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Review Article

MYOTONIC DYSTROPHY – A REVIEW

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ABSTRACT

Myotonic Dystrophy (DystrophiaMyotonica, DM) is an inherited type of muscular dystrophy that affects the muscles and other body systems. People who have myotonic dystrophy have muscle wasting and weakness in their lower legs, hands, neck and face that get worse over time. Signs and symptoms of myotonic dystrophy usually develop when a person is in his or her twenties or thirties. The severity of myotonic dystrophy varies widely among those who have it, even among family members. DM is a multisystem disease with major cardiac involvement. Core features of myotonic dystrophy are myotonia, muscle weakness, cataract, and cardiac conduction abnormalities. Classical DM (first described by Steinert (Steinert's disease) or DM1) has been identified as an autosomal dominant disorder associated with the presence of an abnormal expansion of a CTG tri nucleotide repeat on chromosome 19q13.3 (the DM 1 locus). Based on the nature of the causing mutation, DM1 belongs to "disorders of unstable repeat expansion". Being the first disease described with an RNA gain-of-function mutation effect, DM1 is now the paradigm for RNA toxicity model of the disease pathogenesis, as reviewed elsewhere. Physical therapy offers the most promise in caring for the majority of patients. This article will mainly focus on DM1. It will provide an insight into the basic molecular biological advances together with the clinical manifestations of the muscular dystrophies and the latest approaches to their management and provide up-to-date information on postmortem and clinical findings and on diagnostic and therapeutic options in patients presenting cardiac involvement.

Keywords: Muscular dystrophy, Steinert's disease, Myotonic dystrophy, Classical DM.

INTRODUCTION

The muscular dystrophies (MDs) are a heterogeneous group of inherited disorders characterized by progressive weakness and degeneration of skeletal muscles[1]. MDs is the most frequent type of muscle disorders occurring in adults[2]. It's a neuromuscular disorder and it has got cardiac involvement.This disorder is mainly due to ctg tri nucleotide system[3,4].

Epidemiology and classification of DM1

The incidence of DM1 is estimated to be 1 in 8000 births and its worldwide prevalence ranges from 2.1 to 14.3/100 000 inhabitants. Based on the age of onset and on its clinical features, DM1 can be divided into three forms: congenital, classical, and minimal. Congenital DM1 presents at birth or during the first year of life in a severe form. It is characterized by neonatal hypotonia, facial diplegia, joint contractures, frequent and often fatal respiratory failure, feeding difficulties, and developmental delay. The risk of dying from congenital DM1 in the neonatal period is high. In the classical form, which are the most common symptoms become evident between the second and the fourth decade of life, showing a slow progression over time. The key feature of the disease is myotonia, which is characterized by delayed relaxation after muscular contraction progressive muscular weakness (dystrophy) and wasting are also typical findings; facial, axial, semidistal, and distal compartments are predominantly involved. DM1 is, however, a multisystem disorder; indeed, affected patients can manifest abnormalities of other organs and systems including the eye (cataract), the

endocrine system (diabetes, thyroid dysfunction hypogonadism), the central nervous system (cognitive impairment, mental retardation and attention disorders), the gastrointestinal system (dysphagia, constipation, gallbladder stones, pseudo-obstruction). Minimal DM1 begins later in life, usually after 50 years of age, with a very mild degree of muscle weakness and myotonia or only cataracts, associated with a normal lifespan[3-6].

Genetic alterations of DM1

The genetic basis of DM1 is known to include mutational expansion of a repetitive trinucleotide sequence (CTG) in the 3¢-untranslated region of the DMPK gene on chromosome 19q13.3. While 5-34 CTG repeats are observed in normal alleles, their number may reach 50–2000 in DM1[3]. DM1 is an autosomal dominant disorder with incomplete penetrance and variable phenotypic expression. The process which leads from abnormal expansion of CTG repeats in a non-coding region of DMPK gene to cellular dysfunction is still incompletely understood. DMPK in the heart muscle at the level of intercalated discs, combined with the observation that DMPK reduction in animal models compromise conduction both at the level of the AV node and of the His-Purkinje system, Pathologic expansion of the CTG repeats is unstable both during mitotic and meiotic divisions. Mitotic instability explains the presence of somatic mosaicism, a common feature of DM1.Meioticinstability represents the mechanism underlying the phenomena of “anticipation” and “reverse mutation” observed during parent-to-child transmission in DM1 pedigrees[4].

