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[Duchenne Muscular Dystrophy: An In-depth Understanding of a Devastating Genetic Disorder]

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ABSTRACT

Duchenne Muscular Dystrophy (DMD) is a rare and severe genetic disorder that primarily affects young boys, leading to progressive muscle weakness and disability. This article provides a comprehensive overview of DMD, including its etiology, clinical manifestations, diagnostic methods, treatment options, ongoing research efforts, and potential future therapies. By exploring the underlying genetic mutation, pathophysiology, and impact on affected individuals and their families, this article aims to shed light on the challenges faced by patients with DMD and the strides made in understanding and managing this debilitating condition.Duchenne Muscular Dystrophy (DMD) is a rare and debilitating genetic disorder that primarily affects young boys, causing progressive muscle weakness and loss of mobility. This paper provides an in-depth examination of the pathophysiology, genetic basis, clinical manifestations, diagnostic methods, and current therapeutic strategies for DMD. The disorder arises from mutations in the dystrophin gene, leading to the absence of this essential protein in muscle cells. As a result, muscle fibers are susceptible to damage and degeneration, ultimately leading to severe muscle wasting. Early diagnosis through genetic testing and clinical evaluation is crucial for timely intervention, as the natural course of the disease is characterized by loss of ambulation and life-threatening complications. Various therapeutic approaches, such as corticosteroids, physical therapy, and emerging gene-based therapies, are discussed in detail. This review aims to provide a comprehensive understanding of DMD and highlight the ongoing research efforts to improve the quality of life for affected individuals.

KEYWORDS: Duchenne Muscular Dystrophy (DMD), Genetic disorder, Dystrophin gene Muscle weakness, Clinical manifestations,Physical therapy.

1. INTRODUCTION

Duchenne muscular dystrophy (DMD) is a severe type of muscular dystrophy primarily affecting boys. It is caused by mutations in the dystrophin gene located on the X-chromosome, leading to an almost complete lack of the dystrophin protein in affected individuals. This X-linked recessive disorder results in muscle weakness that typically starts around the age of four and rapidly worsens. Muscle loss usually begins in the thighs and pelvis and progresses to the arms. This can lead to difficulties in standing and walking. By around the age of 12, most affected individuals are unable to walk. Additionally, affected muscles may appear larger due to increased fat content, and scoliosis is a common complication. Some individuals with DMD may also experience intellectual disabilities.

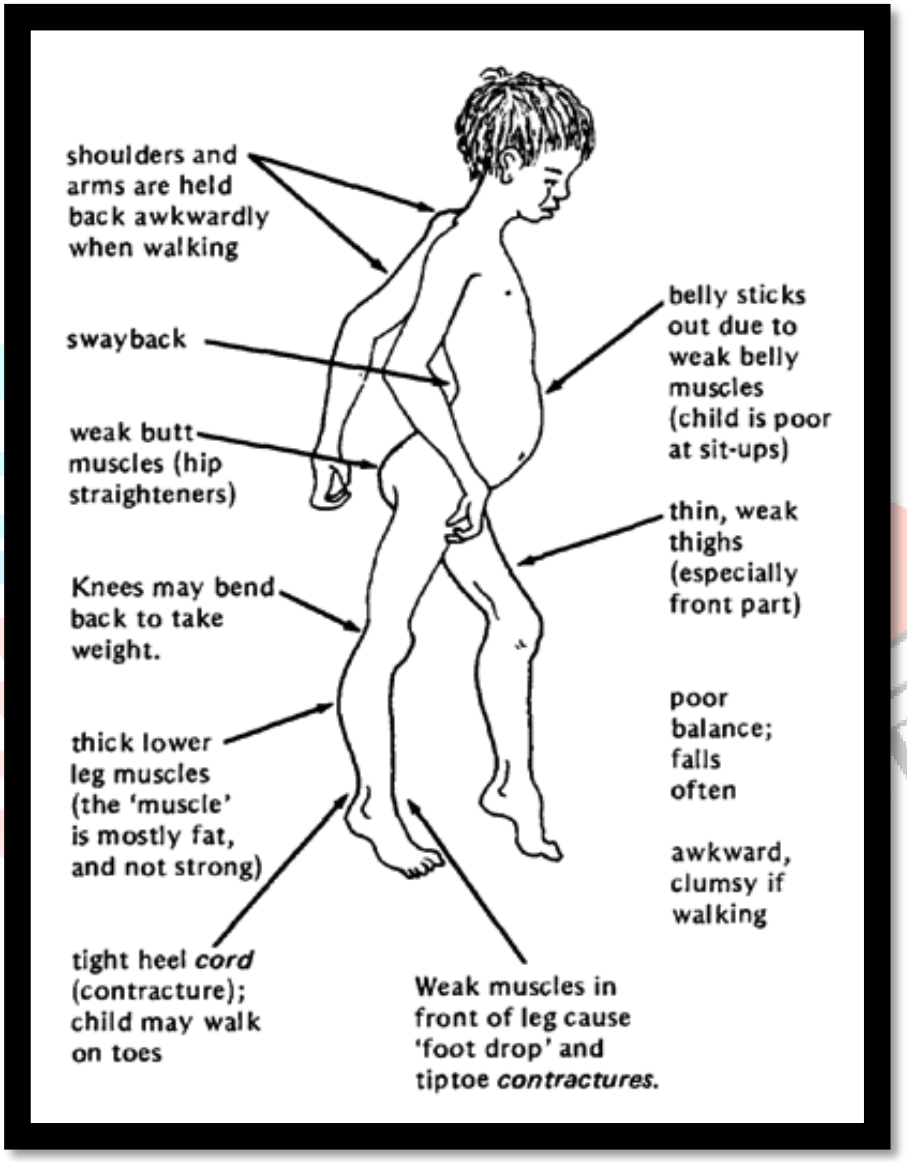


Fig1: Introduction of Duchenne muscular dystrophy (DMD)

Mutations in the dystrophin gene lead to progressive muscle fiber degeneration and weakness. This weakness may present initially with difficulty in ambulation but progressively advances to such an extent that affected patients are unable to carry out activities of daily living and must use wheelchairs. Cardiac and orthopedic complications are common, and death usually occurs in the twenties due to respiratory muscle weakness or cardiomyopathy.

Current therapy for DMD involves glucocorticoid treatment and physiotherapy to prevent orthopedic complications. There is ongoing research into effective therapies, including gene therapy and strategies to restore dystrophin expression to alleviate symptoms. Becker Muscular Dystrophy (BMD) is a milder version of the disease caused by mutations that do not completely eliminate dystrophin expression or

severely alter its structure. It has been observed that a low level of dystrophin restoration may provide effective treatment, but this level has not yet been achieved.

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder affecting approximately 1 in 3,600-6,000 newborn males. It manifests with proximal muscle weakness, Gowers' sign, abnormal gait, calf muscle hypertrophy, and elevated creatine kinase levels. Diagnosis typically occurs around age 5, with progressive muscle weakness affecting cardiac and respiratory function. DMD patients generally lose walking ability by age 13 and face cardiac and respiratory complications leading to early mortality.

1.1 Genetic basis: X-linked recessive inheritance, mutation in the DMD gene

DMD is a genetic disease due to the mutation of the dystrophin gene, located on chromosome Xp21. It is inherited as an X- linked recessive trait; however, approximately 30% of cases are due to new mutations.Mutations in the dystrophin gene result in diseases known as dystrophinopathies, which encompass Duchenne muscular dystrophy, Becker muscular dystrophy, and an intermediate form. Mutations result in a limited production of the dystrophin protein, which results in loss of the myofiber membrane integrity with repeated cycles of necrosis and regeneration. Fibrous connective tissue and fat progressively replace muscle leading to clinical features.Carrier females show no evidence of muscular weakness; however, symptomatic female carriers have been described. About 2.5% to 20% of female carriers may be affected.

