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Muscle Disorders in Childhood: Insights into Myopathy and Dystrophy

Edwin Dias[1,2]*& Jishnu Chandran[3]

[1]HOD and Professor, Department of Paediatrics, Srinivas Institute of Medical Sciences and Research Centre, Mangalore, Karnataka State, India
[2]Adjunct Professor, Srinivas University, Director of Research and Publication, India
[3]Final Year Pharm D, Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka State, India
E-mail:dredwindias@gmail.com[1], [2],jishnuchandranak10@gmail.com
Doi:

ABSTRACT:

Muscle disorders in childhood, including myopathies and dystrophies, encompass a wide spectrum of inherited and acquired conditions that impair muscle function. These disorders range from congenital myopathies to progressive muscular dystrophies, such as Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). Advances in genetic and molecular diagnostics have significantly enhanced our understanding of these conditions, enabling early diagnosis and personalized treatment strategies. Despite progress in therapeutic interventions, challenges remain in providing curative treatments and improving quality of life. This review explores the clinical presentation, underlying mechanisms, diagnostic approaches, and recent advances in the management of pediatric myopathies and dystrophies, with an emphasis on emerging therapies and research directions.

Keywords: *Muscular dystrophies*, Congenital *myopathies, Duchenne muscular dystrophy(DMD), Myotonic dystrophy(MD), Genetic mutation, Next generation sequencing(NGS).*

Introduction

Congenital myopathies are a diverse group of muscle disorders that affect the structure and function of skeletal muscles, causing weakness and low muscle tone. Symptoms can vary widely, from severe movement problems before birth and early death to mild weakness with normal walking, lifespan, and ability to have children. These conditions usually do not affect intellectual abilities and mainly involve skeletal muscles, though some types can also cause heart problems.[1][2]

Muscular dystrophies are a group of inherited disorders that cause similar symptoms, like muscle weakness, and show specific changes in muscle tissue. Learning more about the genetic causes has helped doctors better understand and define the different types. By identifying potential complications early and improving medical care, treatment has improved. This has led to better health, longer life, and improved quality of life for people with these conditions.[3][5]

Recent advances in molecular diagnostics and gene-based therapies are reshaping the understanding and management of these disorders, yet challenges persist in terms of early diagnosis and therapeutic outcomes. [6][7]

A better understanding of the mechanisms underlying the molecular pathogenesis of several disorders and the availability of preclinical models are leading to several new experimental approaches.[3][4] This review focuses on the classification, pathophysiology, diagnostic approaches, and emerging treatments for paediatric myopathies and dystrophies.

CLASSIFICATION AND EPIDEMOLOGY

Congenital myopathies

Congenital myopathies are a group of inherited muscle disorders that cause muscle weakness from birth or early childhood[8]. These conditions share some common muscle biopsy findings like type 1 fiber predominance or uniformity and type 1 fiber hypotrophy.[9] Subtypes include:

1. Nemaline myopathy :

Presence of rod like structures called nemaline bodies in muscle fibre.[9]Incidence of nemaline myopathy is 1/500000 live births.[10]

2. Centro nuclear myopathy :

Nuclei (cell centers) are abnormally located in the middle of muscle fibers instead of at the edges.[9]Incidence of this is rare.[10]

3. Core myopathy

Areas within muscle fibers lack normal energy producing structures(cores).[9]Incidence of core myopathy are rare.[10]

4. Congenital fiber-type disproportion:

Muscle fibers show a big difference between type 1 and type 2 fibers. Muscle biopsy will not show any other structural abnormalities.[9]Incidence is that it is seen in 1% of all muscle biopsies.[10]

5. Myosin storage myopathy

This congenital myopathy was originally called hyaline body myopathy because of the appearance of abnormal structures called hyaline bodies in the muscle fibers. However, after discovering that mutations in the MYH7 gene cause this condition, it is now referred to as myosin storage myopathy.[9]

Pediatric dystrophies

Pediatric dystrophies refer to a group of inherited disorders that primarily affect the structure and function of muscles, leading to progressive muscle weakness and degeneration. Here are the major types of pediatric dystrophies.

