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Duchenne Muscular Dystrophy: An Overview of Diagnosis, Management, and Pharmacological Treatment

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Abstract

Duchenne muscular dystrophy (DMD) is a severe inherited neuromuscular disorder, primarily affecting males, characterized by progressive muscle weakness due to mutations in the dystrophin gene. This gene encodes dystrophin, a protein crucial for maintaining muscle cell integrity. DMD leads to the progressive loss of muscle function, cardiac complications, and intellectual disability. The disease typically results in wheelchair dependence by the early teens and early mortality due to respiratory or cardiac complications in the twenties.This overview aims to examine the diagnosis, management strategies, and pharmacological treatments for Duchenne muscular dystrophy. The article reviews current literature on the genetic basis, epidemiology, pathophysiology, and clinical manifestations of DMD. It also explores diagnostic methods including serum biomarkers, genetic testing, and muscle biopsy, as well as treatment options, particularly glucocorticoid therapy, and ongoing pharmacological interventions.Early detection of elevated serum creatine kinase (CK) levels, along with genetic testing, is key to confirming DMD. Current pharmacological treatments primarily focus on corticosteroids to slow muscle degeneration, and new investigational therapies are exploring gene editing and protein restoration. Additionally, cardiomyopathy, a major complication, requires regular monitoring and management.Duchenne muscular dystrophy remains a challenging condition with significant impact on patients and their families. Early diagnosis and intervention are essential for improving outcomes, while ongoing research offers hope for more effective therapies. Effective management includes a multidisciplinary approach focusing on pharmacological, physical, and cardiac care.

Keywords: *Duchenne Muscular Dystrophy, Dystrophin, Genetic Mutations, Pharmacological Treatment, Muscle Degeneration, Cardiomyopathy, Gene Therapy.*

Introduction

Duchenne muscular dystrophy (DMD) represents one of the most severe manifestations of inherited muscular dystrophies. It is the most prevalent hereditary neuromuscular disorder, with no particular preference for any specific racial or ethnic groups. The condition arises due to mutations in the dystrophin gene, which result in progressive degeneration and weakening of muscle fibers. Initially, the clinical presentation may include difficulty in walking, but over time, the condition progresses to such an extent that individuals are unable to perform activities of daily living and ultimately require wheelchair assistance. In addition to muscular weakness, patients frequently experience cardiac and orthopedic complications, with mortality typically occurring in their twenties, primarily due to respiratory muscle weakness or

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cardiomyopathy. The standard approach to managing DMD involves glucocorticoid treatment and physiotherapy, which aim to mitigate the orthopedic complications associated with the disease [1][2][3].

Etiology

DMD is a genetic disorder caused by mutations in the dystrophin gene, located on the Xp21 region of the X chromosome. It follows an X-linked recessive inheritance pattern, although approximately 30% of cases arise from new mutations. These mutations result in diseases collectively known as dystrophinopathies, which include Duchenne muscular dystrophy, Becker muscular dystrophy, and an intermediate form. The mutations lead to a diminished production of dystrophin protein, resulting in the disruption of the integrity of the myofiber membrane. This disruption causes repeated cycles of muscle fiber necrosis and regeneration, with fibrous connective tissue and fat gradually replacing muscle tissue, giving rise to the clinical manifestations of the disease. Although female carriers generally do not exhibit muscular weakness, symptomatic female carriers have been reported. Between 2.5% and 20% of female carriers may show symptoms. The Lyon hypothesis helps explain this, as it suggests that the normal X chromosome may become inactivated, while the mutated X chromosome is expressed. Female carriers may develop symptoms if they have conditions such as Turner syndrome (45X) or a mosaic Turner karyotype, which involves balanced X-autosome translocations with breakpoints within the dystrophin gene, or preferential inactivation of the normal X chromosome. In some cases, females with a normal karyotype may exhibit non-random X chromosome inactivation, leading to reduced expression of the normal dystrophin allele. The dystrophin gene is one of the largest in the human genome, comprising 79 exons within a coding sequence that spans 2.5 Mb of DNA. It codes for the dystrophin protein, which weighs 427 kDa. The majority of mutations (70% to 80%) in the dystrophin gene are deletions or duplications, while point mutations account for 20% to 30% of cases. Dystrophin is expressed in striated and cardiac muscles, as well as in the brain and retina, with the expression in the brain being lower than in muscle. This explains some of the central nervous system manifestations observed in DMD [6].