Pathophysiology of Muscular Dystrophy

Muscles are composed mostly of protein in a highly organized system from large groups to small fibers. Muscle units are separated from other muscle groups by plasma membranes called the sarcolemma and the cytoplasm within is called the sarcoplasm. Within the sarcoplasm are multiple long protein bundles called myofibrils, and many ATP producing mitochondria, as well as glycogen (a form of stored glucose for energy) and myoglobin (oxygen stored in blood for the breakdown of glycogen). Bundles of parallel myofilaments make up the myofibrils which is where most of the action takes place. In the myofilaments are contractile proteins called myosin (thick filaments), and actin (thin filaments). When signaled the actin and myosin interlock and slide over each other to stretch or slide into one another to form contraction[7].

There are many other proteins involved in the process. Aside from the contractile proteins, there are regulatory proteins called tropomyosin and troponin which act like a switch to determine when to contract and when to relax. On the muscle fiber the ‘I band’ is the space between the myosin (thick) filaments, where lies only the thin filaments. In the middle of each ‘I band’ is a dark disc called the ‘Z disc’ made of titan, (elastic filament), which is connected to the sarcolemma by the cytoskeleton. The space between each Z disc, where these filaments interact, is called the sarcomere. As the muscle contracts the ‘I band” shrinks and the sarcomere shortens and as the Z disc’s come closer together pulling on the sarcolemma shortening the cell. This is how the muscle contracts. One of the most clinically important accessory proteins here is dystrophin which is located just under the sarcolemma in the cytoplasm in the area of the ‘I band’. It is produced by specific genes and links the actin filaments to the protein extracellular matrix in the membrane known as the dystrophin-associated protein complex. Elements of the dystrophin gene and the protein structure have been identified, yet the exact functional role is still a bit unclear. However as research continues it is thought that its primary function is to provide mechanical reinforcement to the structure of the sarcolemma and thereby protecting the membrane from the stress tearing during contraction.

If dystrophin is defective or absent, the membrane breaks down which then substances and molecules like proteins and enzymes leak out of the fiber into circulation. These enzymes and chemicals that leak out are responsible for certain chemical reactions and necessary for energy production for muscle contraction. At the same time the extracellular substances leak into the fiber through the broken down membrane damaging the fiber and disrupting the process of muscle contraction and may cause irreparable damage. The absence or abnormality of dystrophin results in a condition known as Muscular Dystrophy[7]. Muscular Dystrophy is a crippling disease resulting from mutated genes which slowly wastes away muscle tissue. Without muscular dystrophin to help protect the fiber membrane keeping it intact, and assisting to create energy, the muscles begin to degenerate and atrophy, being replaced by fat and fibrous scar tissue creating fascia adhesions throughout the body. It is thought that the major determinate of the membrane damage would be the level of stress associated with contraction

rather than the number of muscle activations. And according to Petrof, Shrager, Stedman, Kelly & Sweeney in 1993, which would explain why it primarily affects the peripheral limbs.Muscular dystrophies most commonly involve a genetic mutation in the dystrophin genes preventing the production of dystrophin or limiting the amount in subnormal levels. Its normal for small tares on the sarcolemma to occur as the muscle undergoes excessive strain and there are small molecules that enhance the natural repair process.