1. Duchenne muscular dystrophy:

Duchenne Muscular Dystrophy (DMD) is caused by mutations in the DMD gene, one of the largest genes in the human body. This gene makes a protein called dystrophin, which is essential for keeping muscle cells strong and working properly. Without dystrophin, muscle cells become fragile and easily damaged during movement. Over time, this leads to muscle weakness, loss of function, and the symptoms seen in Duchenne Muscular Dystrophy.[11]

Prevalence estimates of Duchenne Muscular Dystrophy (DMD) according to Jean K. Mah et. al systemic review and Meta analysis on the epidemiology of the muscular dystrophies:

- Older estimate: 6.3 per 100,000 people.
- Recent estimate: 4.78 per 100,000 (with a range from 1.94 to 11.81).[13]

2. Becker muscular dystrophy

In BMD (a milder form), the same process as that of DMD happens but at a slower pace because some dystrophin is still present. DMD causes muscles to gradually weaken and be replaced by scar and fat tissue, while BMD has similar but slower and milder effects.[12]

Prevalence estimates of Becker Muscular Dystrophy (BMD) according to Jean K.Mah et.al systemic review and meta analysis on the epidemiology of the muscular dystrophies:

- Older estimate: 2.4 per 100,000 people.
- Recent estimate: 1.53 per 100,000 (with a range from 0.26 to 8.94).[13]

3. Congenital muscular dystrophy

Congenital Muscular Dystrophy (CMD) refers to a group of muscle disorders that appear early in life, often noticeable at birth or within the first six months. CMD results from genetic mutations that disrupt key muscle proteins. These conditions leads to muscle weakness and other symptoms.[13]

CMD is rare, affecting less than 1 person per 100,000, and the estimates are more consistent for all age groups than for children alone.[13]

4. Limb-girdle muscular dystrophy

LGMD is a group of genetic disorders that weaken the hip and shoulder muscles over time. It is caused by mutations in genes that help maintain muscle structure and function.[13][14]

LGMD is divided into two types based on how the genetic mutation is inherited:

- Type 1 (Dominant): Only one mutated gene is needed for the disease to occur.
- Type 2 (Recessive): Both copies of the gene must have mutations for the disease to occur.[13][14]

5. Facioscapulohumeral muscular dystrophy

Facioscapulohumeral Muscular Dystrophy (FSHD) is a genetic muscle disorder that causes progressive weakness and wasting of muscles, mainly in the face, shoulders, and upper arms. It is an autosomal dominant disorder.[13]

Causes of FSHD:

- Type 1 (FSHD1):

It is caused by deletions in a region of DNA called the D4Z4 repeat on chromosome.

- Type 2 (FSHD2):

Caused by mutations in the SMCHD1 gene on chromosome 18, but it also requires a specific variation in chromosome 4 to develop the disease.[13] Both types lead to improper activation of a gene (DUX4), which is harmful to muscle cells.[13]

The prevalence of Facioscapulohumeral muscular dystrophy (FSHD) in children the prevalence is much lower than adult, at 0.29 per 100,000 children. This means less than 1 child in every 100,000 is affected.[13]

6. Myotonic dystrophy

Myotonic Dystrophy (MD) is a genetic condition that causes progressive muscle weakness, difficulty relaxing muscles (Myotonic), and problems in other parts of the body, such as the heart and endocrine system. It is an autosomal dominant disorder, meaning a person needs only one faulty gene to develop the disease.[13]

Types and Causes:

- Type 1 (MD1):

It is caused by the expansion of CTG repeats in the DMPK gene on chromosome 19.

Symptoms are more severe when the number of repeats is larger.

- Type 2 (MD2):

It is caused by the expansion of CCTG repeats in the CNBP gene on chromosome 3.