Epidemiology

Duchenne muscular dystrophy (DMD) adheres to an X-linked recessive inheritance pattern, which results in a higher prevalence in males compared to females. The incidence of DMD is estimated to be approximately 1 in 3,600 live-born male infants, and some studies in the United States report a prevalence of 2 per 10,000 males. This pattern of inheritance explains why DMD is almost exclusively found in males, with females being typically carriers unless they have an associated genetic condition such as Turner syndrome. Due to the genetic nature of the disease, DMD manifests in males when they inherit the mutated X chromosome from their mothers, who are often asymptomatic carriers. As one of the most common and severe congenital myopathies, DMD poses significant health challenges worldwide. The estimated prevalence and incidence statistics suggest that DMD continues to be a leading cause of disability in children and young adults. Furthermore, the severity and early onset of symptoms make DMD a debilitating condition, with affected individuals often requiring wheelchair assistance by their early teens. The impact of DMD is not only physical but also socio-economic, as families and healthcare systems face long-term management costs, with limited therapeutic options currently available. Early diagnosis and intervention are critical in managing the disease and improving quality of life, but the availability of resources and care can vary significantly across regions and healthcare systems.

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	Duchenne muscular dystrophy	Becker muscular dystrophy
Etiology	X-linked recessive, dystrophin gene mutation	
Dystrophin protein	Absent	Reduced
Age of onset	2–5 years	> 15 years
Symptoms	Rapid progression, inability to walk by approx. 12 years	Less severe, slower progression, cardiac involvement is more common
Diagnostics	↑↑ Creatine kinase, ↑ serum aldolase, genetic analysis (confirmatory test), muscle biopsy	
Treatment	Supportive, glucocorticoids	
Life expectancy	~ 30 years	~ 40–50 years

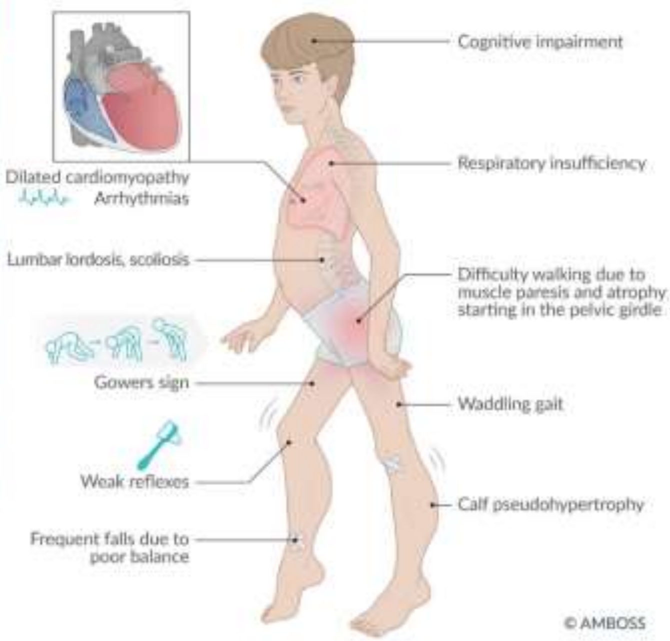

Figure 1. Duchenne muscular dystrophy (DMD)

Pathophysiology

Dystrophin, a crucial cytoskeletal protein, is integral to the structural integrity of muscle cells. It interacts with both the cytoskeleton and extracellular matrix, facilitating the cohesion of muscle fibers and protecting them from mechanical stress during contraction. Dystrophin is particularly abundant in striated muscles, such as skeletal and cardiac muscles, as well as in non-muscle tissues like the brain. It is part of the dystrophin-glycoprotein complex (DGC), which anchors the muscle fiber membrane to the extracellular matrix and stabilizes the sarcolemma. In Duchenne muscular dystrophy (DMD), mutations in the dystrophin gene lead to a complete absence or severe deficiency of dystrophin and DGC proteins. This absence causes a cascade of events detrimental to muscle function. Without dystrophin, the muscle cell membrane becomes fragile, and its permeability increases, making the muscle fibers more vulnerable to damage. The disruption of calcium homeostasis is another significant consequence, as elevated intracellular calcium levels activate proteases and other enzymes that further damage the muscle fibers. Additionally, oxidative stress exacerbates the cellular damage, contributing to the necrosis of muscle cells. Over time, as DMD progresses, the regenerative ability of muscle tissue declines. This exhaustion of muscle regeneration leads to the replacement of muscle fibers by connective and adipose tissue, further impairing muscle function. The pathology of DMD is thus characterized by a progressive loss of muscle tissue and an increasing burden of non-muscle tissue.