However in the absence of dystrophin, the sarcolemma (the membrane) is left unprotected tearing more frequently and more easily therefore muscle degeneration greatly outweighs muscle regeneration eventually leading to death and adhesion of the tissue[7]. There are nine known different types of Muscular dystrophy which are classified depending on distribution of affected muscle groups, severity and prognosis, genetic defects and the means of inheritance. Duchenne muscular dystrophy (DMD) is the most common and most severe as it affects not just all the voluntary muscles but also the heart and respiratory muscles as well shortening one's life span drastically. It's caused by a genetic mutation on the 23rd chromosome, the sex determining chromosome, being an X linked recessive or sex-linked recessive trait. Therefore males are primarily affected from the gene passed down by their mother who most likely was only a carrier. Other types of MD that were inherited through the X-linked recessive trait are Becker and Emery- Dreifuss Muscular Dystrophy. Becker MD is a different mutated gene but located on thesame gene locus as Duchenne MD. Coincidently being very much alike Duchenne MD, Becker MD often affects the heart tissue but in general is less severe and has a longer life expectancy. Other dystrophies are inherited through autosomal dominate traits, meaning the mutated gene is dominate in one of the 22 chromosomes (excluding the 23rd sex chromosome), equally affecting both males and females. The dystrophies inherited in this manner include facioscapulohumeral, distal, and oculopharyngeal muscular dystrophies as well as myotonic dystrophy. Facioscapulohumeral Muscular Dystrophy (FSHD) is caused by a missing piece of DNA on chromosome 4. FSHD primarily affects the face, shoulders and upper arms but later affects certain muscles of the legs, the abdominals and the pelvic girdle leading to extreme lordosis which may eventually require a wheelchair[5,8].

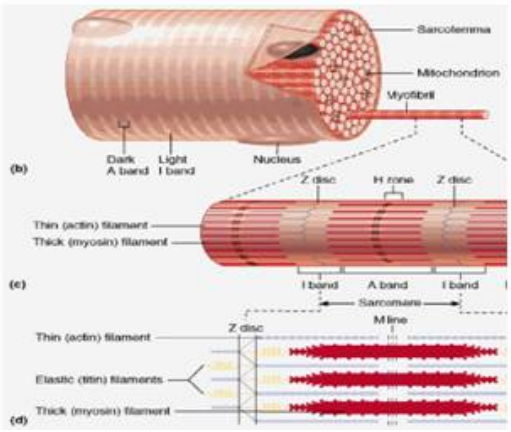

Fig. 1: Histology of Muscle

Management of the patient with DMD in the clinic requires a physically accessible environment and parking structure, with proper equipment (eg, mechanical hoist or sliding board) and trained personnel available for the safe transfer of the nonambulatory patient. The expertise and means to obtain accurate measures of weight, height, and vital signs with appropriately trained staff are essential. Special weight scales that accommodate wheel chairs are available. Height measurements in patients with severe scoliosis are not accurate and can be replaced by arm-span measurements[9].

Diagnosis of DMD

The aim of care around diagnosis is to provide an accurate & prompt diagnosis, allowing initiation of appropriate interventions, continuing support and education, minimising the length and impact of a potentially protracted diagnostic process. Diagnosis should be done by a neuromuscular specialist who can assess the child clinically and can rapidly access and interpret appropriate investigations in the context of the clinical presentation. Family follow-up and support after diagnosis will often be augmented by support from geneticists and genetic counsellors[9].

When to suspect DMD

Suspicion of the diagnosis of DMD should be considered irrespective of family history and is usually triggered in one of three ways: (1) most commonly, the observation of abnormal muscle function in a male child (2) the detection of an increase in serum creatine kinase tested for unrelated indications; or (3) after the discovery of increased transaminases (aspartate aminotransferase and alanine aminotransferase, which are produced by muscle as well as liver cells). The diagnosis of DMD should thus be considered before liver biopsy in any male child

with increased transaminases. Initial symptoms might include delayed walking, frequent falls, or difficulty with running and climbing stairs. Although DMD is typically diagnosed at around 5 years of age, the diagnosis might be suspected much earlier because of delays in attainment of developmental milestones, such as independent walking or language; such delays have been documented prospectively[10].

