes that code for proteases, transcription-regulating enzymes, and proteins that bind to cell membranes. Muscular dystrophies occupy a special place in the history of modern molecular genetics. [3] The first gene to be cloned utilising positional cloning technology was the dystrophin-encoding Duchenne muscular dystrophy (DMD) gene. Over the past three decades, ongoing advancements in gene mapping and identification have expanded our understanding of the genetic spectrum of these disorders; additionally, novel diagnostic and exploratory methods (such as genome-scale sequencing) may reveal additional genes implicated in less common syndromes. Using these similar methods should help us understand molecular pathogenesis better. Although there isn't a recognised cure for muscular dystrophy, this class of disorders is primarily the focus of research into innovative molecular therapy classes, like gene transfer and gene correction treatments. [4]

II. EPIDEMIOLOGY

The most common type of muscular dystrophy is Duchenne Muscular Dystrophy, an X-linked recessive disease. A mutation in the DMD gene results in the loss of function of the dystrophin protein, causing the condition that affects 1 in 3,500 live births. While rare individually, muscular dystrophies account for a significant proportion of patients with neuromuscular illnesses seen in both outpatient and inpatient settings. [5] The most common hereditary muscle illness in childhood is Duchenne muscular dystrophy (DMD), which affects approximately 8.3 out of every 100,000 boys; a relative of DMD, Becker muscular dystrophy, affects approximately 7.3 out of every 100,000 boys. Adults with myotonic dystrophy (affecting 10.6 per 100,000 people) and facioscapulohumeral dystrophy (affecting 3 per 100,000 people) are the two most common kinds of dystrophy. The prevalence of congenital muscular dystrophies varies significantly by region. Fukuyama muscular dystrophy is the most prevalent type in Japan due to a recessive founder mutation, despite Ullrich congenital muscular dystrophy being more common globally. [6]

III. TYPES OF MUSCULAR DYSTROPHY

A. Dystrophy Distal Muscular Dystrophy

Distal muscular dystrophy is most common in people between the ages of 40 and 60 and primarily affects the lower limbs, such as the hands, feet, arms, and legs. It usually affects fewer muscles and progresses more slowly than other forms of muscular dystrophy. [7]

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B. Duchenne Muscular Dystrophy

Duchenne muscular dystrophy is by far the most common kind among paediatric patients. It affects only men and develops swiftly after first emerging in early life. Most children still cannot walk by the time they are 12 years old and need a respirator to help them breathe. This is because the disorder damages the muscles in the body, which makes walking difficult, frequent falls inevitable, and the eventual need for a wheelchair. Complications of Duchenne muscular dystrophy include cardiomyopathy, a deterioration of the heart muscle, and scoliosis, a crippling spinal curvature that can exacerbate breathing issues.[8]

C. Myotonic Muscular Dystrophy

Myotonic muscular dystrophy is by far the most common diagnosis among adults. Both men and women are affected in the same way by it. This type of muscular dystrophy is characterised by problems with relaxation, weakening of the distal limbs (hands, wrists, etc.), cataracts, and gastrointestinal problems (constipation, diarrhoea, etc.). As a result, endocrine illnesses such as diabetes and thyroid problems may arise.[9]

D. Oculopharyngeal Muscular Dystrophy

This type of muscular dystrophy impairs the muscles in the face, neck, and eyelids that are responsible for swallowing and vision. Adults between the ages of 40 and 50 are frequently affected by muscular dystrophy of the oculopharynx.[10]

E. Becker Muscular Dystrophy

Although there are many parallels between Duchenne and Becker's muscular dystrophy, the latter is much less common and progresses much more slowly. It mostly affects boys, and a diagnosis is often made between the ages of 11 and 25. Boys and men alike who suffer from Becker muscular dystrophy experience a progressive loss of strength in their hip, thigh, pelvic, and shoulder muscles. While Becker muscular dystrophy progresses differently in each individual, the condition typically has minimal effect on life expectancy. [11]

F. Congenital Muscular Dystrophy

There are about thirty distinct types of congenital muscular dystrophies that affect both sexes equally. There could be precocious or congenital onsets of the sickness. Children with congenital muscular dystrophy may experience issues such as convulsions, breathing difficulties, swallowing difficulties, scoliosis, joint problems, or vision problems. Eye and speech problems are among the possible impacts on the central nervous system.[12]

G. Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy affects the muscles of the face, shoulder blades, and upper arm. Although it can appear as late as age 40, this condition typically first appears in both boys and females before the age of 20. The first sign of facioscapulohumeral muscular dystrophy is a weakening of the muscles surrounding the lips and eyes, as well as the shoulders, upper arms, and lower legs. Your hip and abdominal muscles will eventually begin to deteriorate as well.[13]