Histopathology

Histopathological examination of muscle biopsies from patients with Duchenne muscular dystrophy (DMD) reveals a distinctive pattern of muscle fiber damage and regeneration. One of the key features is the proliferation of endomysial connective tissue, which occurs as a response to the ongoing cycles of muscle fiber degeneration and repair. This fibrotic tissue gradually replaces the muscle fibers, leading to an increasing loss of muscle function. In addition to connective tissue proliferation, muscle fibers often show signs of degeneration and regeneration. This is reflected in the presence of necrotic muscle fibers, which are typically surrounded by a mononuclear cell infiltrate composed of inflammatory cells. These cells contribute to the tissue damage and are indicative of the chronic inflammatory processes that occur in DMD. As the disease progresses, muscle fibers are increasingly replaced by adipose and fat tissue, a process

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that worsens muscle weakness and functional impairment. The accumulation of fat and connective tissue, along with the lack of functional muscle fibers, results in the characteristic wasting of muscles observed in DMD. These histopathological changes highlight the underlying pathophysiological mechanisms of the disease, which include continuous cycles of muscle fiber necrosis, incomplete regeneration, and eventual replacement with non-muscle tissues such as fat and connective tissue. This histological pattern is crucial for confirming the diagnosis and understanding the progression of DMD.

History and Physical

The initial development of individuals with Duchenne muscular dystrophy (DMD) is typically normal, with milestones generally being reached at a slightly delayed or average rate. However, there is a noticeable delay in growth velocity, leading to short stature. During infancy, mild hypotonia may be observed, and poor head control could be an early indication of muscle weakness. Patients generally do not exhibit atypical facial features, though as facial muscle weakness progresses, a transverse or horizontal sign may become visible in later childhood. The onset of weakness and ambulatory difficulties is often first noted between the ages of 2 and 3 years, marked by signs such as toe walking, difficulty with running, climbing stairs, and frequent falls. Proximal muscle weakness is more prominent than distal weakness, with the lower limbs affected more severely than the upper limbs. In ambulatory individuals, a higher frequency of fractures occurs due to repeated falls. Progressive lumbar lordosis and scoliosis, along with muscle contractures, are common, leading to pulmonary compromise due to impaired respiratory function. Contractures may affect the ankles, knees, hips, and elbows. The calves may become enlarged due to the replacement of muscle tissue with fat, resulting in pseudohypertrophy, which is a hallmark feature of DMD. In addition, hypertrophy of the tongue and forearm muscles, though less typical, may be observed. By the age of 12, most patients require a wheelchair. Pharyngeal weakness may result in aspiration, nasal regurgitation, and a nasal-sounding voice. Late-stage manifestations may include incontinence due to sphincter weakness and, rarely, malignant hyperthermia following anesthesia. Female carriers can occasionally exhibit early and progressive muscular dystrophy.

Intellectual Disability

Intellectual impairment is a consistent feature among patients with Duchenne muscular dystrophy (DMD), though the severity varies. Approximately 20% to 30% of individuals with DMD exhibit an intelligence quotient (IQ) of less than 70, but the degree of cognitive impairment does not necessarily correlate with the severity of the muscular condition. Most individuals display only mild learning disabilities and are capable of functioning in a regular classroom setting. In addition to learning difficulties, patients with DMD are at a higher risk of developing epilepsy compared to the general population, with seizures being a frequent comorbidity. Less commonly, patients may exhibit autism-like behavior, further complicating the clinical picture. The cognitive and behavioral aspects of DMD highlight the multifaceted nature of the disease, which not only affects muscle function but also neurodevelopmental outcomes. These intellectual and behavioral challenges can impact the quality of life for individuals with DMD, as well as their families, requiring additional support services and educational accommodations. While cognitive deficits are often present, the range of intellectual abilities is broad, and many patients can lead relatively independent lives with appropriate interventions. Nevertheless, the dual burden of muscular and cognitive impairments emphasizes the need for comprehensive care plans that address both physical and mental health in DMD management.

