Review Article

Myotonic Dystrophy and the Heart – A Review

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ABSTRACT

Myotonic Dystrophy (Dystrophia Myotonica, DM) is the most frequently inherited neuromuscular disease of adult life. 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 and called 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). DM1 is inherited in an autosomal dominant pattern. And the underlying mutation is an unstable expansion of CTG repeats in the 3′ untranslated region (3′UTR) of the dystrophia myotonica protein kinase gene (*DMPK*, MIM* 605377) and in the promoter of the downstream SIX homeobox 5 gene (*SIX5*, MIM* 600963).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.

A similar but less common disorder was later described as proximal myotonic myopathy, caused by alterations on a different gene on chromosome 3q21 (the DM2 locus). This article will mainly focus on DM1. It will provide an insight into the epidemiology and genetic alterations of the disease and provide up-to-date information on postmortem and clinical findings and on diagnostic and therapeutic options in patients presenting cardiac involvement.

Keywords: Myotonic dystrophy, autosomal dominant disorder, stringer's disease, myotonia, trinucleotide**,** proximal myotonic myopathy

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INTRODUCTION

Muscular dystrophy is the most frequent type of muscle disorders occurring in adults [1]. It's a neuromuscular disorder and it has got cardiac involvement .This disorder is mainly due to ctg tri nucleotide system [2,3].

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, which may occur in the same kindred. 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. Patients who survive exhibit non-progressive psychomotor retardation and may subsequently exhibit the features of the adult-type, classical form of DM1. 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, semi-distal, 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 [2-5].

Genetic alterations of DM1:

DM1 is an autosomal dominant disorder with incomplete penetrance and variable phenotypic expression. 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 [2]. 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 [3].

Clinical Case:

A 37-year-old man, who had been diagnosed two years earlier as myotonic muscular dystrophy by a genetic study and had a family history of the disease (his mother, brother, and maternal uncles and cousins had died), was seen in the emergency service for chest pain, palpitations, diaphoresis, and dyspnea. The physical examination disclosed an arterial pressure of 120/80 mm Hg and heart rate of 110 beats/min. On auscultation, the heart sounds were arrhythmic and tachycardic, without murmurs. The pulmonary fields were well ventilated. Other typical findings of the disease were frontal alopecia, bilateral palpebral ptosis, testicular atrophy, muscular weakness with distal predominant and generalized hyporeflexia and signs of mental retardation were observed. The patient was hospitalized in the cardiology department to begin treatment for atrial fibrillation. Pharmacological treatment with intravenous amiodarone began with an initial dose of 5 mg/kg and continued with a 24-hour infusion of 10 mg/kg. The day after admission, the patient presented an episode of regular tachycardia with a wide QRS complex, heart rate of 160 beats/min, and hemodynamic collapse (blood pressure [BP] 50/0 mm Hg) that required electrical cardio version with a 200-joule discharge. The patient came out of atrial fibrillation, showing an electrocardiogram similar to the one seen at admission (until then, the patient had received 750 mg of amiodarone intravenously). The patient was transferred to the coronary care unit, where a wide QRS complex, regular tachycardia appeared again without hemodynamic impairment. A pattern of left bundle branch block with a left axis was evident. Procainamide, 300 mg, was given intravenously, which resulted in a conversion to sinus rhythm with atrioventricular block [4]. After discontinuing amiodarone 48 h earlier, an electrophysiological study was made via the right femoral vein with quadripolar catheters placed in the upper right atrium, bundle of His region, and right ventricular apex. The intervals of atrioventricular conduction showed first-degree infrahisian atrioventricular block with the following intervals: PA 30 ms, AH 80 ms, and HV 100 ms. Sinus function and Wenckebach AV point were normal. No hidden accessory pathways were appreciated in sinus rhythm. With atrial stimulation at 280 ms, common atrial flutter was induced with a cycle length of 240 ms and 2:1 atrioventricular conduction that required atrial pacing at 200 ms for conversion [5]. During baseline programmed ventricular pacing at 600 ms, ventricular fibrillation was induced with three extra stimuli (S2, 250 ms; S3, 240 ms, and S4, 210

m) that required defibrillation by the application of a 200-joule discharge. With ventricular pacing at 500 ms and 2 extra stimuli (S2, 260 ms, and S3, 330 ms), a regular sustained monomorphic ventricular tachycardia was induced. It was tolerated and had a pattern of left bundle-branch block and a cycle length of 280 ms. Atrio ventricular dissociation and a stable His potential were appreciated before the ventricular electrogram with a constant HV interval (The tachycardia was terminated by a ventricular extra stimulus at 250 ms. A cardiac electrophysiological study was made and the right bundle branch was ablated with a catheter with a 4-mm distal electrode and application of radiofrequency energy for 2 min at a temperature of 60^0C [5].

Muscle Physiology and the Pathology 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 contraction. They are signaled from the nervous system followed by a series of chemical reaction involving ATP, calcium, sodium and potassium ions [6].