H. Emery–Dreifuss Muscular Dystrophy

MDS (Emery-Dreifuss muscular dystrophy syndrome) mainly affects teenage boys, while it can also impact girls. The muscles in the shin, upper arm, and shoulder of those who have this condition may be weaker than typical. Contractures, or muscle rigidity surrounding a joint, can also occur, causing deformity and limiting movement in the affected area. A person's spine becomes less flexible, which limits their range of motion.[14]

I. Limb-Girdle Muscular Dystrophy

Legs, upper limbs, hips, and shoulders are among the muscles affected by limb-girdle muscular dystrophy. There are more than 20 distinct forms of this particular type of muscular dystrophy. People as young as two years old and as elderly as forty years old can begin to experience it. Both men and women are affected in the same way by it. [15]

IV. CLINICAL FEATURES

The signs of Duchene muscular dystrophy commonly appear by the time a kid is six years old, though they might appear as early as infancy. In children whose weakness originates in the pelvis and upper legs, the disorder presents as pseudohypertrophy, recurrent falls, and difficulties with motor abilities (running, leaping, and hopping). Additional symptoms include exhaustion, learning impairments (IQ < 75), and even intellectual impairment. Because Becker is a milder type of the disease than Duchenne muscular dystrophy, persons with it may still be able to walk at the age of 16 (and in some cases, well into old life). [16] Some symptoms include walking on tiptoes, experiencing difficulty getting off the floor, and experiencing muscle spasms. Myotonic muscular dystrophy is characterised by a reluctance to relax muscles after a sharp contraction. Signs and symptoms of facioscapulohumeral dystrophy, a type of muscular dystrophy affecting the shoulders and face, include a lack of strength in the muscles that close the eyes, reduced reflexes in the biceps and triceps, difficulties speaking and eating, and even temporary hearing loss. Additional clinical indicators include testicular atrophy, heart disease, baldness, drooping eyelids and vision problems, swallowing difficulties, a long and thin face, weight loss, and poor anaesthesia responses. Between the ages of 20 and 30, it most frequently affects both men and women. The development of muscle weakness during infancy or early childhood, usually before the age of two, is a common symptom of congenital muscular dystrophy. We refer to this group of conditions as muscular dystrophy. At first, these babies may seem "floppy," and later on, they may have difficulties sitting up, rolling over, and walking. Emery-Dreifuss muscular dystrophy presents early with symptoms like walking on toes, difficulty bending the elbows, and an increased risk of fainting due to cardiac irregularities and tight Achilles tendons in the heels. Common symptoms also include a stiff back and degeneration of the shoulders. Less common forms of congenital muscular dystrophy may be linked to learning disabilities or mental retardation. Additionally, there may be

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a minor atrophy of the facial muscles. The main symptom of limb-girdle muscular dystrophy and related muscular dystrophies is a malfunction of voluntary muscles. One of the most prevalent symptoms of this illness is weakness in the muscles of the hips and legs. Lifting heavy objects above your head is difficult when you have shoulder weakness. The majority of people will become severely disabled after 20 years after diagnosis, regardless of how quickly or slowly limb girdles grow. Distal myopathies are rare forms of muscle diseases that usually do not affect other muscle groups, resulting in weakness and atrophy of the distal muscles. By contrast, when growing ptosis and dysphagia start in late adulthood, oculopharyngeal muscular dystrophy affects other muscles in the head and limbs.[17, 18]