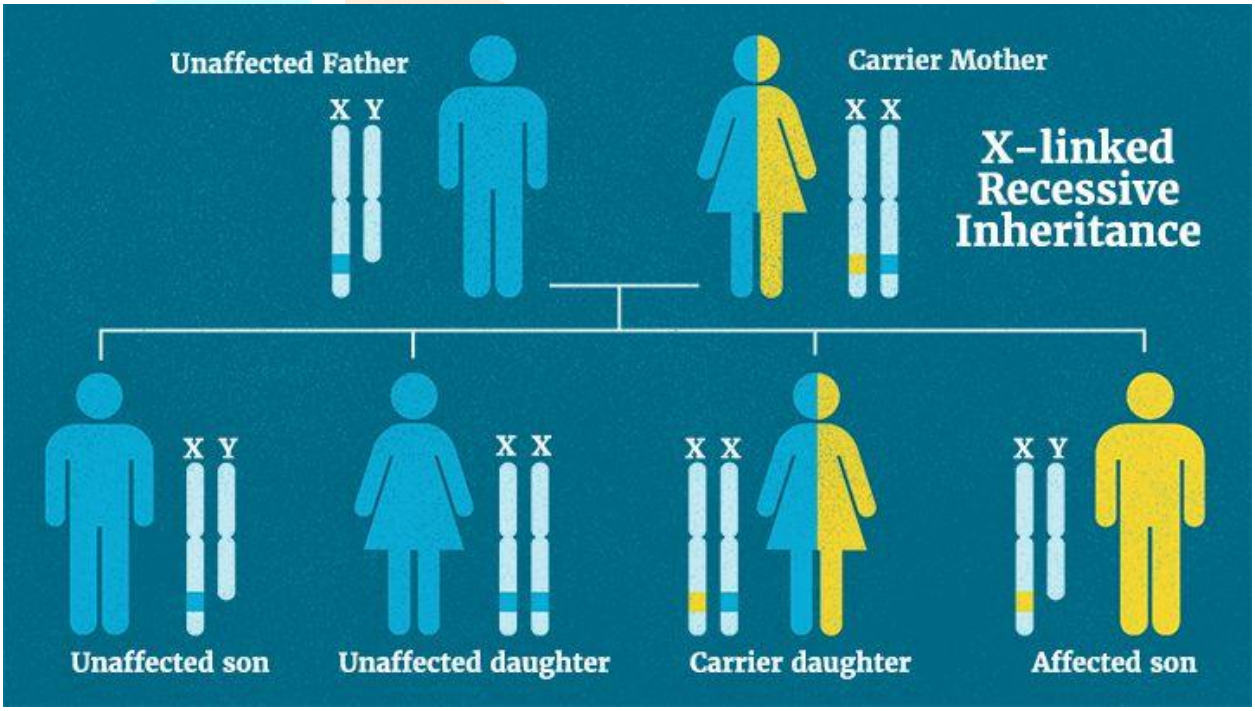


Fig 1.1:Genetic basis: X-linked recessive inheritance, mutation in the DMD gene.

This can be explained by the Lyon hypothesis in which the normal X chromosome becomes inactivated, and the X chromosome with the mutation is expressed.Female carriers can become symptomatic if they are associated with Turners syndrome (45X) or mosaic Turner karyotype, balanced X autosome translocations with breakpoints within the dystrophin gene and preferential inactivation of the normal X, and females with a normal karyotype but with nonrandom X chromosome inactivation with diminished expression of the normal dystrophin allele.

1. ETIOLOGY & PATHOGENESIS

Muscular dystrophy is a group of inherited diseases marked by skeletal muscle degeneration and weakness. This condition progresses due to the loss of healthy muscle fibers over time, which are replaced by fibrosis and fat. This leads to reduced muscle force generation for everyday activities. Different forms of muscular dystrophy can affect various muscle groups differently. Respiratory failure can arise from weakened

breathing muscles, potentially shortening lifespan unless mechanical support is employed. Some types of muscular dystrophy also impact the heart, leading to cardiac issues like heart failure and irregular rhythms.

The dystrophin gene is the largest known human gene, comprising 79 exons spanning over 2,200 kb, which accounts for about 0.1% of the entire genome. The most common mutation causing Duchenne muscular dystrophy (DMD) involves a deletion affecting one or multiple exons, accounting for 60-70% of cases. Point mutations contribute to around 26% of DMD cases, while exonic duplications account for 10-15%. Other mutations, such as subexonic insertions, deletions, splice mutations, and missense mutations, make up the remaining cases. Mutations leading to DMD disrupt the protein's reading frame, causing early stop codons and resulting in unstable or absent protein production in cells.
The dystrophin-associated proteins are categorized based on cellular location: extracellular (α-dystroglycan), transmembrane (β-dystroglycan, sarcoglycans, sarcospan), and cytoplasmic (dystrophin, dystrobrevin, syntrophins, neuronal nitric oxide synthase). α-dystroglycan, a receptor for extracellular ligands, resides on the outer sarcolemma due to its glycosylation and membrane association. It interacts closely with β-dystroglycan, a transmembrane protein also binding to dystrophin. Mutations affecting glycosylation enzymes (POMT1, POMT2, POMGnT1, FKTN, FKRP) lead to limb-girdle muscular dystrophies (LGMD2I, K, M, N, O), while other gene mutations disrupt α-dystroglycan glycosylation and cause congenital muscular dystrophies.

Dystrophin-glycoprotein complex (DGC) consists of dystrophin linking intracellular cytoskeleton to transmembrane components like dystroglycan, sarcoglycans, and sarcospan. Sarcoglycans form a complex with sarcospan, aiding in structural support, signal transduction, and mechanoprotection. At the sarcolemma, the sarcoglycan complex tightly associates with β-dystroglycan. Dystrophin interacts with β-dystroglycan intracellularly, connecting the cytoskeleton to DGC, and further to the extracellular matrix. Cytoplasmic components like α-dystrobrevin, syntrophins, and neuronal nitric oxide synthase (nNOS) are involved in signal transduction and exercise-induced blood flow regulation.

Duchenne muscular dystrophy (DMD) is a lethal condition causing progressive muscle weakness due to mutations in the DMD gene. Dystrophin, encoded by this gene, connects DGC with the intracellular cytoskeleton. Therapies have been developed to manage DMD, although no absolute cure exists. DMD mutations can disrupt the reading frame, leading to severe DMD, or maintain it, causing less severe Becker muscular dystrophy (BMD). Recent findings suggest that DMD could also be a stem cell disease, with abnormalities in muscle stem cells contributing to the pathophysiology.

