“A COMPREHENSIVE REVIEW ON MUSCULAR MYOPATHIES: FROM CLINICAL FEATURES TO FUTURE DIRECTIONS”

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Abstract

Myopathies are a disparate group of muscle disorders that target the structure, metabolism, or function of skeletal muscle. Weakness, stiffness, cramping, and spasms are the most common signs and symptoms, frequently resulting in impaired daily activities. Muscle pain and rhabdomyolysis are also observed in some myopathies. Genetic muscular disorders, e.g., muscular dystrophies, are uncommon yet clinically, genetically, and biochemically heterogeneous, characterized by progressive muscle weakness in the proximal limb muscles and potential impairment of respiratory, cardiac, and swallowing muscles. Congenital myopathies appear in infancy or childhood and are linked to abnormalities in the muscle contractile apparatus. Acquired myopathies, e.g., inflammatory, metabolic, endocrine, and drug-induced, have varied clinical presentations. Diagnosis usually depends on an integration of history, clinical presentation, laboratory studies, imaging, biopsy, and genetic analysis. Treatment approaches depend on etiology, from immunosuppressive treatment in inflammatory patterns to gene-based and supportive therapies in genetic patterns. Gene editing, stem cell therapies, personalized medicine, and drug repurposing are among the directions that are being considered for the future, all of which are toward moving away from symptomatic relief and into curative treatment.

Key words - Muscular Myopathy, muscle weakness, skeletal muscles disorder, clinical diagnosis.

Introduction

Myopathy is derived from the Greek terms "myo" (muscle) and "pathy" (disease), which relate to diseases that involve the muscles. The most frequent symptoms are muscle weakness, stiffness, cramping, and spasms, which tend to disrupt normal activities. Muscle aching and rhabdomyolysis (muscle breakdown) can also happen in some instances. [1]

Inherited muscular diseases are a general category encompassing dystrophic and non-dystrophic myopathies. Of these, muscular dystrophies (MD) are uncommon but debilitating inherited

disorders. They are genetically and clinically heterogeneous, but they share the common feature of progressive muscle weakness, often initiating in the limb, face, or trunk muscles, and extending to the cardiac, respiratory, and swallow muscles. Muscle biopsy in MD usually shows muscle fiber degeneration, fibrosis, and occasionally inflammation (e.g., in dysferlinopathies). [2]

History

Muscular myopathies have existed throughout human history for centuries, although back then, individuals didn't know why some individuals increasingly weakened or had trouble with basic activities such as walking, going up stairs, or raising their arms. During the 19th century, physicians started examining muscles more intensely, employing microscopes to observe that these issues originated within the muscles themselves and not from nerves.

In the early part of the 20th century, Duchenne muscular dystrophy was first described in children by Dr. Guillaume Duchenne, who meticulously documented their struggles and charted the disease's course. Physicians around the same time recognized inflammatory myopathies such as polymyositis and dermatomyositis, observing how muscle weakness may be accompanied by joint pain or characteristic rashes on the skin.

As medicine and genetics improved, scientists learned that most myopathies are inherited, and a few are associated with autoimmune or hormonal issues, like thyroid illness. Now, with today's science, we are able to accurately identify these diseases and investigate treatments designed to allow individuals to lead more complete, more powerful lives, transforming what was an enigmatic, debilitating illness into one that is familiar and treatable. [3]

Types of Myopathies:

- Inherited Myopathies: Genetic mutations disrupt muscle protein production, leading to progressive muscle weakness and wasting. Examples include muscular dystrophies and congenital myopathies.

- Inflammatory Myopathies: Autoimmune disorders cause muscle inflammation and damage, resulting in muscle weakness. Examples include polymyositis and dermatomyositis.

- Metabolic Myopathies: Impaired muscle energy processing and utilization lead to muscle weakness, cramps, and exercise intolerance. Examples include glycogen storage diseases and lipid storage myopathies.

Pathophysiology

"Myopathy" is a term used for a collection of disorders in which the basic lesion is in skeletal muscle fibers, impairing muscle function.

1. Genetic & Structural Defects

Genetic defects in structural proteins (e.g., dystrophin, sarcoglycans, laminin) → destabilization of the sarcolemma.

Weak membranes microtear with contraction → increased calcium influx, CK leakage into blood.

Increased calcium activates proteases → fiber necrosis. [4]

2. Metabolic Defects

Mutations in enzymes of glycogen, lipid, or mitochondrial metabolism → defective ATP production.