V. PATHOPHYSIOLOGY

Contraction of Muscles: An understanding of the fundamental principles underlying muscle function is necessary. According to the sliding filament model, muscular tension results from filament contraction, which is aided by calcium. Calcium is delivered from the sarcoplasmic reticulum and causes the muscle to depolarize. When the anionic charge of troponin C is bound by intracellular calcium, tropomyosin can separate from the G-actin site. A myosin head that has been exposed attaches to the designated G-actin location to form a pivot that is powered by ATP. This pivot transfers the process of muscle shortening to the glycoprotein-rich cytoskeleton of the muscle cell, enabling actin filaments to pass through myosin filaments. Only the inner surface of the muscle fibre's plasma membrane contains dystrophin, which connects the extracellular matrix and the cytoskeleton within via glycoproteins that pass through the membrane. The structural stability of a protein complex in cell membranes is provided by this cytoskeletal protein. Specifically, dystrophin anchors the actin cytoskeleton to the basement membrane within a membrane-glycoprotein complex.[17,19] Dystrophin and laminin are two of the proteins that comprise this cytoskeletal framework. Before adhering to α-dystroglycan and laminin, dystrophin binds to F-actin and β-dystroglycan in the extracellular matrix (ECM). Dystrophin is responsible for integrating the extracellular matrix and cytoskeleton. Therefore, when a contracting muscle is not working properly, dystrophin modifies the transmission of tension in that muscle. Myosin and contractile actin proteins typically shorten with muscle injury, resulting in weaker muscles and increasing destruction of cell membranes. [20] Muscle injury also causes creatine kinase to leak out of every cell and into the plasma at abnormally high amounts. Muscular dystrophy is characterised by pseudohypertrophy, which is the outcome of scar tissue formation brought on by this inflammatory response to CK release. Although muscles seem hypertrophied, they are weak because the tissue does not contain any functional contractile filaments. The deficit is common starting in foetal development. [21] Inflammatory cells phagocytose damaged muscle cells, causing scarring and increasing dysfunction. The dystrophin-glycoprotein complex is a protein network that appears to strengthen the sarcolemma. Other nodes in the network may move as a result of a node being down. For instance, if dystrophin is eliminated first, other sarcoglycans may also be removed. The weakening of the membrane leads to the death of muscle cells. Skeletal muscle is finally almost completely replaced by fat and connective tissue. The skeleton deteriorates with time, gradually impairing movement. In the smooth and cardiac muscles of the gastrointestinal system, fibrosis is frequently seen. The brain has a variety of inconsistent structural abnormalities.[19.22]

VI. DIAGNOSIS

The first step in diagnosing MD is a hands-on examination by a medical practitioner. The doctor will perform a comprehensive review of the patient's medical history, including any history of muscular problems, as well as their family's medical history, including any members who have MDs. Certain molecules detected in the blood may be excessively high in an MD patient.[23] If these substances are found at increased levels, further testing may be required since they may be indicative of disease, injury, or weakening of the muscles. Damage to muscle fibres brought on by the circulation's production of the enzyme serum creatine kinase is one possible example of this. Serum aldolase is one enzyme that helps turn carbs into energy. [24] Myoglobin is a protein that stores and transports oxygen. A small sample of muscle tissue is taken for a muscle biopsy using a needle or very small incision. Medical personnel examine the tissue under a microscope to check for telltale symptoms of MD. For patients whose muscle biopsy reveals genetic abnormalities, genetic testing is frequently required to confirm the findings. genetic testing to find genes associated with or known to cause hereditary muscular disease. DNA and enzyme tests may corroborate the diagnosis of MD, among other neuromuscular conditions. [22,24] Neurological tests are used to rule out other nervous system issues, identify patterns of muscle weakness and wasting, assess reflexes and coordination, and identify contractions. Electrocardiograms (ECGs) and echocardiograms (Echos), which measure the heart's force and structural integrity, are two diagnostic procedures for the heart. Certain kinds of MD might cause irregular heartbeats and other cardiac problems as symptoms. assessments of the patient's breathing and muscular strength during exercise, as well as the identification of any spikes in the rates of specific indicators after activity.[21] Ultrasound and magnetic resonance imaging (MRI) tests that take pictures of the interior of the body using sound waves or radio waves allow physicians to view characteristics such as muscle mass and quality as well as the amount of fat that has replaced muscle.

VII. COMPLICATIONS

The majority of MD types frequently result in respiratory issues that affect the diaphragm and other breathing muscles. Lung infections are another consequence of respiratory insufficiency that can be deadly at times. Breathing problems are a common symptom of muscular dystrophy, which can present at quite various ages. Cardiomyopathy or cardiac arrhythmias are linked to several MD subtypes. [25] These problems frequently appear in the later stages of the disease and are extremely dangerous for the patient's survival. The three muscular dystrophies most

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commonly associated with cardiac issues are Emery-Dreifuss, LGMD, and DMD. Dilated cardiomyopathy will occur in almost all cases. In both DMD and BMD, ventricular arrhythmias are seen. In LGMD, loss of fatty tissue in the RV and LV is common, as are conduction issues. Nearly everyone has scoliosis as a result of muscular dystrophy. [6] The inability to walk or stand up straight is frequently the initial sign of this disorder, which arises when the muscles supporting the spine weaken. In certain instances of congenital MD, scoliosis may be present from birth [21, 25].