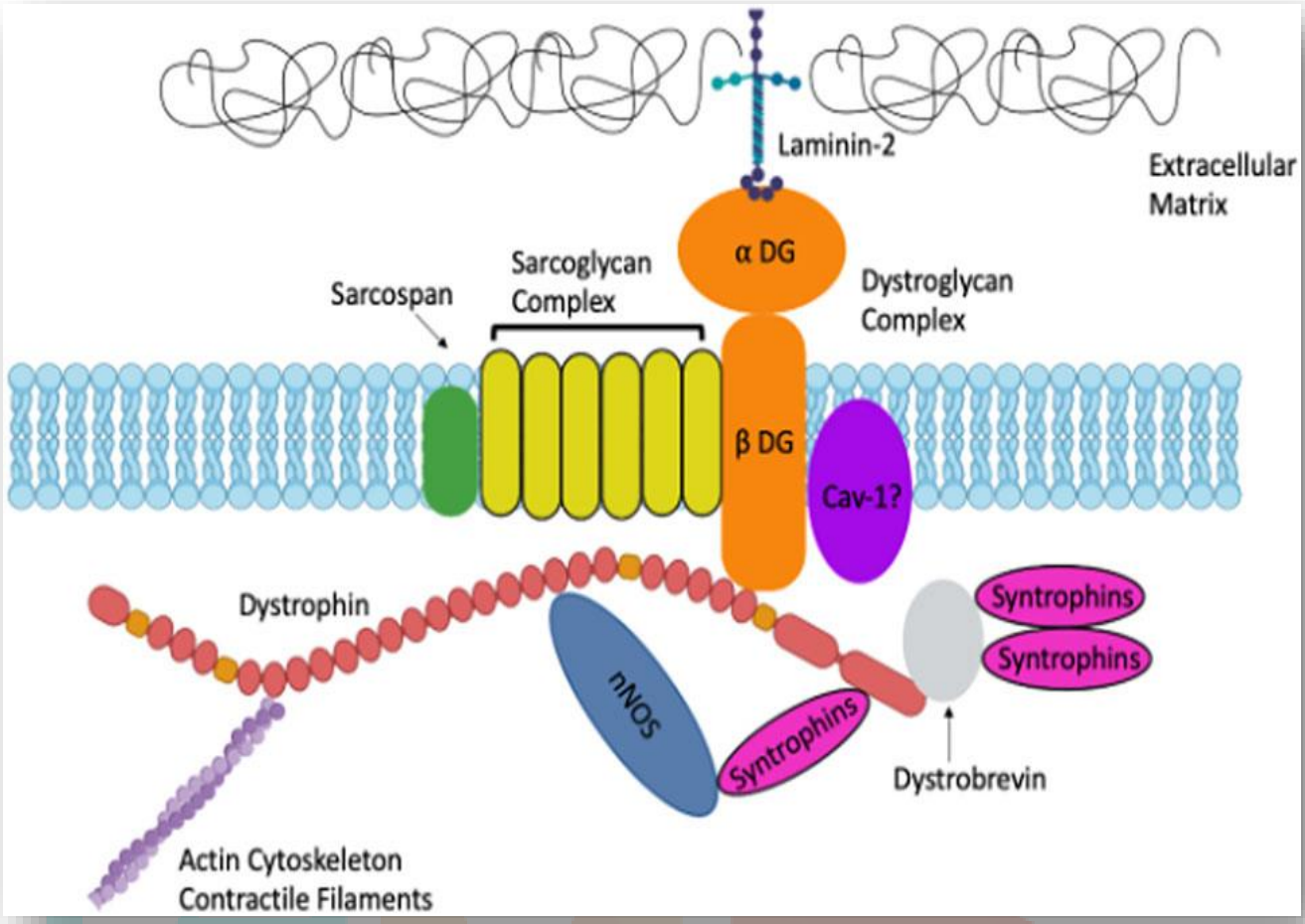


Fig 2 : Dystrophin-glycoprotein complex

Dystrophin is a large cytoskeletal protein that facilitates interactions between the cytoskeleton, cell membrane, and extracellular matrix. It is located at the plasma membrane in both muscle and non-muscle tissues. Dystrophin is a critical part of the dystrophin-glycoprotein complex (DGC), which plays an important role as being a structural unit of muscle. In DMD, both dystrophin and DGC proteins are missing, leading to excessive membrane fragility and permeability, dysregulation of calcium homeostasis, oxidative damage. These factors play a crucial role in muscle cell necrosis. As patients with DMD age, the regenerative capacity of the muscles appears to be exhausted, and connective and adipose tissue gradually replaces muscle fibers.

2.1 Dystrophin's Role in Muscle Integrity and Duchenne Muscular Dystrophy

Dystrophin is a critical protein involved in maintaining the integrity of muscle cells during repeated cycles of contraction and relaxation associated with muscle activity. It acts as an anchor between the actin cytoskeleton and the Dystrophin-associated glycoprotein complex (DGC) at the muscle cell membrane, known as the sarcolemma. This connection helps stabilize the muscle cell and prevents damage caused by mechanical stress. The extracellular domain of the DGC binds to the extracellular matrix protein laminin, further contributing to muscle stability.

Duchenne muscular dystrophy (DMD) is a severe X-linked disorder affecting approximately 1 in 3600 males during early childhood. It results from mutations in the dystrophin gene, leading to a loss of functional dystrophin protein. This absence of dystrophin makes the sarcolemma unstable, causing muscle fibers to be susceptible to damage following muscle contractions. Muscle weakness in DMD arises from a cycle of damage and regeneration, which eventually exhausts the muscle's regenerative capacity. This leads

to muscle fiber necrosis and replacement with adipose and connective tissue, resulting in fibrosis that further impairs muscle regeneration.

2.2 Inflammatory Response in DMD

Muscle damage in healthy muscles triggers an inflammatory response, involving immune cell recruitment, chemokine and cytokine secretion, and oxidative stress. Immune cells aid tissue regeneration by promoting the proliferation and maturation of satellite cells, which are precursor cells for muscle fibers. However, in DMD, the prolonged activation of the innate immune response results in chronic inflammation and additional tissue damage. The continuous damage-repair cycle causes the release of damage-associated molecular patterns (DAMPs) from muscle cells into the extracellular space. These DAMPs, including proteins like HMGB1, ATP, and RNA, sustain immune cell activation and lead to chronic inflammation.

2. Multi-System Abnormalities and Clinical Manifestations

DMD's impact is not limited to muscles; it also affects multiple systems. Patients experience progressive muscle weakness, with initial symptoms appearing in early childhood. As the disease progresses, muscle weakness spreads, affecting different muscle groups and causing difficulties in motor skills. Cognitive dysfunction, orthopedic complications, and cardiac issues are common. With advancements in management and therapies, individuals with DMD are living longer, and heart problems have become an important cause of mortality.

3.1 Signs and Symptoms of Duchenne Muscular Dystrophy (DMD)

Duchenne muscular dystrophy (DMD) is a progressive X-linked disorder primarily affecting limb muscles closer to the trunk, with legs being impacted before arms. Early signs include delayed walking and growth velocity. Enlarged calf muscles, known as pseudohypertrophy, might be observed. Preschoolers may appear clumsy, struggle with stairs, and exhibit difficulty running. By school age, a waddling gait and frequent falls can develop. Wheelchair use often begins around age 12, leading to improved independence once fully transitioned. Activities involving limbs or trunk may require support in the teen years. Cardiomyopathy, conduction issues, and respiratory insufficiency may cause mortality in late teens or 20s. Learning disabilities can manifest, affecting attention, verbal learning, memory, and emotional interaction.

- **The Gowers' sign is a distinctive maneuver seen in children with Duchenne muscular dystrophy (DMD). It involves the child starting in a hands-and-knees position and then gradually climbing to a standing position by "walking" their hands up their shins, knees, and thighs. This maneuver is used to compensate for the weakness in the leg muscles, especially the proximal muscles, which is a characteristic feature of DMD. It's a classic clinical sign associated almost exclusively with this genetic disease.**