Causes exercise intolerance, cramps, rhabdomyolysis, and myoglobinuria.[5]

3. Inflammatory Pathways

In autoimmune myopathies (e.g., polymyositis, dermatomyositis):

CD8+ T-cells and autoantibodies attack muscle fibers.

Inflammatory cytokines induce necrosis and regeneration cycles.

Results in fibrosis and fatty infiltration of muscle tissue. [6]

4. Degeneration–Regeneration Cycle

Damaged muscle fibers → macrophage invasion → activation of satellite cells.

Repeated damage-repair cycle → loss of muscle fibers, replaced by connective tissue and fat.

Clinical result → progressive weakness and atrophy. [7]

5. Clinical Correlation

Proximal muscle weakness (difficulty climbing stairs, lifting objects).

Muscle wasting in advanced stages.

Fatigue, cramps, and myoglobinuria in metabolic myopathies.

Elevated serum CK as a biomarker of muscle breakdown. [8]

- Definition: Myopathy = a disorder where the muscle fibers themselves are structurally and functionally abnormal, not caused primarily by nerve problems.

- Underlying causes:

Genetic (hereditary): mutations in muscle proteins (e.g., dystrophin, sarcoglycan, channels, enzymes).

Acquired: inflammation (polymyositis, dermatomyositis), metabolic disorders, endocrine disturbances, toxins/drugs (e.g., statins, steroids). [9]

- Cellular mechanisms:

* Cycle of muscle fiber degeneration/regeneration, resulting in fibrosis and fat replacement.

* Inflammatory infiltration in autoimmune/inflammatory myopathies. [10]

* Mitochondrial dysfunction or enzyme deficiency in metabolic myopathies, resulting in impaired ATP production.

* Channelopathies impair calcium/sodium management, causing disruption of contraction. - Outcome: Progressive weakness through diminished contractile force, energy disturbance, and loss of muscle fibre. [11]

[Etiological Factors]

- Genetic mutations (dystrophin, sarcoglycan, myosin, etc.)
- Acquired causes (drugs, toxins, infections, autoimmune)
- Metabolic or mitochondrial defects

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[Molecular & Cellular Alterations]

- Abnormal protein synthesis
- Enzyme deficiencies
- Ion channel dysfunction
- Impaired mitochondrial function

↓

[Structural & Functional Abnormalities]

- Instability of sarcolemma
- Dysregulation of calcium influx
- Depletion of energy (↓ ATP)
- Abnormal glycogen / lipid accumulation

↓

[Muscle Fiber Damage & Degeneration]

- Fiber necrosis
- Inflammatory cell infiltration
- Oxidative stress (ROS generation)
- Loss of contractile proteins

↓

[Repair Attempts & Chronic Changes]

- Incomplete regeneration (failure of satellite cells)
- Fibrosis & replacement by connective tissue
- Fatty infiltration
- Progressive atrophy of muscle

↓

[Clinical Manifestations]

- Weakness of muscle (proximal/distal)
- Fatigue & exercise intolerance
- Myalgia & cramps
- Contractures & muscle wasting
- Severe: weakness of respiratory muscles, cardiomyopathy. [12]

Etiology

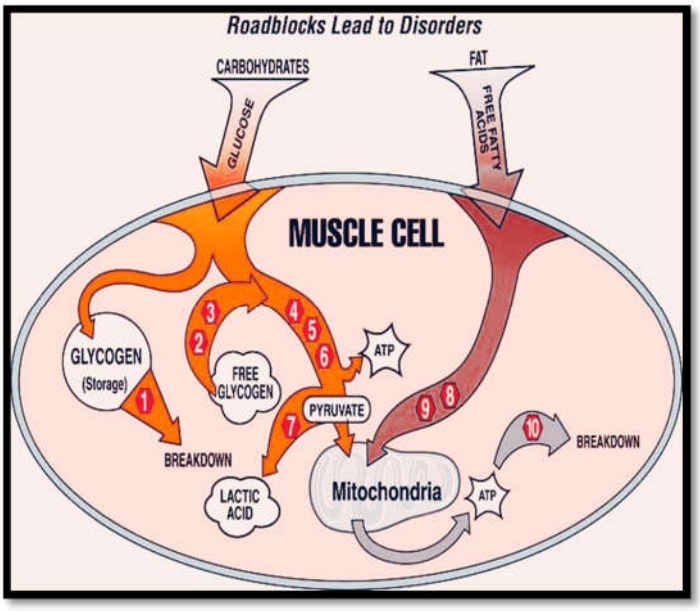

Fig.01

Problems lie in each Disease are:

