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Case Report

Cases of muscular dystrophy: Two incident reporting studies

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ABSTRACT

The muscular dystrophies are deemed to constitute a significant proportion of neuromuscular diseases, which occur at a frequency of approximately 1:3000 births. Today, in light of developments in Molecular Genetics, the term muscular dystrophy refers to a "heterogeneous group of genetic diseases that cause progressive damage to the primary muscle due to the disorder in one or more muscle proteins". At an advanced stage of disease could possibly be observed heart attack and myocardial infraction. An important indicator of the disease is elevated CK, aldolase and transaminases which observed at the birth of patients and which many times in small groups detected by random clinical and laboratory tests. The onset of disease could be started in infant, child or adult life. The classification currently applied concerns 8 groups muscular dystrophies based on the distribution of the main weakness and the molecular disorder. Duchenne muscular dystrophy (DMD) is an inherited, neuromuscular disorder. DMD is a sex-linked recessive disease, which results in the absence of dystrophin, a protein found inside the muscle cell membrane. The case reported below, concerns the death of a 9-year-old child diagnosed to have DMD, due to myocardial infarction. Histopathology examination concluded in characteristic results indicating the role of the coding gene of dystrophin. Steinert's disease (Myotonic Dystrophy or DM1) is a long term genetic disorder that affects muscle function. Symptoms include gradually worsening muscle loss and weakness. Muscles often contract and are unable to relax. Other symptoms may include cataracts, intellectual disability, and heart conduction problems. In men there may be early balding and an inability to have children. Myotonic dystrophy affects more than 1 in 8,000 people worldwide. While myotonic dystrophy can occur at any age, onset is typically in the 20s and 30s. It is the most common form of muscular dystrophy that begins in adulthood.

KEYWORDS: Forensic pathology; Muscular dystrophy; Duchenne muscular dystrophy; Steinert's disease.

INTRODUCTION

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is the most common (1/3,500 male patients), inherited, progressive neuromuscular disorder with specific phenotypic and genetic characteristics. In some cases, fatty and fibrous tissue replace muscle groups, therefore it is called as pseudo-hypertrophic muscular dystrophy.[1-3]

The gene involved, is the "dystrophin gene", largest of all the genes ever to be found (2.6×106 bp). It is located on X chromosome at the Xp21.2 locus. Deletions are the most common mechanism to cause the disease (60%), while point mutations take place in only 20-30% of the cases. The dystrophin protein is a structural component of major importance, which provides structural

stability to the dystroglycan complex (DGC) on the cell membrane.[4-6]

However, there is no structurally or functionally abnormal protein known that might represent the primary gene product, nor has any pathogenetic mechanism leading to the observed biochemical and histological alterations been elucidated. Among the numerous pathogenetic concepts the hypothesis of a structural or/and functional defect of the muscular plasma membrane is still the most attractive. It would explain both the excess of muscular constituents found in serum of patients and carriers, such as creatine kinase (CK), as well as the excessive calcium uptake by dystrophic muscle fibres, which, prior to necrosis, could lead to hypercontraction, rupture of myofilaments in adjacent sarcomeres and by excessive Ca uptake to mitochondrial damage causing crucial energy loss.[5-8]

This condition is characterized by progressive symmetric wasting of the leg and pelvic muscles, skeletal-spinal deformities, limb contractures, and restrictive lung disease. DMD appears between 3 to 5 years of age and spreads from the leg and pelvic muscles to the involuntary muscles. By the age of 12, the cardiac muscle progressively weakens, causing tachycardia and pulmonary problems. The cardiac muscle is the last one to fail, resulting in myocardial infarction and death, such as in the case registered in this report.[2,7,9]

Steinert's Disease

Steinert's disease is the first type of Myotonic Dystrophy (DM1) and is inherited as a neuromuscular autosomal dominant disorder. It is the most frequent syndrome with a genetic background to be apparent in adults (1/8,000) and its effect is multisystemic as the majority of the human body systems collapse.