DMD Associated Cardiomyopathy

Cardiomyopathy associated with Duchenne muscular dystrophy (DMD) generally begins to manifest in the early teens and becomes prevalent in nearly all patients by their twenties. Common early signs include persistent tachycardia and heart failure. The progression of the disease results in dilated cardiomyopathy, characterized by extensive fibrosis in the posterobasal left ventricular wall, which is often the earliest site of involvement. As the disease advances, this fibrosis may spread to the lateral free wall of the left ventricle, contributing to further functional deterioration. The involvement of the posterior papillary muscle can lead to significant mitral regurgitation, which exacerbates the heart's inefficiency. Conduction abnormalities,

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particularly within the inter- and intra-atrial pathways, can also be observed, sometimes affecting the atrioventricular (AV) node. Supraventricular arrhythmias are common in patients with DMD-related cardiomyopathy, and the risk of other arrhythmias increases as the disease progresses. Physical examination findings in these patients often include pseudohypertrophy of the calf muscles and, less frequently, the quadriceps. A shortening of the Achilles tendon may also be noted, which contributes to the characteristic gait abnormalities observed in DMD. Reflexes are typically diminished or absent in the later stages of the disease; for instance, ankle reflexes tend to be preserved until late, while deep tendon reflexes (DTRs) in the knees may be lost by the age of six. Gowers' sign, where patients use their arms to rise from a seated position, is another hallmark of DMD. These cardiovascular and neuromuscular findings underscore the multifaceted nature of DMD, which necessitates regular cardiovascular monitoring and intervention.

Evaluation

The evaluation of Duchenne muscular dystrophy (DMD) begins with a clinical suspicion based on the patient's presentation of muscle weakness, characteristic physical findings, and a potential family history of the disease. Diagnostic testing includes measuring serum creatine kinase (CK) levels, conducting muscle biopsies, genetic testing, and performing electrocardiograms (ECG) to assess for cardiomyopathy. Serum CK levels are typically elevated even before clinical symptoms become evident and may also be elevated in neonates. These levels peak by age two and may exceed 10 to 20 times the normal range. As the disease progresses and muscle tissue is replaced by fibrous and adipose tissue, serum CK levels generally decline. Additionally, other muscle enzymes, such as aldolase and aspartate aminotransferase (AST), may also be elevated. Elevated CK levels may also be present in asymptomatic carriers, with the highest levels typically observed between ages 8 and 12. A muscle biopsy is an essential diagnostic tool for confirming DMD, revealing characteristic findings such as endomysial connective tissue proliferation, scattered degeneration and regeneration of muscle fibers, muscle fiber necrosis with mononuclear cell infiltration, and replacement of muscle tissue by fat. The quadriceps femoris and gastrocnemius muscles are most commonly biopsied. Electromyography (EMG) may show myopathic features, although it is nonspecific, with normal motor and sensory nerve conduction velocities and no evidence of denervation. Genetic analysis is a key diagnostic method, identifying mutations in the dystrophin gene. Immunoblotting for dystrophin can predict disease severity, with DMD patients exhibiting less than 5% of normal dystrophin levels. Polymerase chain reaction (PCR) and multiplex ligation-dependent probe amplification (MPLA) are highly sensitive methods used to detect genetic mutations, including deletions and duplications. Fluorescence in situ hybridization (FISH) is occasionally used to identify small mutations. ECG findings are indicative of DMD-associated cardiomyopathy, with tall R waves in leads V1-V6, deep Q waves in leads I, aVL, and V5-6, and conduction abnormalities such as supraventricular arrhythmias and intra-atrial conduction issues. Finally, echocardiography is crucial for detecting dilated cardiomyopathy, which is almost universally present by the patient's twenties [7] [8] [9].

Treatment / Management

Currently, no medical cure exists for Duchenne muscular dystrophy (DMD), and the disease generally carries a poor prognosis. Management strategies primarily focus on glucocorticoid therapy, preventing contractures, and providing medical support for cardiomyopathy and respiratory issues [10][11].

Glucocorticoid Therapy

Glucocorticoid treatment plays a pivotal role in managing DMD by reducing myotube apoptosis and slowing myofiber necrosis. Prednisone is typically administered to patients aged four years and older, especially when muscle function begins to deteriorate or plateaus. The standard dosage of prednisone is 0.75 mg/kg daily, or alternatively, 10 mg/kg per week, administered over two consecutive days during the weekend. An alternative to prednisone is deflazacort, an oxazoline derivative, which is often favored due to its superior side-effect profile. Its recommended dosage is 0.9 mg/kg per day, with a 1:1.3 dose equivalency to prednisone. Clinical studies have demonstrated that glucocorticoid therapy can lead to significant improvements in pulmonary function, delay scoliosis onset, and slow the progression of cardiomyopathy, ultimately enhancing overall survival rates.