Symptoms tend to be milder and do not worsen across generations as much as DM1.[13]

Here, Myotonic dystrophy type 1 is the most common type of muscular dystrophy in both children and the overall population. Study estimate its prevalence as 8.26 per 100,000 people.[13]

7. Oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is a muscle disease that starts later in life and progresses slowly. It is characterized by slowly progressing ptosis, dysphagia and proximal limb weakness. The cause of OPMD is a genetic change (mutation) in the PABPN1 gene. Normally, this gene has 10 repeats of a sequence of DNA letters called GCN repeats. In people with OPMD, this repeat expands to 11–18 repeats.

This abnormal expansion leads to the production of a faulty version of the PABPN1 protein, which forms clumps in muscle cells, making them weaker and less functional over time.[15]

Oculopharyngeal muscular dystrophy (OPMD) is found worldwide, but its prevalence differs among ethnic groups.

High Prevalence Groups:

- Bukhara Jews in Israel: 1 in 600 people.
- French-Canadians: 1 in 1,000 people.
- Hispanic populations in New Mexico: also high.[15]

Lower Prevalence:

In European populations, the prevalence is much lower, ranging from 1 in 100,000 to 1 in 1,000,000.[15]

8. Distal muscular dystrophy

Distal Dystrophies (Distal Myopathies) are genetic muscle diseases that cause progressive muscle weakness and shrinking (atrophy). The weakness starts in the hands, forearms, lower legs, or feet and slowly gets worse over time.[16]

According to a nationwide, population based prevalence study of genetic muscle disorders the prevalence of distal muscular dystrophy 0.21 prevalence per 100,000.[17]

DIAGNOSTIC APPROACH

Diagnosing neuromuscular diseases in children can be tricky because of the variety of possible conditions, the technical difficulties of performing some tests on children, changes in muscles and nerves depending on the child's age, tests like medical history, clinical examination, lab tests, EMG, and muscle biopsy help in diagnosing these diseases, newer tools like imaging (e.g., MRI) and genetic testing are becoming more important in the diagnostic process.[19]

Role of Electromyography (EMG) is that it helps differentiate between Neurogenic diseases (nerve-related issues) , Myopathic diseases (muscle-related issues) and disorders of neuromuscular transmission (how signals travel from nerves to muscles) they are useful in locating where the problem is in the nervous system, grading the severity of the disease , monitoring disease progression.[19]

Muscle Biopsy was once considered the "gold standard" for diagnosing muscle diseases. It allows detailed analysis of muscle tissue under a microscope.[19]

There are some motor difficulties and developmental delays often seen in children with Duchenne muscular dystrophy (DMD). Common Motor Symptoms in DMD (Ages 3–4) are difficulty in activities like, running, jumping, or climbing stairs, rising from the floor (using hands and legs, called Gower's sign), hopping or walking normally, frequent falls or trips, waddling gait, or toe-walking, enlarged calf muscles (calf hypertrophy) or muscle pain/cramps. These signs usually lead doctors to investigate further, resulting in a DMD diagnosis.[22]

The importance of early eye exams for infants and children who show signs of nystagmus (uncontrolled eye movements) or suspected vision loss.[22] Prompt and thorough eye exams, along with recognizing early signs of IRDs, are crucial for helping children receive treatments and therapies as soon as possible.[18]

Newer diagnosing technique such as next-generation sequencing (NGS) is changing the way myopathies (muscle diseases) are diagnosed. NGS makes diagnosis faster and less invasive, helps doctors manage the disease better and provide accurate prognoses, supports genetic counseling for families, including identifying carriers and assisting with prenatal testing. There's a need for more research on how accurate and efficient NGS is in diagnosing myopathies across a wide range of patients, not just specific subgroups.[20]

Challenges and Limitations

The challenges in diagnosing and treating congenital myopathies (a group of inherited muscle disorders) are the complexity in its diagnosis. While identifying congenital myopathies (muscle disorders present from birth) is relatively straightforward, finding the exact genetic cause is difficult because the same genetic mutation can cause different muscle abnormalities and different genes can cause similar muscle abnormalities.[20]

Challenges in conducting EMG in children are the technical difficulties and changes in muscle size and structure as children grow.[19]