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. Muscular Dystrophy is a crippling disease resulting from mutated genes which slowly wastes away muscle tissue. Without 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, according to Petrof, Shrager, Stedman, Kelly, & Sweeney, 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. Generally in muscle tissue 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 [6].

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 [7,8].

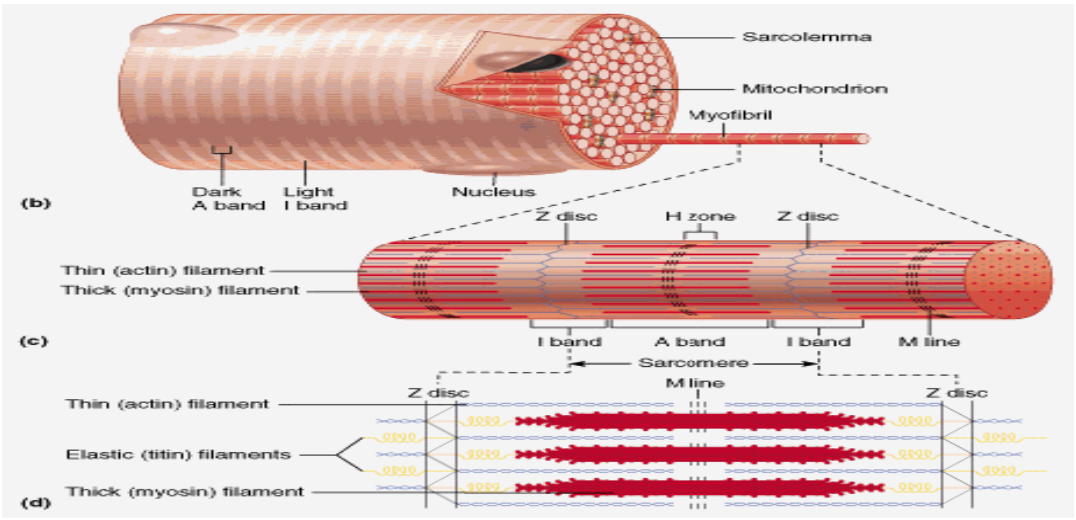

Figure 1: Histology of Muscle

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 non-ambulatory 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 and prompt diagnosis, allowing initiation of appropriate interventions, continuing support and education, and 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:

[10] Dystrophinopathy diagnosis confirmed • 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: dystrophin protein absent Not DMD: 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 confi rmed by absent dystrophin protein on muscle biopsy even if all genetic testing is negative. If a dystrophinopathy diagnosis is not confirmed by either muscle biopsy or genetic testing, the diagnosis of alternative muscular dystrophies is complex and requires specialised input. CK=creatine kinase. DMD=Duchenne muscular dystrophy. Strength testing Manual muscle testing (MRC scale)50 Quantitative myometry (benefi cial if muscle strength 3–5 on MRC scale)* Serial assessment: to identify outliers from expected clinical course; to monitor disease progression and predict functional losses; to assess response to treatment; and to monitor muscle imbalance Test lower extremity strength by manual muscle testing every 6 months [7] Early stages: test upper and lower extremity strength every 6 months Later stages: value of testing is less certain Range of motion Goniometry51 Baseline: to identify emerging muscle hypoextensibility and joint contractures that might contribute/lead to functional deterioration or musculoskeletal or integumentary problems To identify need for additional or altered therapeutic/surgical intervention (ie, orthoses, splinting, use of standers, iliotibial band lengthening) Lower extremities: hip, knee, ankle joints; iliotibial band; hamstrings, gastrocnemius Lower extremities: hip, knee, ankle joints; iliotibial band; hamstrings, gastrocnemius Upper extremities: elbow, wrist, long fi nger fl exors Timed testing Standardised use of timed function tests 50, 52 Easy and relevant measure of daily functional status; responsive to change Timed 10 m walk, timed Gowers' manoeuver, time to climb 4

stairs, time to rise from chair, 6-min walk test Time to put on a shirt might be relevant in late ambulatory stage Time to put on a shirt might be relevant in early non-ambulatory stage, timed testing not applicable in late non-ambulatory stage Activities of daily living Assessment of impairment in daily activities in the home, school, and community settings Highly relevant to targeted input with aids, adaptations, and access to environmental controls Frequency of falls, step activity monitoring, self-care skills, writing, computer use Functioning in school and community settings Self-care skills, writing, computer use, control of manual and electric wheelchair Functioning in school and community settings Motor function scales Assessment of motor function in specific domains to give a composite score Allows monitoring of progression and response to therapy Vignos lower extremity scale, North Star Ambulatory Assessment, motor function measure Brooke upper extremity scale, Egen Klassifi kation functional assessment, Hammersmith motor scales, motor function measure Routine clinic appointments should be every 6 months, unless otherwise specified. 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, with limited data to date 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. Prednisolone is often used in Europe instead of prednisone. Deflazacort, a similar glucocorticoid available in many countries, but not currently approved [15,16,21].

Treatment:

MD responses well with 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, limb-girdle, 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 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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