The gene involved, is the *DMPK* coding for myotonic dystrophy protein kinase (myotonine), and is located on the long arm of chromosome 19 (19q13.3). DM1 is caused by an extended repetition of the CTG triplet in *DMPK*, which if more expanded than 37 repeats, leads to pre-mutation, and if even longer to symptomatic disease. Due to the fact that alleles with more than 37 repeats are unstable during mitosis and meiosis, individuals with this abnormal trinucleotide repeat are more likely to give birth to children with an even larger sequence, and therefore believed to undergo through an earlier onset and symptoms with greater severity.[10-13]

Recently, there has been found a direct connection between the number of this repetition and the cardiac muscle complications, however, the function of the protein produced and the molecular mechanism responsible for muscle weakness are yet to be characterized. Dysregulated Ca2+ homeostasis is considered a key initiator of muscle degeneration, as the transcripts of DMPK are also affected here. Intracellular Ca2+ is a regulator of both cell proliferation and apoptosis.[14,15]

Two major clinical forms can be distinguished, although both due to defects to the same gene. The common forms in adults, which combines progressive muscular dystrophy (weakness and atrophy of muscles), myotonia (delayed relaxation of a muscle after an initial contraction) and defects on other organs such as:

- Eyes , cataracts in nearly all patients aged 40 and more
- Neural system, sleep defects and cognitive function
- Heart, heart rhythm disorders
- Respiratory system, pneumopathies

The congenital form, which combines clinical picture of neonatal hypotonia and severe acute respiratory distress. If the child survives, the disease progresses to became a disabling condition, especially all the intellectual level. Its exclusive maternal transmission pattern is still not clearly understood.[11,14]

MATERIALS/METHODS

The incident concerning childhood boy with record of duchenne muscular dystrophy, whose death was due to a recent heart attack on ground of old. We received in plastic containers with formalin the following biological samples:

- Brain
- Heart
- Lung tissue sample
- Liver tissue sample
- Spleen tissue sample
- Part of muscle tissue
- Triangular part of muscle tissue

The incident concerning adult boy with record of Steinert's dystrophy, whose death was due to a recent heart attack. We received in plastic containers with formalin the following biological samples:

- Brain
- Heart
- Lung tissue sample
- Liver tissue sample
- Spleen tissue sample
- Flattened muscle tissue sample
- Kidney tissue sample

The tissue sections were stained with Hematoxylin and Eosin (H & E) staining technique. The procedure was:

- Deparaffinize the section: flame the slide on burner and place in the xylene. Repeat the treatment.
- Hydration: Hydrate the tissue section by passing through decreasing concentration of alcohol baths and water. (100%, 90%, 80%, 70%).
- Stain in hematoxylin for 4 minutes.
- Wash in running tap water until sections "blue" for 5 min-

utes or less.

- Differentiate in 1% acid alcohol (1% HCl in 70% alcohol) for 1 second.
- Wash in running tap water.
- Stain in Eosin for 2 minutes.
- Dehydrate in increasing concentration of alcohols and clear in xylene.
- Mount in mounting media.

After the staining procedure the sections observed under microscope and the results conducted.[16-18]

RESULTS

Duchenne Muscular Dystrophy

By histological examination conducted regions by varying the size of muscle fibers, severe degenerative changes, strong presence of interstitial fat (Figure 1), while the characteristic presence of spheroid muscle fibers (Figure 2).

Steinert's Disease

The myocardium presents areas with increased interstitial edema, focal interstitial fibrosis (Figure 3) and inflammatory infiltrates. The myocardial fibers present in places undulating topography, with relative disarray in their layout.

Also recognized moderate adipose infiltration (Figure 4), arterioles with thickened wall and in places narrowing of the coronary artery lumen at a rate of around 10-30%, while in two vessels the rate reaches 60-70%. Aorta relatively thickened wall and in places little evidence of atherosclerotic lesions. Lung tissue sample with extensive edema, cells filled with homogeneous eosinophilic material, sometimes in another degree haemorrhagic filling the alveoli, in the presence of granules haemosiderin positions, strong capillary hyperemia, with wall thickening of the arterioles and mild inflammatory infiltrates. Muscle tissue sample in which there are muscle fibers of varying size, in places with presence eccentric condenser cores, while recognizing fibers as annular fibers.

DISCUSSION

Duchenne Muscular Dystrophy

The purpose of the report is to study the disease in order to understand the genetic and molecular background, so that it becomes possible to early diagnosis and specific therapy. Conclusionally, the gene encoding a dystrophin protein of 3685 amino acids that is organized as follows into 4 groups:

- Triple helix group
- TERMINAL-C group
- Tether actin group
- Rich in cystein group

They have found at least seven different primers for each gene and is responsible for the production of a tissue-specific or deployable-specific isoform of the protein. Also at the

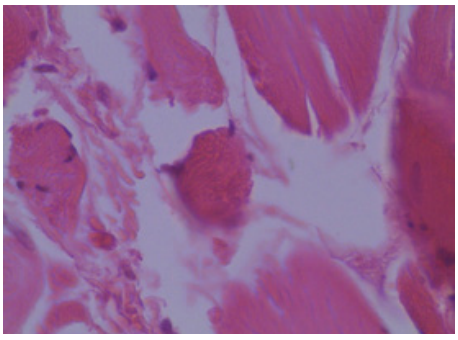

Figure 1: Histological examination.