Challenges with muscle biopsy is that it is invasive (requires removing a piece of muscle) and diseases can have overlapping features, making diagnosis harder. Moreover only a small piece of muscle is available for testing.[19]

In NGS identifying the exact mutation that causes the disorder can be tricky because some harmless genetic variations (called population polymorphisms) can look like disease-causing mutations. A patient may have mutations in multiple genes, and it's not always clear which one is responsible for the disease. To avoid false positives, genetic testing should only be done after collecting detailed clinical, imaging, or muscle biopsy data.[20] Current limitation is that there are no universal guidelines or standardized methods for using NGS in myopathy diagnosis. Fewer studies have looked at how well NGS works in diagnosing all types of myopathies in mixed patient group.[21]

Advancements in Genetic Testing

Next-Generation Sequencing (NGS) (especially gene panels that test multiple genes at once) is now the most efficient and cost-effective way to diagnose congenital myopathies. It's faster and cheaper than older methods like Sanger sequencing, especially for large genes like NEB, TTN, and RYR1.[20][21]

There is a growing importance for combining Clinical and Genetic Data. Genetic testing without clinical context can lead to misdiagnosis or unnecessary testing. Doctors should first gather as much clinical and muscle-related evidence as possible before moving to genetic testing.[20][21]

Treatment

Management of Childhood dystrophy and myopathy involves a multidisciplinary team to manage symptoms, reduce complications, and monitor health. The team may include Genetic counselors , Nurses and educators, Physiotherapists, speech therapists, and occupational therapists, Social workers and dieticians, Medical specialists.[17]

Physiotherapy: It helps prevent joint problems and supports walking. These principles work for different types of limb-girdle muscular dystrophy (LGMD).[17][20]

Knee-Ankle-Foot Orthoses (KAFOs): Special braces used when walking independently becomes hard. Using these braces can help people keep walking for an extra 18 months to 2 years. This also lowers the risk of spine problems like scoliosis.[20]

In Steroid Treatment (Glucocorticoids) medications like prednisolone or deflazacort improve muscle strength, walking ability, breathing, and heart health. They also reduce the chances of scoliosis (spine curve problems).[20][21][22]

Dosage: A common dose is prednisolone (0.75 mg per kg body weight daily) or deflazacort (0.9 mg/kg daily). Steroids work best when started early (ages 4-6 years) or even later if walking is still possible.[20][21][22]

Side Effects : Steroids can cause weight gain in the short term and bone fractures in the long term (about 1 in 3 patients).To reduce side effects, some use a 10-day-on, 20-day-off schedule instead of daily doses. Researchers are studying how different schedules affect side effects.[20][21][22]

Monitoring Bone Health and regular check-ups are needed to adjust the dose and check for side effect. Since steroids can weaken bones, patients need a diet rich in calcium and vitamin D. Supplements are given if vitamin D levels are low. If fractures occur, certain medications (like bisphosphonates) can help repair bones. However, they are not used to prevent fractures.[20]This treatment plan requires careful supervision by doctors to balance the benefits with managing side effects.

Breathing Problems in Muscular Dystrophy:As teenagers with muscular dystrophy grow older, their breathing muscles become weaker, leading to problems like troubled breathing during sleep (called sleep-disordered breathing), Low oxygen levels during REM sleep, causing symptoms like, Morning drowsiness, fatigue, headaches, nausea, Poor appetite, trouble concentrating, and slower growth, Weak coughing, which makes it harder to recover from minor infections.[20]

Treatment with Non-Invasive Ventilation (NIV) commonly works as a small, portable ventilator which helps with breathing during sleep. A mask (covering the nose or face) connects to the machine. It improves oxygen levels during sleep and relieves symptoms like tiredness and headaches. It also prolongs survival, sometimes into the 30s or 40s. It's easy to use at home and doesn't limit travel or daily life.[20]

If coughing becomes weak, cough assisting devices can help clear mucus, especially during infections, to prevent breathing failure.