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Cardiomyopathy

The treatment for cardiomyopathy in DMD typically includes angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, which, according to early studies, may delay disease progression and prevent heart failure onset. In cases of advanced heart failure, digoxin and diuretics are used, as in other forms of cardiomyopathy. Regular cardiology assessments, including ECGs and echocardiograms, are essential, starting at diagnosis or by age six. Surveillance should continue biennially until age 10, after which annual assessments are recommended. If cardiomyopathy is detected, more frequent monitoring every six months is advised.

Pulmonary Interventions: Pulmonary function tests should be conducted before the patient begins to rely exclusively on a wheelchair. After reaching age 12, testing should be repeated biannually or if vital capacity falls below 80% of the predicted value.

Orthopedic Interventions: The primary orthopedic approach involves physiotherapy aimed at preventing contractures. Patients may benefit from passive stretching exercises, the use of ankle-foot orthoses during sleep, and long leg braces for ambulation assistance. Surgical intervention may be necessary in advanced stages for contracture release, and scoliosis correction surgery can improve pulmonary function.

Nutrition: Malnutrition, including obesity, poses a significant risk to DMD patients. Calcium and vitamin D supplementation is critical to prevent osteoporosis, a side effect of prolonged steroid use. Dual-energy X-ray absorptiometry (DEXA) scans are recommended starting at age three, followed by annual evaluations.

Exercise: Gentle exercises are encouraged for all patients to prevent disuse atrophy, with swimming and recreational exercises being particularly beneficial. Physical activity should be reduced if muscle pain or myoglobinuria develops.

Novel Therapies: Emerging gene therapies, such as those involving RNA-binding medications that bypass defective codons, are being explored. Eteplirsen, an FDA-approved exon 51-skipping antisense oligonucleotide, is one such treatment, offering the potential for producing a shortened but functional version of dystrophin.

Differential Diagnosis

Becker Muscular Dystrophy (BMD): BMD shares similarities with DMD but has a later onset and longer survival expectancy. Patients with BMD typically present with higher levels of dystrophin protein, distinguishing it from DMD.

Intermediate Form of Muscular Dystrophy: This variant exhibits dystrophin levels between those seen in DMD and BMD, resulting in a clinical presentation that falls between the two conditions.

Myotonic Muscular Dystrophy: An autosomal dominant inherited disorder, myotonic dystrophy primarily affects the distal muscles. Unlike DMD, the ability to walk is often preserved, and the disease typically manifests later in life.

Limb-Girdle Muscular Dystrophy: This hereditary form of muscular dystrophy primarily targets the muscles of the hip and shoulder girdles, differing from DMD's more widespread muscle involvement.

Congenital Myotonic Dystrophies: This category includes several inherited disorders associated with muscular dystrophy, characterized by greater severity at birth but generally a more benign progression through life. There is a notable association with brain malformations. Examples include Ullrich-type muscular dystrophy, Fukuyama-type congenital muscular dystrophy, and muscular dystrophy linked to Walker-Warburg syndrome.

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Prognosis

The prognosis for individuals with DMD is generally poor, with most patients becoming wheelchair-dependent by age 12. The primary causes of death are respiratory and cardiac complications, which usually arise in the teens or 20s. Additional causes of mortality include pneumonia, aspiration, and airway obstruction.

Enhancing Healthcare Team Outcomes

The management of Duchenne muscular dystrophy (DMD) requires a collaborative approach involving an interprofessional healthcare team. This team should consist of specialty-trained nurses, therapists, and various healthcare providers working together to ensure optimal care for patients. Neuroscience and rehabilitation nurses play a crucial role by providing direct care, monitoring patient progress, and communicating any changes to the team. Primary care providers, physiatrists, and neurologists are key contributors in the management process. Additionally, consultations with orthopedists and thoracic surgeons may be necessary to address specific complications that arise. Pharmacists are integral in reviewing the patient's medication regimen, ensuring proper drug selection, and identifying potential drug-drug interactions. Since DMD currently has no cure, all therapeutic interventions are aimed at alleviating symptoms and improving quality of life, making them palliative in nature. As the disease progresses, the involvement of palliative care physicians and nurses becomes essential to manage end-of-life issues and provide comfort. The central goal in managing DMD is to ensure that patients maintain a good quality of life despite the limitations imposed by the disease. It is important to recognize that aggressive treatments, while well-intentioned, may sometimes cause more harm than benefit, highlighting the need for careful consideration of treatment options and prioritizing the patient's comfort and well-being [12-13].