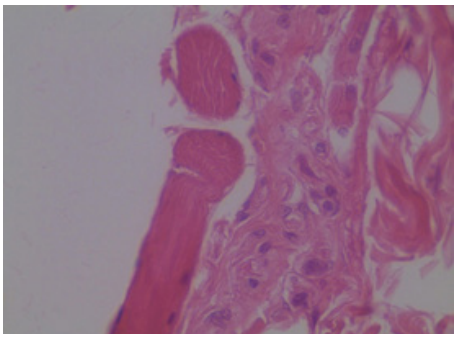

Figure 2: Characteristic presence of spheroid muscle fibers.

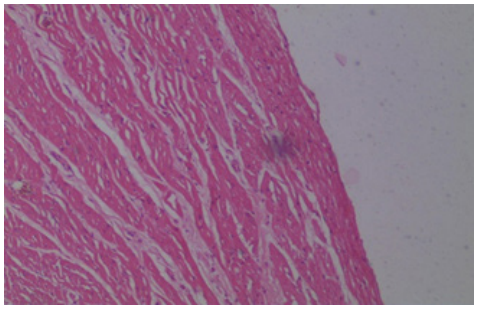

Figure 3: Myocardium presents areas.

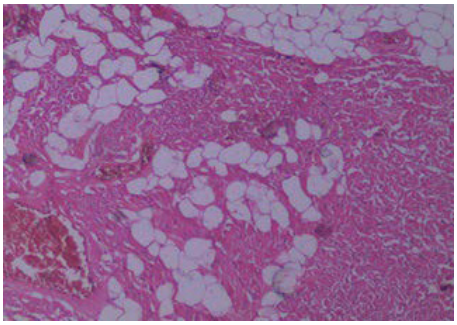

Figure 4: Moderate adipose infiltration.

gene, in mRNA level, occurs different splicing that respectively leads to increase of isoforms of dystrophin. Mutations in the dystrophin gene, usually deletions or duplications of exons, encoding alternative forms of the protein with unknown functional role that influence the stability and normal functioning of the muscles, leading to muscle weakness.[19]

At the present there is no cure for DMD syndrome, although various treatment techniques take place. Symptoms of muscle contractures and dystrophy delay to appear thanks to active physiotherapy, scoliosis can be managed, pulmonary morbidities are reduced or even prevented *via* airway clearance routine, and noninvasive or assisted ventilation is achieved through tracheostomy. The improvements in general care, myocardiopathy and scoliosis management are significant, thus giving the opportunity of a higher life expectancy, so that reaching adulthood is nowadays a possibility for DMD patients.

Though DMD is a syndrome with no current cure, it can be localized through prenatal control and diagnosis. Amniocentesis is the most common method used for detection of chromosomal mutations regarding the removal of a small amount of amniotic fluid. The amniotic fluid is later on analyzed, cultivated and the cells are submitted in DNA analysis. Before amniocentesis supportive and thorough genetic counseling is required for indications, benefits, hazards, and constraints of the technique.

Steinert's Disease

The diagnosis of disease is based on several criteria. First is the hereditary factor, when there are many cases present in the family. Second is the clinical factor, when subjects present characteristic signs of the disease. When these two factors are present the diagnosis is easy. Sometimes the diagnosis is more complex because certain subjects have very few signs of the disease while others have no signs at all. In DM1, the genetic anomaly is an increase in CTG repetitions in the DM1 gene. Within the normal population, the number of repetitions is always inferior to 40, while in subjects with the disease the number of repetitions can be as high as 4000 to 5000. There is currently no curative treatment available for this disease. It can be managed through various means including medication and/or methods aiming to improve the individual's quality of life (QoL). Cardiac monitoring is especially required to prevent these complications and is performed through a pacemaker. Myotonia, pain, mood disorders may all be treated through efficient medications. Kinesitherapy provides some relief and comfort to these patients. Some safety measures should be followed regarding medication and anesthesia during surgical interventions, in particular because the intervention is minor and the disease often remains unknown; the most common interventions in these patients are cataract interventions or gall bladder removal surgery.[16,17]

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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