Monitoring and Starting NIV early is other measure that can be taken if the measure of Forced Vital Capacity (FVC) drops below 50%, it's time to start closely monitoring breathing. It's better to begin using NIV at night when early breathing problems occur, even if daytime breathing is still normal. Starting early helps the patient get used to the machine and prevents sudden breathing failure during illnesses.[20]

Supportive Care in Duchenne Muscular Dystrophy (DMD)

1. Genetic Diagnosis: Identifying the specific genetic mutation helps with accurate diagnosis, personalized treatment, and genetic counseling for families.
2. Emotional and Family Support: Families face significant stress from the challenges of caring for a child with DMD. Parents often worry about their child's future, and caregivers may experience emotional strain. Siblings and caregivers' needs often take a backseat. Family-centered care and community support can help parents manage and normalize their daily routine.
3. Health Monitoring for Carrier Mothers: Women who carry dystrophin mutations should be monitored for potential heart problems, muscle pain, or weakness.[21]

Future of Treatment

Accurate genetic diagnosis is crucial for identifying the best treatment options. Since some treatments may work for multiple types of congenital myopathies, precise patient classification and outcome tracking are essential for future clinical trials. Advances in genetic testing and new therapies offer hope for better diagnosis and treatment in the future.[20]

Currently, there are limited treatments for congenital myopathies, but new therapies are being developed:

Gene Therapy: Introducing healthy genes to replace faulty ones (e.g., for X-linked myotubular myopathy).

Enzyme Replacement Therapy: Replacing missing enzymes (e.g., for MTMR14-related myopathies).

Anti-Atrophy Treatments: Preventing muscle wasting.

Activating Fetal Proteins: Using proteins normally active in fetal muscles to compensate for defective adult proteins.

Conclusions

Pediatric myopathies and dystrophies encompass a wide range of inherited and acquired muscle disorders that lead to progressive muscle weakness and functional impairments. Advances in molecular genetics and diagnostic techniques have significantly improved early detection, enabling more precise classification and personalized treatment approaches. Despite these advancements, challenges remain in developing curative therapies, as current management primarily focuses on symptom relief, delaying disease progression, and improving the quality of life.

Early and accurate diagnosis is critical, as it allows for timely intervention and better prognosis. The integration of genetic testing, including next-generation sequencing (NGS), has revolutionized the identification of causative mutations, paving the way for targeted therapies. However, limitations such as diagnostic complexity, overlapping clinical features, and accessibility to genetic testing remain significant hurdles. Muscle biopsies and electromyography (EMG) continue to play vital roles in diagnosis, but non-invasive imaging techniques are emerging as valuable complementary tools. Multidisciplinary management, including physiotherapy, orthopedic support, respiratory care, and pharmacological interventions, is essential in slowing disease progression and addressing complications such as contractures, scoliosis, respiratory failure, and cardiomyopathy. The use of corticosteroids in dystrophies, particularly in Duchenne muscular dystrophy (DMD), has been shown to prolong ambulation and preserve respiratory and cardiac function, though side effects such as osteoporosis and weight gain need careful monitoring.

Emerging therapies, including gene therapy, exon-skipping approaches, and enzyme replacement therapies, offer hope for more effective disease-modifying treatments. Advances in genetic editing techniques like CRISPR-Cas9 hold potential for correcting underlying mutations, but challenges such as immune response, delivery mechanisms, and long-term efficacy must be addressed before widespread clinical application. Supportive care plays a crucial role in enhancing the quality of life for affected children and their families. Psychological support, genetic counseling, and community-based interventions are necessary to help families cope with the emotional and financial burdens associated with these chronic conditions. Carrier screening and prenatal testing can provide at-risk families with informed reproductive choices.

In conclusion, while significant progress has been made in understanding and managing pediatric myopathies and dystrophies, there is still a long way to go in achieving curative treatments. Continued research, global collaborations, and advancements in molecular medicine are key to overcoming current limitations and developing innovative therapies. The future of pediatric neuromuscular disease management lies in precision medicine, where genetic, molecular, and clinical data will be integrated to provide individualized treatment plans, ultimately improving outcomes and the quality of life for affected children.

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