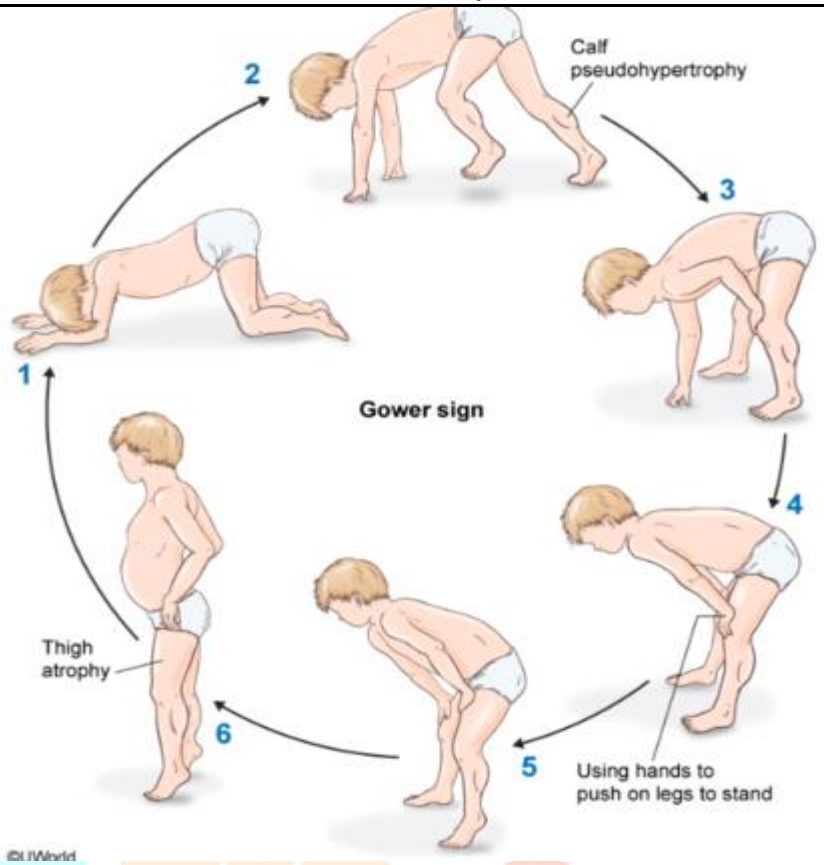


Fig 3.1: Gowers' sign

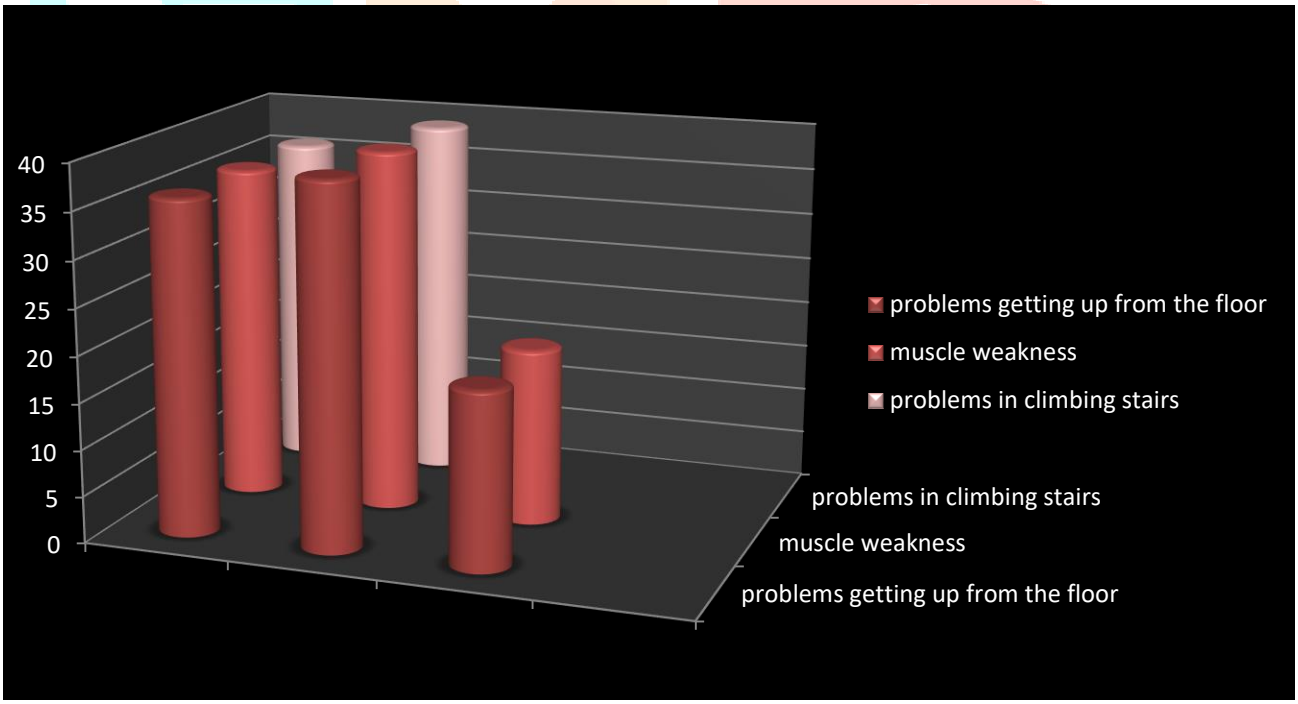
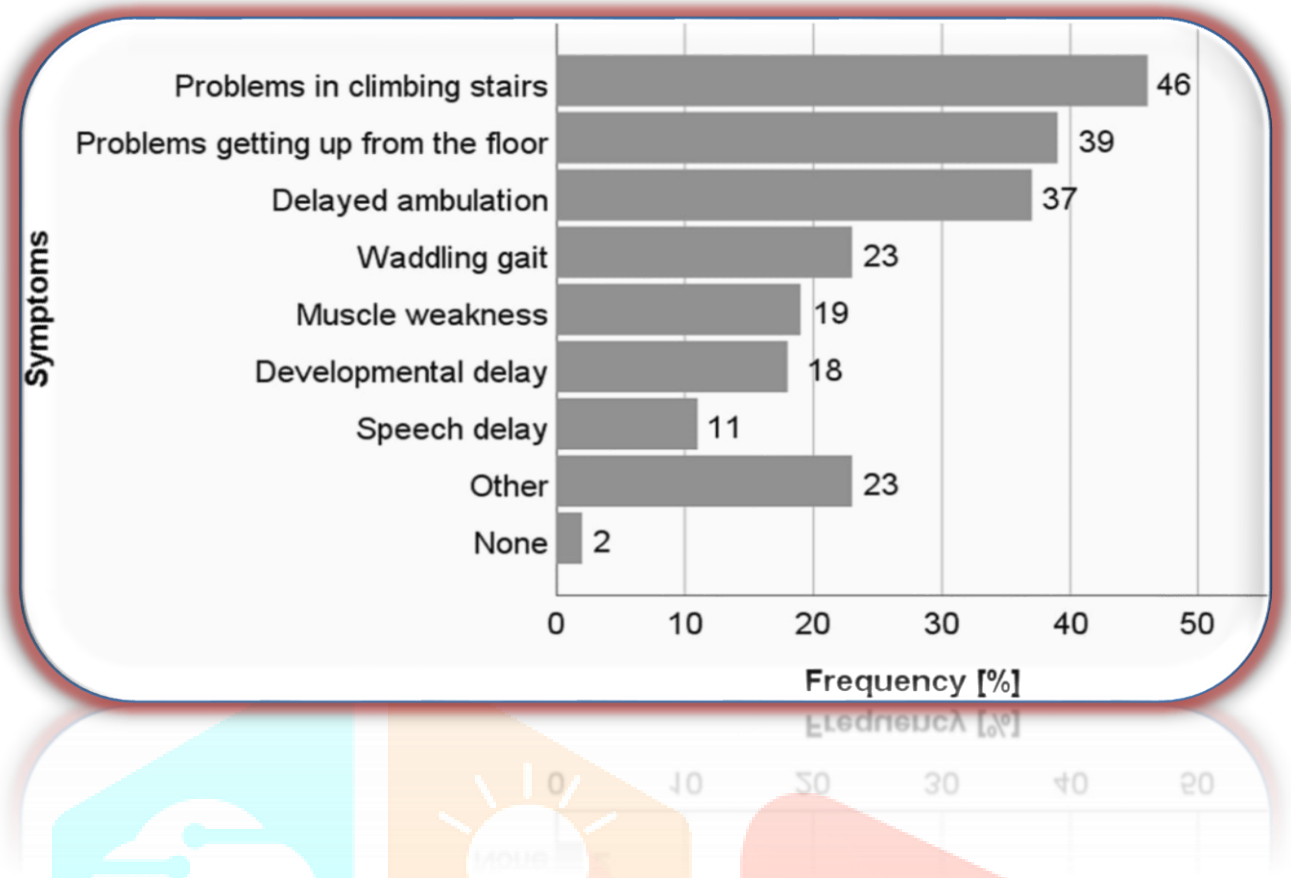


Fig 3.2: Ratio of **Signs and Symptoms of Duchenne Muscular Dystrophy (DMD)**

Fig3.3: Signs and Symptoms of Duchenne Muscular Dystrophy (DMD) order of Frequency



4.Diagnosis and Genetic Testing

4.1 Diagnostic Approaches:

- Serum creatine kinase (CK) levels are elevated before clinical symptoms and peak by age two, often 10 to 20 times the upper limit of normal.
- Muscle biopsy reveals connective tissue proliferation, muscle fiber necrosis, and replacement with adipose tissue.
- Genetic testing detects mutations in the dystrophin gene. Immunoblotting can predict disease severity.

