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A REVIEW ON DUCHENNE MUSCULAR DYSTROPHY: PATHOGENESIS, DIAGNOSIS, AND ADVANCEMENTS IN THERAPEUTIC STRATEGIES

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Abstract

Duchenne muscular dystrophy (DMD) is a severe X-linked neuromuscular disorder characterized by progressive muscle degeneration due to mutations in the DMD gene, which encodes the structural protein dystrophin. This condition primarily affects boys, leading to early loss of ambulation, cardiopulmonary complications, and premature death. Advances in molecular diagnostics and therapeutic approaches, including gene therapy, exon skipping, and cellular therapies, have revolutionized disease management. This review summarizes the current understanding of DMD's pathogenesis, clinical features, diagnostic modalities, and evolving therapeutic strategies.

Keywords: Duchenne muscular dystrophy, dystrophin, gene therapy, corticosteroids, exon skipping, muscle biopsy

Introduction

Duchenne muscular dystrophy (DMD) is the most common and severe form of muscular dystrophy, affecting approximately 1 in 3,500 to 5,000 live male births worldwide. It is inherited in an X-linked recessive pattern and caused by mutations in the DMD gene on chromosome Xp21.2, which codes for the dystrophin protein. Dystrophin is a vital component of the dystrophin-glycoprotein complex that maintains the integrity of muscle cell membranes.[1] In the absence of functional dystrophin, repeated muscle contractions lead to myofiber damage, inflammation, and fibrotic tissue replacement, culminating in progressive muscle weakness and disability.[2]

Pathophysiology

Dystrophin acts as a mechanical stabilizer during muscle contraction and provides signaling functions critical for cellular survival. Without dystrophin, muscle fibers are susceptible to mechanical stress, leading to sarcolemma damage, increased calcium influx, and activation of proteolytic enzymes. This cascade results in muscle necrosis, chronic inflammation, and replacement of muscle tissue with fibrotic and fatty tissue. Cardiomyopathy and respiratory muscle weakness are common complications due to the involvement of cardiac and diaphragm muscles.[3,4]

Clinical Presentation

Symptoms of DMD typically begin between the ages of 2 and 5 years. Early signs include delayed motor milestones, difficulty climbing stairs, waddling gait, frequent falls, and Gowers' sign. By the age of 12, most patients lose independent ambulation.[5] Skeletal deformities, including scoliosis, develop as the disease progresses. Cardiomyopathy becomes evident during adolescence, often progressing to heart failure. Respiratory insufficiency due to diaphragm and intercostal muscle involvement leads to reduced pulmonary function and increased risk of infections. Cognitive impairment, although variable, may occur due to dystrophin isoform expression in the brain.[6]

Diagnosis

Serum creatine kinase (CK) levels are significantly elevated in DMD and often provide the first clue. Genetic testing is the gold standard for diagnosis and can detect deletions, duplications, or point mutations in the DMD gene. Multiplex ligation-dependent probe amplification (MLPA) and next-generation sequencing (NGS) are commonly used techniques. Muscle biopsy, although rarely required due to the efficacy of molecular diagnostics, may show absent dystrophin on immunohistochemistry or Western blot analysis. Prenatal diagnosis is possible through chorionic villus sampling or amniocentesis in families with known mutations.[7]

Management

Corticosteroids (prednisone and deflazacort) remain the cornerstone of pharmacological treatment, slowing disease progression and improving motor and pulmonary function.[8] Cardiac care involves the use of ACE inhibitors and beta-blockers for early cardiomyopathy. Pulmonary support includes nocturnal non-invasive ventilation and cough-assist devices.[9] Physiotherapy, orthopedic interventions for scoliosis, and nutritional counseling are essential aspects of multidisciplinary care. Bisphosphonates may be prescribed to manage steroid-induced osteoporosis.[10]

Emerging Therapies

Exon-skipping therapy aims to restore the reading frame of the DMD gene, enabling production of a truncated but functional dystrophin protein. Eteplirsen (exon 51 skipping) and golodirsen (exon 53 skipping) are FDA-approved for specific mutations. Gene therapy using adeno-associated virus (AAV) vectors to deliver micro-dystrophin has shown promise in early trials. CRISPR/Cas9 genome editing is being explored to achieve permanent correction of DMD mutations.[11] Cell therapy, including transplantation of mesoangioblasts and induced pluripotent stem cells (iPSCs), represents a future avenue for muscle regeneration.[12]

Therapy Type	Therapy Name / Agent	Mechanism of Action	Stage of Use	Comments
Corticosteroids	Prednisone / Deflazacort	Anti-inflammatory, slows muscle degeneration	Standard of care	Improves muscle strength and function
Exon Skipping	Eteplirsen (Exon 51)	Restores reading frame to produce truncated dystrophin	FDA Approved (specific mutations)	Mutation-specific therapy
Exon Skipping	Golodirsen (Exon 53)	Same as above	FDA Approved (specific mutations)	Limited to ~8% of DMD cases
Gene Therapy	Micro-dystrophin (AAV vectors)	Delivers functional miniaturized dystrophin	Clinical trials	Ongoing safety/efficacy studies
Genome Editing	CRISPR/Cas9	Gene correction at DNA level	Preclinical/early clinical	Potential for permanent correction
Cell Therapy	Mesoangioblasts / iPSCs	Muscle regeneration via stem cells	Experimental	Challenges in cell delivery and survival
Cardiac Care	ACE inhibitors / Beta-blockers	Delay onset/progression of cardiomyopathy	Routine management	Standard in advanced stages
Respiratory Support	NIV / Cough-assist	Support weakened respiratory muscles	Supportive therapy	Improves quality of life and survival

Table 1.1 Current and Emerging Therapies for Duchenne Muscular Dystrophy

Prognosis and Quality of Life

With advances in multidisciplinary management, the life expectancy of individuals with DMD has increased into the third or even fourth decade. Cardiac and respiratory complications remain the leading causes of mortality. Psychosocial support, assistive technologies, and patient advocacy play crucial roles in improving quality of life. Regular monitoring and early intervention for complications are critical for optimizing outcomes.[13]

Conclusion

Duchenne muscular dystrophy is a complex genetic disorder with devastating consequences. However, advancements in genetic diagnostics and therapeutic modalities offer hope for improved outcomes. Continued research into disease-modifying treatments and supportive care strategies will be pivotal in transforming DMD from a fatal disease into a manageable chronic condition.

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