VIII. TREATMENT

Current MD treatments can reduce the severity of symptoms or at least diminish their impact. There is promise in this area because of current research, including certain gene-based medicines, which aim to treat or at least lessen the symptoms of certain forms of MD. Any treatments or medications discussed here might not be appropriate for or suggested for those with MD. If you're unsure about how to treat MD, consult your physician. [26] The National Institute of Neurological Disorders and Stroke (NINDS) is in charge of NIH research regarding MD. The NINDS website on MD has more information about therapies.[27]

➢ *MD Treatments May Include the Following.*

- *Physical Therapy*

Early onset of physical treatment is critical for maintaining strong, flexible muscles throughout life. A routine that combines more passive stretching techniques with planned exercise may be beneficial for MD patients.[28]

- *Respiratory Therapy*

Since the body requires muscles like the diaphragm to breathe, weakening of these muscles may affect breathing due to MD. Many MD patients may be unaware that their respiratory strength has decreased until they experience difficulty coughing or develop pneumonia due to an infection. As soon as an MD diagnosis is made, specialists may offer treatments to prevent or delay respiratory problems. At some time throughout their illness, some MD patients might need a ventilator.[29]

- *Speech Therapy*

Strengthening exercises for the face and throat muscles in speech therapy may provide comfort for patients suffering from myofascial weakness. There are several ways to improve communication: speaking more slowly, pausing more frequently in between breaths, and using specialised communication aids. [30]

- *Occupational Therapy*

When a person's physical abilities change, occupational therapy can help persons with MD regain lost motor skills or find new ways to exercise weak muscles. Through occupational therapy, people with MD can learn how to use wheelchairs, cutlery, and personal items like combs and hairbrushes.[25,29]

- *Surgery*

Many patients with multiple sclerosis (MD) eventually need surgery to relieve the disease's symptoms. Patients with myotonic MD may need heart operations (pacemaker implantation) or vision correction surgeries (cataracts, clouding of the eye's lens that stops light from reaching the retina) to address vision problems. For certain MD patients, spinal curvature, or scoliosis, may require surgical correction.[30]

- *Drug Therapy*

Certain medications can delay the weakening of muscles or lessen the symptoms of MD. Among them, you might discover that the US has approved the prescription of glucocorticoids such as deflazacort and prednisone. FDA's (Food and Drug Administration) guidelines for DMD treatment in 2017. Regular use of prednisone has been shown to strengthen muscles, improve respiratory function, and slow down the loss of strength in multiple sclerosis [15,13]. Vamorolone is a new glucocorticoid medication that is being tested in experimental trials to treat Duchenne muscular dystrophy in boys. In animal models, researchers funded by the NICHD found that nandrolone reduced the symptoms of limb-girdle MD; early results suggested that the drug was as effective as prednisone but without undesirable side effects. medicine for seizures. [28] Epilepsy medications may help MD patients control seizures and certain kinds of muscle spasms. medications that suppress the immunological system. Immunosuppressive drugs, which are typically used for autoimmune conditions such as lupus and dermatitis, may delay the death of some muscle cells in MD patients. The use of beta-blockers, ACE inhibitors, and other medications used to treat cardiac disorders such as high blood pressure and heart failure has been connected to certain kinds of MD [29].

- *Gene-Based Therapy*

There are currently relatively few alternatives available for treating MD, but researchers are actively searching for a means to restore a gene's ability to produce proteins. Some tactics focus on correcting the function of a particular gene, while others scan the entire genome.[30] One example of a gene-based strategy is the medication eteplirsen, which uses a method called "exon skipping" to create functional dystrophin protein by removing the faulty gene's section. Exon skipping improves the quantity of usable muscle protein even though it is shorter than normal protein.[23] The FDA approved the use of Goodison in 2019 and Viltolarsen in 2020 for the treatment of Duchenne muscular dystrophy (DMD). While all three of these drugs are still in the research stage and are not a cure for Duchenne muscular dystrophy, there is hope that they will provide therapeutic benefits beyond merely producing more dystrophin. These therapies need weekly injections into an IV. Since the DMD-causing gene is so large, less than 25% of patients may respond well to current treatments. Research is also ongoing into substitute drugs that improve foetal dystrophin synthesis and deal with other problems related to protein synthesis and instruction.[28, 30]

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IX. CONCLUSION

Muscular dystrophies represent a diverse group of genetic disorders characterized by progressive muscle weakness and degeneration. While there is considerable variability in clinical presentation, genetic underpinnings, and prognosis among different types of muscular dystrophy, they all share common pathological features such as fibrosis and fatty replacement of muscle tissue. Diagnosis typically involves a combination of clinical evaluation, genetic testing, and muscle biopsy, with treatment aimed at managing symptoms and improving quality of life. Current therapeutic approaches include physical therapy, respiratory support, surgery, drug therapy, and emerging gene-based treatments. While there is no cure for muscular dystrophy yet, ongoing research holds promise for more effective interventions in the future.

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