Polymerase chain reaction (PCR) and multiplex ligation-dependent probe amplification (MLPA) are used to identify mutations

Cardiac and Respiratory Involvement:

- DMD leads to dilated cardiomyopathy in most patients by their teens or twenties.
- Respiratory complications are common, and patients may die due to respiratory and cardiac issues by their early twenties.

Management:

- There's no cure for DMD, but management focuses on symptom relief, complications, and improving quality of life.
- Treatments include glucocorticoids, rehabilitation, cardiac and respiratory management, and psychosocial care.

4.2 Diagnostic Testing:

- Creatine kinase (CK) testing is commonly used for diagnosis. It shows high specificity (90%) and sensitivity (80%) in detecting DMD.
- Elevated CK levels are indicative of muscle damage and are present even before symptom onset.

Neonatal Screening and CK:

- Neonatal screening for DMD using CK testing has been discussed. It offers the advantage of early diagnosis and intervention.
- CK testing in neonatal screening has shown high specificity and sensitivity in identifying true DMD cases.

Limitations:

- While CK testing is useful, it's important to note that the test itself does not determine the specific type of muscle disorder.

The provided data offers a comprehensive overview of DMD, including its clinical presentation, diagnostic methods, genetic aspects, and management strategies. If you need more detailed information or specific insights from the data, feel free to ask.

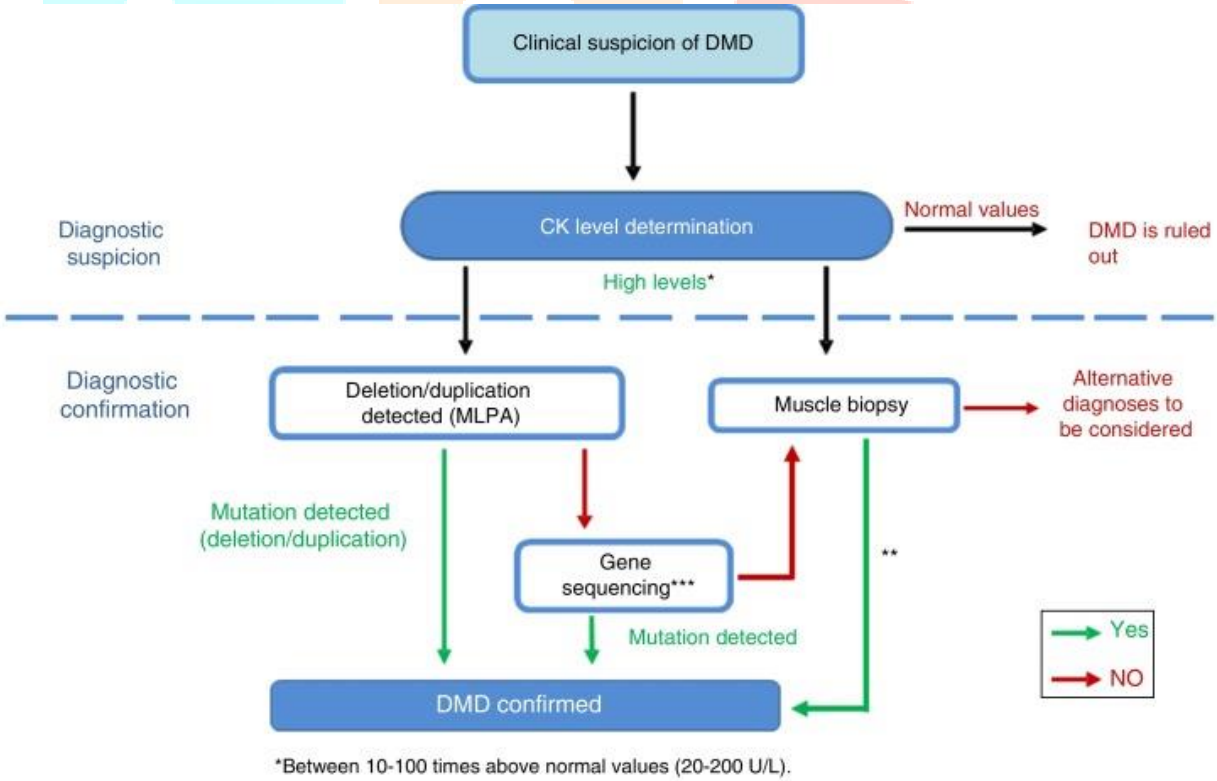


Fig 4.1: Diagnostic decision to confirm the genetic diagnosis of dystrophinopathies.

4.3 Genetic Testing and Biomarkers in Duchenne Muscular Dystrophy (DMD)

Genetic testing is pivotal in diagnosing Duchenne Muscular Dystrophy (DMD), a severe muscle-wasting disorder caused by mutations in the dystrophin gene. This gene, the largest known human gene, comprises 79 exons spanning 2.2 Mb. The mutation rate is relatively high, with about one in three DMD cases resulting from de novo mutations. DMD is characterized by impaired muscle function, frequent falls, delayed speech, and elevated muscle enzymes in affected boys.

Genetic Diagnosis: Diagnostic strategies involve identifying mutations through multiplex ligation-dependent probe amplification (MLPA), array comparative genome hybridization (array CGH), or Sanger sequencing. MLPA and array CGH detect exon deletions and duplications, with MLPA also detecting small mutations. Sanger sequencing is used for confirming exon-level mutations. The shift towards next-generation sequencing (NGS) techniques is promising but currently not as cost-effective as traditional methods.

Biomarkers for DMD: Biomarkers are vital for monitoring DMD progression and assessing treatment efficacy. Creatine kinase (CK) is a well-known biomarker for muscle damage, though not specific enough for diagnosis. Other proteins, including carbonic anhydrase 3 (CA3), malate dehydrogenase 2 (MDH2), myosin light chain 3 (MYL3), troponins, and inflammatory markers, show potential as biomarkers for different aspects of DMD progression. These biomarkers often exhibit declining abundance trajectories as the disease advances, making them more informative during early stages.

Complexity of Biomarkers: DMD's multifaceted nature necessitates the use of biomarker panels or signatures to comprehensively describe disease progression. Different biomarkers are associated with muscle function, inflammation, fibrosis, and cardiac status. As the disease evolves, a combination of biomarkers offers a more accurate representation of its progression.

Importance of Early Diagnosis: Early diagnosis of DMD is crucial for timely intervention. Genetic confirmation assists in family planning and carrier analysis for females. It aids in understanding disease severity and guides treatment decisions. However, challenges such as lack of awareness, resources, and societal stigmatization contribute to diagnostic delays.

4.4 Evaluation

- **Muscle Biopsy**
- A muscle biopsy will demonstrate endomysial connective tissue proliferation, scattered degeneration, and regeneration of myofibers, muscle fiber necrosis with a mononuclear cell infiltrate, and replacement of muscle with adipose tissue and fat.
- The muscled biopsied are the quadriceps femoris and the gastrocnemius.
- **Electromyography**
- Characteristic myopathic features can be seen; however, this is nonspecific. Motor and sensory nerve conduction velocities are normal, and denervation is not present.
- **Gene Analysis**
- Patients with DMD demonstrate the complete or near-complete absence of dystrophin gene. Dystrophin immunoblotting can be used to predict the severity of the disease. In DMD, patients are found to have less than 5% of the normal quantity of dystrophin.

- Polymerase chain reactions (PCR) can also be used and detect up to 98% of mutations. Multiplex ligation-dependent probe amplification (MPLA) is also used to identify duplications and deletions. Duplications can lead to in-frame or out of frame transcription products. Fluorescence in situ hybridization (FISH) is used less frequently but is useful to identify small point mutations.

- Dystrophin immunocytochemistry can also be sued to detect cases not identifies by PCR.

- **Electrocardiogram (ECG)**

- Characteristic ECG changes are tall R waves in V1-V6 with an increased R/S ratio and deep Q waves in leads I,aVL, and V5-6. Conduction abnormalities with arrhythmias may be identified with telemetry. As mentioned previously, supraventricular arrhythmias are more common. Intra-atrial conduction abnormalities are more common than AV or infra-nodal defects in DMD.