1. Acid maltase deficiency

2. Muscle phosphorylase deficiency

3. Debrancher enzyme deficiency

4. Phosphofructokinase deficiency

5. Phosphoglycerate kinase deficiency

6. Phosphoglycerate mutase deficiency

7. Lactate dehydrogenase deficiency

8. Carnitine palmitoyl transferase deficiency

9. Carnitine deficiency

10. Myoadenylate deaminase deficiency

Skeletal muscles usually rely on carbohydrate and fat for their energy supply. Such fuels may be stored within the muscle (glycogen) or brought in directly from the blood (glucose and fatty acids).

When a gene defect disrupts the processing of specific fuels, energy deficits can occur, along with the production of toxic byproducts.

Certain individuals can avoid their defects by modifying their diet or exercise to extract energy more effectively from unaffected pathways. [13]

Clinical feature

Myopathy is a general term applied to disorders that are mainly characterized by skeletal muscles. The characteristic feature of myopathy is weakness in the muscles, which may develop gradually or even more rapidly in some cases, based on the type of myopathy. The weakness is most commonly symmetric in nature, implying that it is equal on both sides of the body. Proximal muscles, including those in the shoulders, upper arms, hips, and thighs, are usually involved first. Consequently, patients will find it hard to perform activities such as climbing stairs, standing up from a seated position, picking up objects, or brushing hair.

Aside from weakness, muscle fatigue is also a common complaint. Patients can complain of being excessively exhausted following even slight physical exertion. The tiredness is usually attributed to the compromised capacity of muscles to produce force or sustain contraction.

Even though weakness is the most outstanding symptom, other signs may occur as well. Muscle pain (myalgia), cramps, or stiffness appear in some patients, but these symptoms are generally milder than weakness. In some metabolic or toxic myopathies, pain is more evident.

As the disease worsens, muscle atrophy can occur due to chronic weakness. In others, such as certain inherited myopathies (e.g., Duchenne muscular dystrophy), calf muscles can even appear to be swelling, a condition termed pseudohypertrophy that is actually due to replacement of muscle tissue by fat and fibrous tissue.

Involvement of the particular groups of muscles can cause characteristic clinical issues.

Such as:

Oropharyngeal muscles: Impairment of these muscles can result in swallowing difficulty (dysphagia) or nasal speech.

Respiratory muscles: In extreme cases, paralysis of the diaphragm and chest muscles results in respiratory distress and, eventually, in advanced cases, respiratory failure.

Neck and axial muscles: Head drooping or poor posture may be seen in the patient.

The pattern of weakness is also useful for giving clues to the diagnosis. For example, inflammatory myopathies such as polymyositis and dermatomyositis usually present with proximal weakness, while distal weakness (hands and feet) is characteristic of some genetic myopathies.

Other systemic manifestations may occasionally be associated with muscle involvement. In the inflammatory myopathies, patients are sometimes seen with skin rashes, arthralgias, or interstitial lung disease. In the metabolic myopathies, intolerance to exercise and the occurrence of episodes of muscle breakdown (rhabdomyolysis) can occur.

Generally, the clinical presentation of myopathy is heterogeneous based on its etiology—genetic, inflammatory, metabolic, endocrine, or drug-induced. Nevertheless, the fundamental features are weakness, fatigue, and potential muscle wasting, with other symptoms depending on the muscle groups affected. Scrutiny by clinical examination, complemented by laboratory and imaging studies, facilitates differentiation among various myopathies.

- Muscle weakness, particularly in proximal muscles

- Muscle cramps and stiffness

- Exercise intolerance and fatigue

- Muscle wasting and atrophy [14]

Symptoms

- Weakness of muscles (characteristically symmetric, proximal > distal in most varieties).

- Intolerance to exercise and premature fatigue.

- Wasting (atrophy) of muscle or occasionally pseudohypertrophy.

- Pain and cramps in some metabolic or inflammatory varieties.

- Impairment of motor function: stair climbing, getting up from a sitting position, and lifting arms.