Conclusion

Duchenne muscular dystrophy (DMD) is a devastating genetic disorder primarily affecting males due to mutations in the dystrophin gene, leading to progressive muscle weakness and debilitating complications. Early clinical signs, including delayed motor milestones, muscle weakness, and gait abnormalities, are critical for initial suspicion, with diagnosis confirmed through elevated serum creatine kinase (CK) levels, genetic testing, and muscle biopsies. As the disease progresses, it involves a progressive loss of muscle fibers, replaced by fibrous and adipose tissue, resulting in muscle wasting and weakening, affecting mobility and respiratory function. The management of DMD requires a multifaceted approach. Currently, glucocorticoids are the mainstay of pharmacological therapy, aimed at slowing muscle degeneration and improving strength, while physiotherapy helps mitigate the orthopedic complications associated with the disease. However, as DMD progresses, other complications such as cardiomyopathy and intellectual disabilities must be addressed. Cardiac involvement, which typically manifests in the early teens, is a leading cause of morbidity and requires vigilant monitoring and timely intervention. Intellectual disabilities and other neurodevelopmental challenges in DMD patients further complicate care, emphasizing the need for educational and psychological support. In addition to glucocorticoids, emerging therapies such as gene editing, exon skipping, and protein restoration therapies are being explored to target the underlying genetic mutations and improve clinical outcomes. These therapeutic advancements offer hope for future treatments that may slow disease progression or even halt its effects. Given the severity of DMD and the current limitations of treatment options, early diagnosis remains crucial. Genetic counseling is important for family planning, especially for females who are carriers. While DMD continues to be a condition with no definitive cure, ongoing research offers optimism for breakthroughs in gene-based therapies. With advancements in both pharmacological and gene-based treatments, the future of DMD care looks promising, though continuous management and support remain essential to improving the quality of life for patients and their families.

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التصلب العضلي الدوشيني: نظرة عامة على التشخيص والإدارة والعلاج الدوائي

الملخص :

الخلفية: التصلب العضلي الدوشيني (DMD) هو اضطراب عصبي عضلي وراثي شديد، يؤثر أساسًا على الذكور، ويتميز بضعف العضلات التدريجي بسبب الطفرات في جين الديستروفين. يرمز هذا الجين إلى الديستروفين، وهو بروتين حاسم للحفاظ على تكامل خلايا العضلات. يؤدي DMD إلى فقدان تدريجي لوظائف العضلات، والمضاعفات القلبية، والإعاقة الفكرية. عادة ما يؤدي المرض إلى الاعتماد على الكراسي المتحركة في سن المراهقة المبكرة والموت المبكر بسبب المضاعفات التنفسية أو القلبية في العشرينات.

الهدف: تهدف هذه النظرة العامة إلى دراسة التشخيص واستراتيجيات الإدارة والعلاجات الدوائية لمرض التصلب العضلي الدوشيني.

الطرق: يستعرض المقال الأدبيات الحالية حول الأساس الوراثي، وعلم الأوبئة، والفسيولوجيا المرضية، والتظاهرات السريرية لـ DMD.كما يستكشف طرق التشخيص بما في ذلك المؤشرات الحيوية في المصل، والفحوصات الجينية، والخزعة العضلية، بالإضافة إلى خيارات العلاج، خاصة علاج الجلوكوكورتيكويد، والتدخلات الدوائية المستمرة.

النتائج: يعد الكشف المبكر عن مستويات عالية من الكرياتين كيناز (CK) في المصل، إلى جانب الفحوصات الجينية، أمرًا أساسيًا لتأكيد تشخيص DMD. تركز العلاجات الدوائية الحالية أساسًا على الستيرويدات القشرية لإبطاء تدهور العضلات، بينما تستكشف العلاجات التجريبية الجديدة تقنيات تعديل الجينات واستعادة البروتينات. بالإضافة إلى ذلك، تتطلب اعتلال عضلة القلب، وهو من المضاعفات الرئيسية، مراقبة وإدارة منتظمة.

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الخلاصة: يظل التصلب العضلي الدوشيني حالة صعبة ذات تأثير كبير على المرضى وأسرهم. يعد التشخيص المبكر والتدخل أمرين أساسيين لتحسين النتائج، بينما يقدم البحث المستمر أملًا في العلاجات الأكثر فعالية. يشمل الإدارة الفعالة نهجًا متعدد التخصصات يركز على الرعاية الدوائية، والبدنية، والقلبية.

الكلمات المفتاحية: التصلب العضلي الدوشيني، الديستروفين، الطفرات الجينية، العلاج الدوائي، تدهور العضلات، اعتلال عضلة القلب، علاج الجينات.