Confirming the diagnosis

- For patients diagnosed by muscle biopsy, dystrophin genetic testing is also necessary
- For patients diagnosed by genetic testing, muscle biopsy is optional to distinguish DMD from milder phenotypes
- Referral to specialised multidisciplinary follow-up is needed
- Genetic counselling is highly recommended for any at-risk female family members
- Patient and family support and contact with patient organisations should be offered
- Muscle biopsy
- Consider alternative diagnoses:

Dystrophin deletion/duplication testing: Deletion or duplication mutation found If there is no family history: not walking by >16–18 months; Gowers' sign (any age, especially <5 years old)

- Screening for DMD: creatine kinase concentrations markedly increased
- Genetic sequencing: Mutation found, if there is a positive family history of DMD: any suspicion of abnormal muscle function Patient with unexplained increase in transaminases - In cases in which DMD is suspected, the route for further diagnostic testing depends on the increase in CK. In rare cases, a dystrophinopathy diagnosis could be confirmed by absent dystrophin protein on muscle biopsy even if all genetic testing is negative.
- Specialist physical and occupational therapy assessments are recommended every 4 months[10-12].

Pharmacological interventions for muscle strength and function

Pharmacological intervention has begun to change the natural history of DMD, and further advances and more effective treatment of the underlying pathology of DMD should continue to offer an improved course, potentially including small-molecule and gene therapies[13]. The most devastating and obvious effect of DMD is on the skeletal musculature with resulting loss of strength and function. The progression of muscle degeneration in DMD is well documented both in terms of pathophysiology and path kinesiology (with a proximal-to-distal progression of muscle weakness, leading to progressive losses in activities of elevation against gravity with eventual loss of ambulation Several panels have addressed treatments aimed at optimizing strength and function, which include pharmacological interventions, such as glucocorticoids, and physical therapy interventions (involving the use of gentle exercise and activity, and management of the musculoskeletal system to prevent/minimize contracture and deformity [12,14].

Glucocorticoids

Glucocorticoids are the only medication currently available that slows the decline in muscle strength and function in DMD, which in turn reduces the risk of scoliosis and stabilizes pulmonary function. Cardiac function might also improve, indicating a slower decline in echocardiographic measures of cardiac dysfunction, although these measures are not necessarily predictive of the delay in cardiac symptoms, signs, or cardiac-related mortality[21]. Initial RCTs in patients treated with prednisone for up to 6 months showed an improvement in muscle strength, with 0·75 mg/kg daily having the most favorable profile. Use of a higher dose of 1·5 mg/kg daily was no more effective, and a lower dose of 0·3 mg/kg daily was less beneficial. Daily administration was more effective than treatment on alternate days. Deflazacort, a similar glucocorticoid available in many countries, but not currently approved[15,16,21].

Treatment

MD responses well with breast cancer drugs Tamoxifen. Drugs that correct the translation of mutated m RNA like Aminogylcosides. Drugs that decrease muscle regeneration e.g protease inhibitors Drugs that increase muscle regeneration Ex: Myostatin inhibition, IGF1, Follistatin stimulation[17,18].

CONCLUSION

The muscular dystrophies are a group of chronic diseases that cause weakness and progressive degeneration of skeletal muscles. There are many forms of MD, including[19,20] Duchene, Becker, limbgirdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-dreifuss dystrophies. MD can affect people of all ages; however, some forms first become apparent in childhood, while others appear later in life[18-20]. While the genes responsible for some forms of the MDs have been identified, a causative gene has not been found for other forms. Currently,

there is no treatment that can stop or reverse the progression of any form of MD, and symptomatic treatment is aimed at improving the quality of life for individuals with these disorders. Within the National Institutes of Health (NIH), the three institutes most involved in MD-related research activities are the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Child Health and Human Development (NICHD).

SUMMARY

The muscular dystrophy is the most frequent type of muscle disorders occurring in adults. The muscular dystrophies (MD) are a group of inherited genetic conditions that gradually cause the muscles to weaken. This leads to an increasing level of disability. MD is a progressive condition, which means that it gets worse over time. It often begins by affecting a particular group of muscles before affecting the muscles more widely.

Some types of MD eventually affect the heart or the muscles used for breathing, at which point the condition becomes life threatening. There is no cure for MD, but treatment can help manage many of the symptoms.

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