- With severe disease: respiratory weakness, dysphagia, and cardiac manifestations. [15]

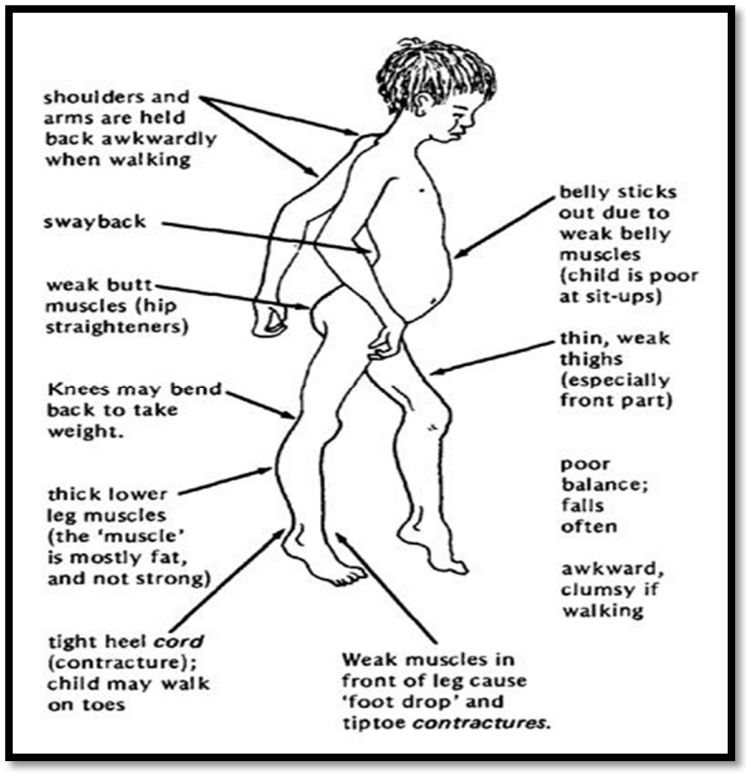

Fig.02

Diagnosis

The diagnosis of myopathies is a combination of clinical assessment, laboratory investigations, imaging, and occasionally genetic analysis or biopsy. The initial step is a thorough history and clinical examination. History entails the age of presentation, rate of progression of weakness, family history, and history of drug or toxin exposure. On examination, the pattern and degree of weakness, muscle wasting, and associated systemic signs narrow down the etiology.

Laboratory investigations give valuable hints. Serum creatine kinase (CK) is one of the most commonly used investigations because the levels of CK increase with muscle damage. Blood investigations like lactate, thyroid function, or autoimmune markers can be employed based on the suspected cause.

Electromyography (EMG) and nerve conduction studies (NCS) are useful to differentiate myopathies from neuropathies. EMG is usually a "myopathic pattern" with short-duration, low-amplitude motor unit potentials.

Imaging methods like muscle MRI or ultrasound can identify patterns of muscle involvement, fatty replacement, and inflammation. These are particularly helpful in choosing the optimal site for biopsy and in following the progression of disease.

Muscle biopsy is still the gold standard for most cases, especially in inflammatory, metabolic, and certain hereditary myopathies. Biopsy may reveal muscle fiber necrosis, inflammation, or accumulation of abnormal substances. Special stains and immunohistochemistry assist with further diagnosis.

Genetic testing has become more relevant over the last few years. Panels of next-generation sequencing can detect mutations causing hereditary myopathies, limiting the use of invasive biopsies in certain patients.

In general, diagnosis of myopathies is done with a multidisciplinary approach based on clinical features along with specific investigations. Early and proper diagnosis helps in directing the treatment, avoiding complications, and providing genetic counseling to the families affected. [16]

Prevention

General Prevention Measures

These are used for most types of myopathy:

1. Routine Exercise

Do low to moderate-intensity exercise to build muscles and enhance endurance.

Do not overexert, particularly in metabolic or mitochondrial myopathies.

2. Healthy Diet

Muscle health is aided by protein-rich foods.

Anti-inflammatory foods (e.g., leafy greens, fish, berries) could benefit in inflammatory myopathies.

Do not take too much alcohol, which would lead to alcoholic myopathy.

3. Avoid Toxins and Drugs

Some medications (e.g., statins, corticosteroids, colchicine) cause myopathy.

Illegal drugs, alcohol, and certain supplements also harm muscles.

4. Prevent Infections

Viral or bacterial infections trigger or exacerbate myopathies (particularly in inflammatory types).

Get vaccinated and avoid poor hygiene. [17]

Treatment

Management of myopathy largely varies with the nature and etiology of the muscle disorder. In general, the strategy involves:

1. General Measures

Rest and activity modification – no excessive overexertion, but gentle exercise.