- **Echocardiogram**

- Evidence of dilated cardiomyopathy is present in almost all patients by the end of their teens or in their 20s

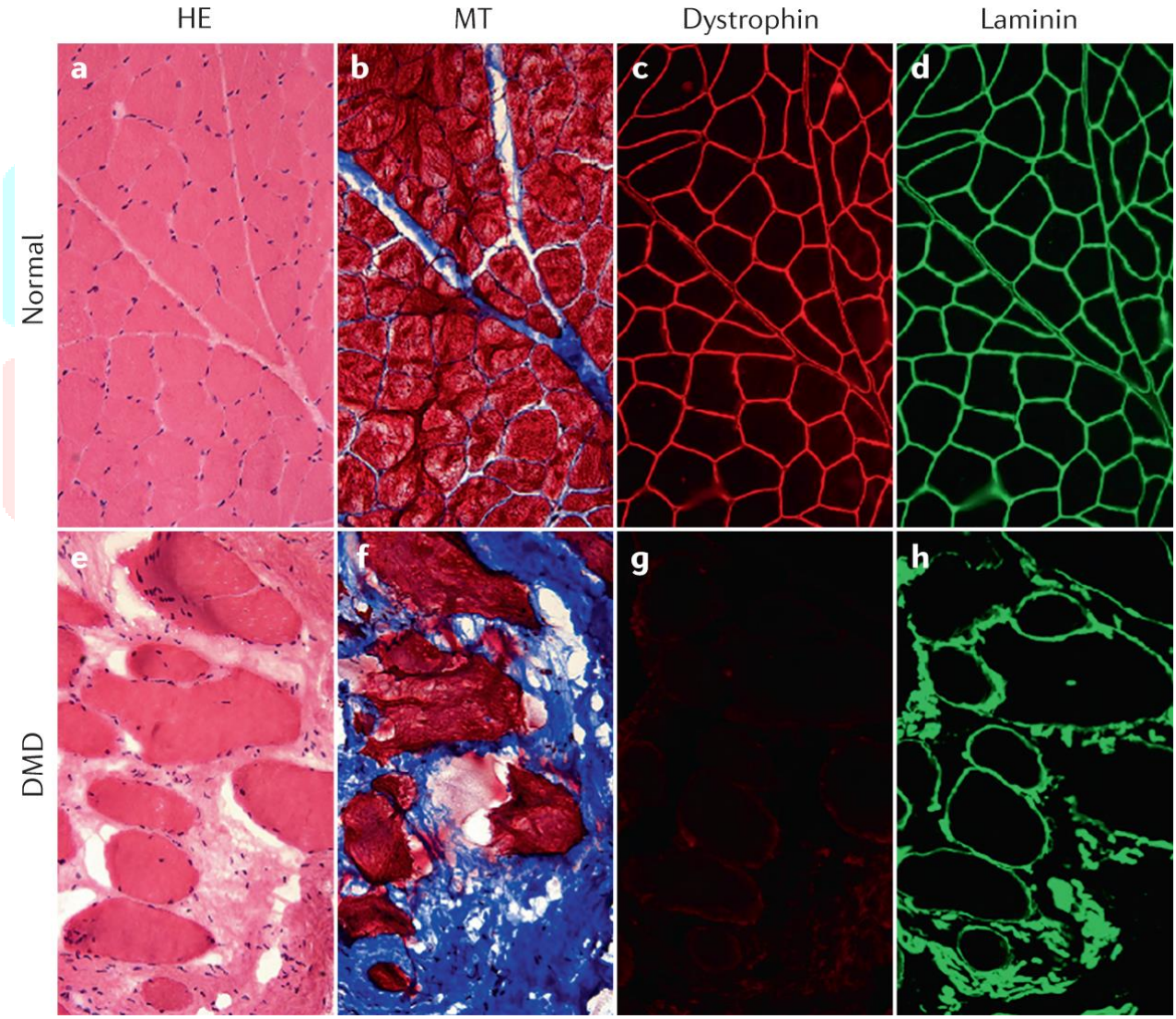


Fig4.4.1: Healthy muscle and DMD muscle histology.

Cross-sectional staining of healthy muscle (panels a–d) and skeletal muscle from a patient with Duchenne muscular dystrophy (DMD; panels e–h). Haematoxylin and eosin (HE) staining shows centrally nucleated myofibers, inflammatory cell infiltration, variable myofiber size, and endomysium and perimysium connective tissue deposition (panels a and e). Masson trichrome (MT) staining shows increased fibrosis (blue staining) in a patient with DMD compared with healthy muscle (panels b and f). Immunofluorescence labelling of dystrophin

and laminin shows a lack of dystrophin in a patient with DMD compared with healthy muscle (panels c and g) and variation in myofiber size in DMD muscle (panels d and h).

3. TREATMENT AND MANAGEMENT

- **Glucocorticoid Therapy**
- Glucocorticoid therapy decreases the rate of apoptosis of myotubes and can decelerate myofiber necrosis. Prednisone is used in patients four years and older in whom muscle function is declining or plateauing.
- Prednisone is recommended at a dosage of (0.75 mg/kg per day or 10 mg/kg per week is given over two weekend days).
- Deflazacort, an oxazoline derivative of prednisone, is sometimes preferred over prednisone as it has a better side effect profile and has an estimated dosage equivalency of 1:1.3 compared with prednisone. The recommended dosage is 0.9 mg/kg/day.
- Studies have shown that glucocorticoid treatment is associated with improved pulmonary function, delayed development of scoliosis reduces incidence and progression of cardiomyopathy and overall improved mortality.
- **Cardiomyopathy**
- Treatment with angiotensin-converting enzyme (ACE) inhibitors and/or beta-blockers is recommended. Early studies suggest that early treatment with ACE inhibitors may slow progression of the disease and prevent the onset of heart failure.
- Overt heart failure is treated with digoxins and diuretics as in other patients with cardiomyopathy.
- Surveillance consists of a cardiology assessment with ECG and echocardiogram. This should be performed at the time of diagnosis or by the age of 6 years. Routine surveillance should be performed once every two years until the age of 10 and then yearly after that. If evidence of cardiomyopathy is present, surveillance every six months is indicated.
- **Pulmonary Interventions**
- Pulmonary function must be tested prior to the exclusive use of a wheelchair. This should be repeated twice a year once the patient reaches 12 years of age, must use a wheelchair or vital capacity is found to be less than 80% of predicted.
- **Orthopedic Interventions**
- Physiotherapy to prevent contractures is the mainstay of the orthopedic interventions. Based upon patient requirements, passive stretching exercises, plastic ankle-foot orthosis during sleep, long leg braces to assist in ambulation may be used. Surgery to release contractures may be required for advanced disease. Surgery to correct scoliosis may improve pulmonary function.
- **Nutrition**
- Patients are at risk for malnutrition, including obesity. Calcium and vitamin D should be supplemented to prevent osteoporosis secondary to chronic steroid use. DEXA scanning should be obtained at age three and then repeated yearly.

- **Exercise**

Fig 5.1: exercise of DMD

Guidelines recommend all patients participate in a gentle exercise to avoid disuse atrophy. A combination of swimming pool and recreation-based exercises is recommended. Activity should be reduced if myoglobinuria is noted or significant muscle pain develops.

- **Novel Therapies**

- Gene therapies include medications that bind RNA and skip over the defective codon. This produces a shorter but potentially functional protein. Eteplirsen us an exon 51 skipping antisense oligonucleotides medications used for this purpose. Eteplirsen has been approved by the FDA for this purpose.

Corticosteroids: prednisone and deflazacort

Glucocorticoids, more precisely prednisone and deflazacort, are the main drug treatment for DMD. They have been used for over two decades and the benefits are well known now. They are the only medication that has been shown to increase muscular strength. Early studies have proved that their use prolonged ambulation and improved their functionality in everyday activities. Longterm studies have shown that they also reduce the need for scoliosis surgery, enhance lung function, and help maintain cardiac function.