Physiotherapy – to preserve muscle power, avoid contractures, and enhance mobility.

Occupational therapy aids in activities of daily living and the use of assistive devices if required.

Nutritional supplementation – high-protein diet, vitamin D, calcium supplementation if low.

2. Medical Treatment (Cause-specific)

Inflammatory myopathies (e.g., polymyositis, dermatomyositis):

Corticosteroids (Prednisolone) – first line.

Immunosuppressants (Methotrexate, Azathioprine, Cyclophosphamide).

IV Immunoglobulin (IVIG) in resistant cases.

Biologics (Rituximab) in refractory disease.

Endocrine-related myopathy (thyroid, Cushing's, diabetes):

Treat the underlying hormonal imbalance.

Drug-induced myopathy (statins, steroids, alcohol):

Discontinue or replace offending drug.

Metabolic myopathies (glycogen storage, mitochondrial disorders):

Dietary modifications (high-carb meals before exercise, ketogenic diet in some cases).

Supplements (Coenzyme Q10, L-carnitine, riboflavin) in selected mitochondrial myopathies.

Muscular dystrophies:

No definitive treatment; supportive treatment (braces, ventilatory support, physiotherapy).

Corticosteroids (Duchenne muscular dystrophy) to reduce progression.

Gene therapy and exon-skipping medications (Eteplirsen, Golodirsen) – in certain situations.

3. Supportive Care

Pain relief (NSAIDs, heat therapy, physiotherapy).

Orthopedic management of scoliosis and contractures.

Respiratory assistance (CPAP/BiPAP, tracheostomy in severe weakness).

Psychological counseling for the patient and family.

Briefly, the management of myopathy is based on the etiology—autoimmune types are treated with steroids and immunosuppressants, endocrine types with hormone correction, drug-induced types with drug withdrawal, whereas genetic types are treated with supportive care and new gene therapies. [18]

Future direction

Future research directions for muscular myopathy include a transition from symptom management to treatment of the root cause of muscle degeneration and weakness. The new directions include gene-based therapies, drug repurposing, stem cell therapy, and personalized medicine.

Gene-Based Therapies:

These treatments seek to repair genetic defects behind most types of muscular myopathy. Some of them employ CRISPR-Cas9 gene editing to correct defective genes directly. Another approach is antisense oligonucleotide (ASO) therapy, where small fragments of DNA or RNA are used to "jump over" a mutated part of a gene, allowing the body to create a more functional protein. Such treatments are only in initial stages, but have a great future for diseases like Duchenne muscular dystrophy.

Drug Repurposing:

Rather than creating new drugs from the ground up, scientists are looking at already-existing drugs that were initially made to treat other ailments. For example, certain medications for heart disease or cancer might have unrecognized properties for benefiting muscles. This process is considerably quicker and less expensive since the drugs have already undergone testing to ensure safety.

Stem Cell Treatments:

Stem cell therapies utilize unique cells capable of becoming various kinds of muscle cells. The aim is to introduce healthy stem cells into injured muscle tissue, which can repair and regenerate the muscles. Though still in its developmental stages, it has the promise of restoring muscle function in patients with advanced myopathies.

Personalized Medicine:

This is a personalized treatment where treatments are specifically tailored to a person's particular genetic profile and characteristics of their disease. Through the examination of a patient's DNA, physicians can gain a clearer picture of why their myopathy is developing in a particular manner and select the most beneficial and safest course of treatment for them. This is a departure from a one-size-fits-all to a more specific, individualized strategy. [19]

Conclusion

Muscular myopathies represent a diverse group of disorders with multifactorial origins, ranging from genetic mutations and metabolic defects to autoimmune and acquired causes. Despite their heterogeneity, these conditions share common hallmarks such as progressive muscle weakness, fatigue, and, in severe cases, respiratory or cardiac involvement. Advances in diagnostic modalities, including genetic testing, imaging, and biopsy techniques, have significantly improved early recognition and precise classification of these disorders. While current treatment largely focuses on supportive care, physiotherapy, and cause-specific interventions such as immunosuppressants or hormonal correction, the future of myopathy management lies in precision medicine. Emerging approaches such as gene therapy, stem cell transplantation, and drug repurposing hold promise in addressing the underlying pathophysiology rather than just alleviating symptoms. Ultimately, a multidisciplinary strategy that integrates early diagnosis, targeted therapies, and continuous research is essential to improve outcomes and quality of life for individuals affected by muscular myopathies.

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