The new drugs approved by the FDA for the treatment of Duchenne muscular dystrophy (DMD) are:

• **Amondys 45 (casimersen)**
• **Elevidys (delandistrogene moxeparvovec)**
• **Emflaza (deflazacort)**
• **Exondys 51 (eteplirsen)**
• **Viltepso (viltolarsen)**
• **Vyondys 53 (golodirsen)**

Table:1 new drugs approved by the FDA for the treatment of DMD

Fig 5.2: Deflazacort Tablets

- **Current Treatment and Management:** Despite its known molecular origins, DMD lacks a curative treatment. Corticosteroids, particularly prednisone and deflazacort, are the primary drugs for slowing disease progression. Studies demonstrate that corticosteroids increase muscular strength, prolong ambulation, improve lung and cardiac function, and reduce scoliosis surgery frequency. Long-term controlled trials revealed that treated patients can walk 2 to 5 years longer and experience delayed respiratory interventions. Cardiac function is better preserved, and life expectancy has increased. Adverse effects include weight gain, stunted growth, cataracts, osteoporosis, and adrenal suppression.

- **Dosing and Initiation:** Initiating corticosteroid treatment during the "plateau phase" around ages 4 to 6 is recommended. Prednisone dosage is typically 0.75 mg/kg/day, or deflazacort at 0.9 mg/kg/day. Side effects must be explained, and vaccinations completed. Dosage adjustments may be needed to manage side effects. Continuing treatment after loss of ambulation can preserve upper limb function, reduce scoliosis progression, and slow cardiac and respiratory decline.
- **Transition and Monitoring:** Transitioning off steroids requires gradual reduction to avoid adrenal crises. Monitoring adrenal function is crucial. Rehabilitation management involves multidisciplinary evaluations, individualized therapies, home stretching, and upper limb guidance. Orthopaedic management includes orthoses, leg surgery, and addressing scoliosis. Orthotics, surgery, and interventions are tailored to disease stage and patient preferences.

5.1 Future Directions: While corticosteroids are beneficial, ongoing research explores additional DMD treatments. These include exon skipping, gene therapy, myostatin inhibition, and more. Individualized decisions based on benefits and side effects are crucial in managing DMD.

Corticosteroids are currently the most effective pharmacological treatment for Duchenne muscular dystrophy, preserving walking ability and improving cardiac and respiratory function. Their use should be tailored to individual needs, with careful consideration of benefits and potential side effects. As research

continues, new treatment options are being explored to further enhance management strategies for DMD patients.

The provided text discusses various aspects of the management and treatment of Duchenne muscular dystrophy (DMD). It covers topics such as cardiac management, genetic therapy, pulmonary management, exon skipping, phosphodiesterase inhibitors, exercise, standards of care, vitamin D supplementation, and available medications for DMD treatment.

1. **Cardiac Management:** The text suggests that in the ambulatory stages of DMD, cardiac function should be assessed at diagnosis using methods like ECG and echocardiogram. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are recommended by age 10, and cardiac function should be assessed annually. After the loss of ambulation, regular assessment continues, and heart failure medical therapy is initiated if needed.
2. **Genetic Therapy:** Genetic therapy, involving the insertion of the dystrophin gene, is explored. Challenges like gene size have led to the development of smaller genes. A virus-associated with adenovirus is used as a vector, but immune responses hinder success.
3. **Pulmonary Management:** Most individuals with DMD eventually face respiratory complications. Muscle weakness affects inspiratory and expiratory muscles, leading to hypoventilation and elevated CO2 levels. This places patients at risk of pneumonia.
4. **Exon Skipping:** Exon skipping aims to restore reading frames. Synthetic RNA molecules, antisense oligonucleotides (AO), are developed. Studies target specific exons like exon 51 using 2'-O-methyl-phosphorotioates (2OMP) and phosphorodiamidate morpholino oligomers (PMOs).
5. **Phosphodiesterase Inhibitor:** Sildenafil, a phosphodiesterase type 5 inhibitor, improves nitric oxide signaling, benefiting vasculature, muscle mass, and fiber type. It's muscle-specific and improves force production.
6. **Exercise:** Limited motor abilities are common in DMD. Physiotherapy focuses on stretching upper and lower extremity muscles, pool therapy, and gentle physical activity. Disease-specific physical therapy maintains strength, flexibility, and function.
7. **Standards of Care:** International standards of care for DMD guide clinical decision-making in diagnosis, monitoring, and treatment. Expert reviews contribute to recommendations.
8. **Vitamin D Supplement:** DMD patients are at risk of fractures due to decreased bone density and corticosteroid treatment. Vitamin D supplementation is advised for those with deficiency. Orthopedic appliances and respiratory support are important.
9. **Medications:** Eteplirsen, ataluren, golodirsen, and viltolarsen are approved medications for specific mutations in DMD. Comprehensive care guidelines have been developed by the CDC.
10. **Social Issues:** As the adult DMD population grows, social issues like quality care, personal independence, education, employment, relationships, and sexual activity become important. Occupational therapists, care coordinators, and social workers aid in addressing these issues.

4. Current Research

Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle degeneration and weakness. Research into potential therapies for DMD is ongoing, and several approaches are being explored. Here are some of the key areas of research in DMD therapy:
1 .Gene Therapy: Gene therapy aims to correct the underlying genetic mutation that causes DMD. One approach is using CRISPR-Cas9 technology to edit the mutated dystrophin gene or replace it with a functional copy. Several clinical trials are underway to assess the safety and efficacy of these gene-editing techniques.
2. Exon Skipping: Many individuals with DMD have specific mutations that cause certain exons in the dystrophin gene to be skipped during transcription, resulting in a non-functional dystrophin protein. Exon skipping therapies, such as Eteplirsen and Golodirsen, aim to "skip" over problematic exons, allowing for the production of a shorter but partially functional dystrophin protein. Other exon-skipping drugs are also in development.
3. Stop Codon Readthrough: Some DMD patients have mutations that introduce premature stop codons in the dystrophin gene. Stop codon readthrough drugs, like Ataluren, encourage the translation machinery to bypass these premature stop codons, potentially enabling the production of a partially functional dystrophin protein.
4. Utrophin Modulation: Utrophin is a protein similar to dystrophin, and some research focuses on upregulating utrophin production to compensate for the lack of dystrophin. Utrophin modulators aim to enhance the expression and function of utrophin in muscle cells.
5. Cell and Gene Therapies: Stem cell-based therapies and gene therapies that introduce functional dystrophin genes into affected muscles are under investigation. These therapies aim to replace damaged muscle cells with healthy ones.
6. Pharmacological Approaches: Various drugs are being explored to address the symptoms and complications of DMD, such as inflammation, fibrosis, and muscle weakness. These may help improve the quality of life for individuals with DMD.

7. Combination Therapies: Some research focuses on combining multiple therapeutic approaches to maximize benefits. For example, a combination of exon skipping and gene therapy may provide better outcomes than either treatment alone.
8. Supportive Care: In addition to disease-modifying therapies, providing comprehensive supportive care is crucial. This includes physical therapy, respiratory support, orthopedic interventions, and cardiac management to address the complications associated with DMD.
Clinical trials are an essential part of the research process for evaluating the safety and efficacy of these potential therapies. It's essential for individuals with DMD and their families to stay informed about ongoing research and consider participation in clinical trials when appropriate.

Table2: Research in DMD therapy

- **It's important to note that while there have been significant advancements in DMD therapy research, many of these treatments are still in experimental stages, and their long-term effectiveness and safety are not fully established. Patients and their healthcare providers should carefully consider the potential risks and benefits of these therapies.**

6.1 Advances in regenerative medicine and stem cell therapy in DMD

advances in regenerative medicine and stem cell therapy hold promise for Duchenne muscular dystrophy (DMD) treatment. Here are some key points:

1. Stem Cell Types: Various types of stem cells, including mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), are being investigated for their potential to repair and regenerate muscle tissue in DMD patients.

2. Cell Replacement: Stem cells can be differentiated into muscle precursor cells and transplanted into DMD-affected muscles. This can help replace damaged muscle cells and improve muscle function.

3. Exosome Therapies: Researchers are exploring the use of exosomes, which are small vesicles released by stem cells. These exosomes contain bioactive molecules that can promote muscle regeneration and reduce inflammation.

4. Combination Therapies: Combinations of stem cell therapy with other approaches, such as gene therapy or exon skipping, are being studied to enhance their effectiveness.

5. Clinical Trials: Clinical trials are ongoing to evaluate the safety and efficacy of stem cell-based therapies in DMD. These trials are essential for understanding the real-world potential of these treatments.

6. Challenges: Challenges include optimizing the delivery of stem cells to target muscles, ensuring their long-term survival, and addressing potential immune responses.

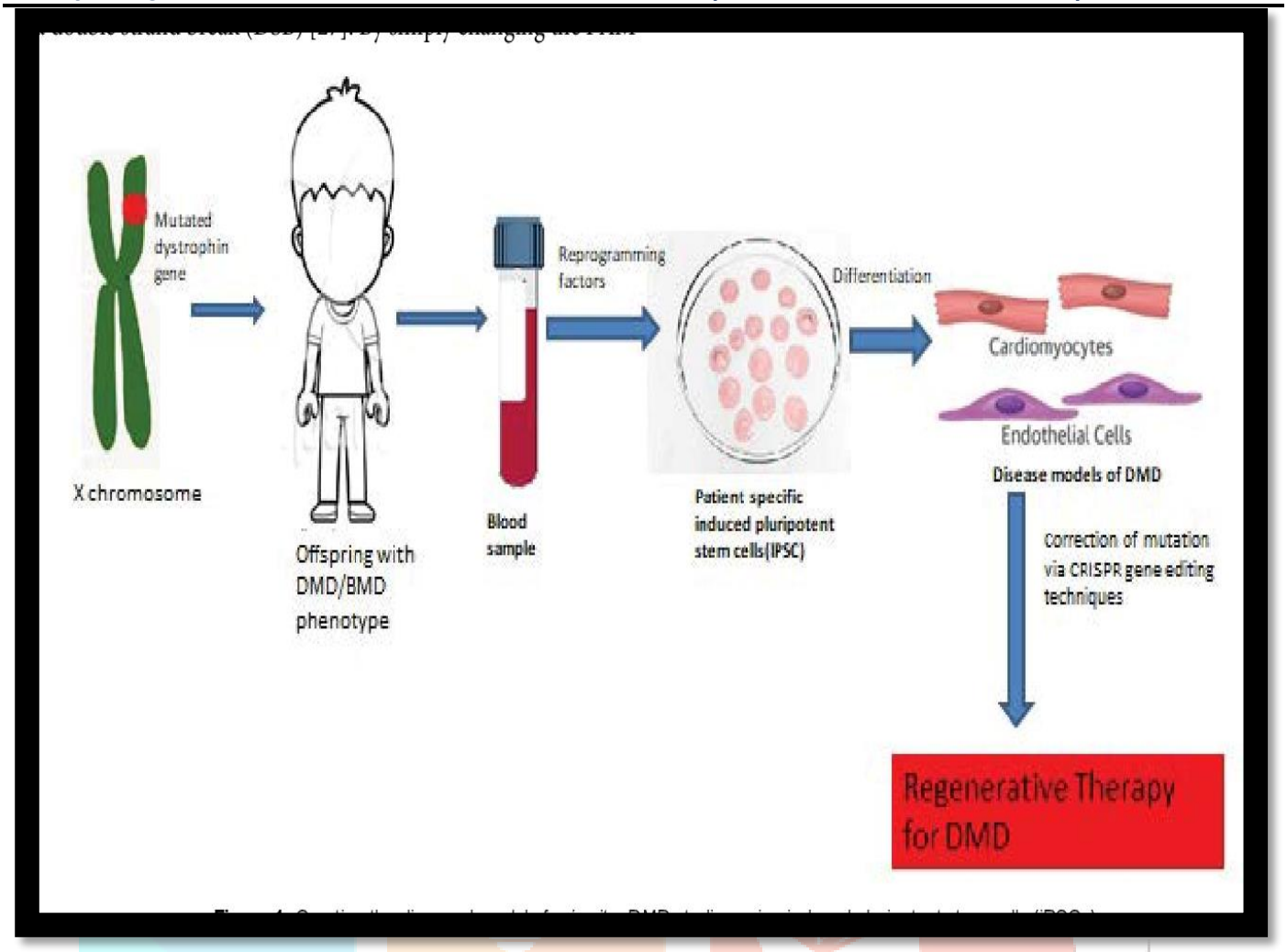


Fig 6.1: Regenerative Therapy of DMD

5. Impact on Patients and Families

The impact of Duchenne muscular dystrophy (DMD) on patients and their families is profound, extending to psychological and emotional aspects. Here are some key points:
1. Emotional Distress: DMD's progressive nature and its impact on mobility can lead to emotional distress for both patients and their families. Feelings of sadness, frustration, and anxiety are common.
2. Quality of Life: DMD can significantly affect a patient's quality of life due to the loss of physical abilities. This can lead to feelings of social isolation and a sense of missing out on typical childhood experiences.
3. Coping Mechanisms: Patients and families develop various coping mechanisms to deal with the challenges of DMD. These can include support groups, counseling, and learning to adapt to new routines and requirements.
4. Caregiver Stress: Family members, often parents, who serve as primary caregivers for DMD patients may experience high levels of stress and burnout due to the demanding nature of caregiving.
5. Hope and Resilience :Despite the challenges, many individuals and families affected by DMD demonstrate remarkable resilience and find hope in research advancements and support networks.

6. Impact on Siblings: DMD also affects siblings, who may feel neglected or burdened by the condition's demands. Open communication within the family is essential to address these issues.
7. Support Networks: Patient and family support networks, advocacy organizations, and access to mental health services play crucial roles in helping individuals cope with the psychological and emotional aspects of DMD.
It's important for healthcare providers to recognize and address these emotional and psychological aspects by offering psychological support, connecting families with resources, and fostering a holistic approach to care. Additionally, raising awareness about DMD and promoting inclusion and understanding within communities can contribute to a more supportive environment for affected individuals and their families.

Table3 : The impact of Duchenne muscular dystrophy (DMD) on patients and their families

6. Support networks and patient advocacy organizations

Support networks and patient advocacy organizations are invaluable for individuals and families affected by Duchenne muscular dystrophy (DMD). These organizations provide information, emotional support, and resources to help navigate the challenges associated with DMD. Some prominent DMD advocacy groups and support networks include:

1. Parent Project Muscular Dystrophy (PPMD): PPMD is one of the largest and most well-known advocacy organizations dedicated to DMD. They focus on research, education, and advocacy, providing a range of resources and support for patients and families.

2. Muscular Dystrophy Association (MDA): While MDA covers a range of neuromuscular disorders, they offer support and resources for individuals and families affected by DMD. They also fund research to find treatments and a cure.

3. CureDuchenne: This organization focuses on accelerating research and drug development for DMD. They also provide educational resources and support for families.

4. Jesse's Journey: Based in Canada, Jesse's Journey is a leading organization dedicated to funding research into DMD and providing support for Canadian families affected by the condition.

5. Action Duchenne: This UK-based organization supports research, advocates for better care, and provides resources and support to individuals and families living with DMD in the United Kingdom.

6. Duchenne Parent Project Belgium: This organization serves as a resource for families in Belgium and provides information, advocacy, and support related to DMD.

7. Local and Online Support Groups: Many local and online support groups exist, often organized by parents and caregivers of DMD patients. These groups can be a source of practical advice, emotional support, and camaraderie.

Fig 8: patient advocacy organizations

- These organizations offer a range of services, including information on the latest research, financial assistance, emotional support, and connections to specialists and medical professionals. They play a vital role in helping families affected by DMD feel less isolated and more empowered as they navigate the challenges associated with the condition.

Conclusion

- In conclusion, Duchenne muscular dystrophy is a severe neuromuscular disorder primarily affecting boys due to mutations in the dystrophin gene. The disease leads to progressive muscle weakness, cardiac complications, and orthopedic issues, ultimately impacting the quality of life and lifespan of affected individuals. Ongoing research aims to develop effective therapies to alleviate symptoms and restore dystrophin expression.

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