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ON THE EARLY DIAGNOSIS OF MUSCULAR DYSTROPHY

Yengibaryan A.A., Matevosyan R.Sh., Hovsepyan M.E., Krasnikov N.F.

Chair of Medical Biology, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia

Abstract

According to the brief survey of literature data on muscular dystrophies or myodystrophies of different nosological types, all the changes taking place in skeletal muscles, biochemical, morphological, pathogenetic and other type changes, the type of mutation and consequence possibility of pathological gene penetration and efficacy of current methods of differential diagnostics are investigated. Since myodystrophies have a progressive course, particularly Duchenne and Becker, and their rate is significantly resulting in disability and death, it is verified that early differential diagnostics is very important for patients' social and psychological rehabilitation. However, the existing diagnostic methods are not always effective.

Nowadays it is extremely important to elaborate more effective methods for early diagnosis and their application in clinic.

Although there is a method of morphological examination of biopsy material, today it is noninformative, because the dystrophic changes in different types of myodystrophies are nonspecific.

Taking into consideration all the above mentioned we offer to make qualitative and quantitative histological examination of reparative myogenesis providing myoblasts and myotubules in biopsy material of skeletal muscles after genealogical examination in the groups of risk for diagnostic purposes. These cells arise after activation of stem cells (myosatellites) during initial changes in skeletal muscles.

All this can be informative in early period of myodystrophy. It may be informative about the direction, type of muscle lesions and prognosis.

Keywords: *myodystrophy, dystrophin, X-linked, dominant, recessive, myosattelite, myoblast, myotubule.*

The term "muscular dystrophy or myodystrophy" means a group of clinically polymorphic genetically determined diseases based on progressing degenerative changes in the fibers of skeletal muscles in the absence of primary pathology of peripheric motor neuron.

The cause of these diseases is either complete absence of highly molecular protein, i.e. dystrophin, or synthesis of defective or functionally unstable dystrophin stabilizing the muscular membrane (Figure 1).

Address for Correspondence:
Yerevan State Medical University after M. Heratsi,
2 Koryun Street, 0025, Yerevan, Armenia
Tel.: (374 10) 522279
E-mail: ripmatev@mail.ru

Lack of dystrophin in myofibrils brings to disintegration of the whole dystrophin-protein complex providing structural and functional organization of the cytoskeleton.

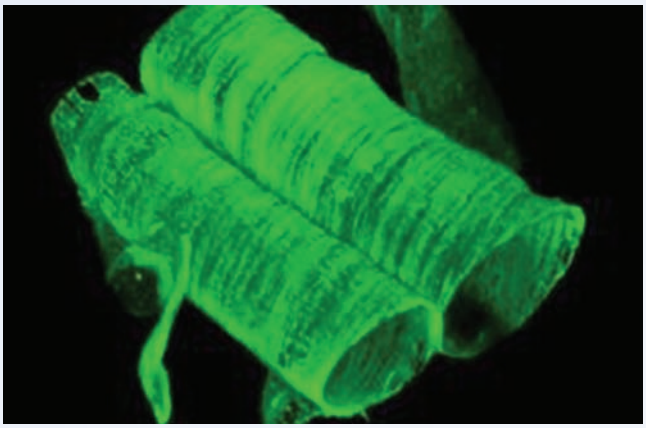

Figure 1. *Three-dimensional picture of muscular protein, dystrophin, using green fluorescent dye.*

Muscular dystrophy has a hereditary character. Duchenne and Becker dystrophies are inherited as X-linked recessive traits. In case of such inheritance heterozygote mothers are practically healthy but half of their sons suffer from this disease. Duchenne and Becker myodystrophies result from mutations in the gene for dystrophin in Xp21. They are allelic variants of this gene expression. This gene is the largest one consisting of 79 informative DNA segments – exons. The occurred mutation is a result of dystrophin gene deletion in 60-70%; its duplication in 5-10%; in 30% of cases point mutations are observed.

The incidence of Duchenne dystrophy is about 1 in 3.500 male births. Other clinical phenotypes are also associated with Xp21, e.g. familial X-linked myalgia, McLeods syndrome, quadriceps myopathy.

There are also types of muscular dystrophy, which are inherited by autosomal recessive pattern and sometimes by autosomal dominant. In these cases both sexes are affected. It is not an exception: the mutant alleles can arise under the influence of various mutagens.

A great variety of muscular dystrophies is described. They differ from each other by various progression rate of muscular lesion, character of morphological changes on cellular and subcellular levels, the location and, hence, clinical manifestation, age of disease onset, pattern of inheritance. All the mentioned varieties are united by the same pathological process and similar clinical picture: initial symptoms of pelvic and shoulder muscle weakness, typical gait, specific girdle deformations and progressive worsening of the disease.

Manifestation of various types of myodystrophies becomes evident at the age since 1 to 10-30. Progressive disability occurs in a few years and premature death as a consequence of cardiac disorder (Duchenne and Becker myodystrophies, respiratory muscles, pharyngeal muscles), oculopharengial dystrophy.

Unfortunately, nowadays these diseases are incurable and progressive to a certain extent. Therefore, early diagnosis of muscular dystrophies is of a great sociopsychological importance for patients.

The precise diagnosis can:

a). in some cases help to treat the patients by the moderate complex of therapeutic gymnastics and physiotherapy to maintain the function of healthy muscles and delay destructive process;

a). implement a course of symptomatic treatment delaying the course of the disease and promoting patients adaptation to progressive disability to arrange his/her working activity, position in family, community, pastime in a proper way.

Possibilities of differential diagnosis of muscular dystrophies

Among the existing diagnostic methods the following ones are mostly important:

a). genealogical method allows to diagnose a genetic disease if any relative has a similar disorder. However, this method is non informative in case new mutation occurs;

a). creatine (C) is the most commonly used enzyme for diagnostic purposes. This test is specific, and high serum content of C is usually indicative of disease of the skeletal muscle. High content of C is revealed in urine due to the increase of cell membrane permeability. However, this test is not specific since findings are typical of myositis and myopathies of other genesis. That is why this finding can not be considered as basic to make a diagnosis;

a). muscle biopsy is used for biochemical and morphological analysis, but specificity, which is typical of some dystrophies, is not detected by this method;

a). electromyography (EMG) is a very sensitive electrophysiological method; however, it is difficult to define the character of muscular lesions and to make an accurate diagnosis;

a). serum enzyme determination is one of the most conventional method to make a diagnosis of muscular dystrophies. The content

of enzymes such as aldolase, dehydrogenase, lactase, transaminase, glutaminase, etc. exceeds the norm long before the first clinical symptoms occur. However, their content has a tendency to decrease along with the acute condition of muscle tissue disintegration.

Creatine phosphokinase is the most commonly used enzyme for diagnostic purposes; it is present in skeletal muscles in high concentration. However, high concentration of creatine phosphokinase is detected mainly in Duchenne and Becker dystrophies. In other types of dystrophies this enzyme content increases slightly and maintained within the norm. Note should also be taken that diagnostic efficacy of this enzyme content in serum of a sick person is 70-80%.

Thus, we can state that there is no specific and highly effective method for diagnosis of muscular dystrophies yet.

Our version of increasing the efficacy of muscular dystrophy differential diagnosis

Since muscular dystrophies sooner or later result in disability and are actually incurable it is very important to set an early differential diagnosis for psychological, physical and social rehabilitation. For this purpose besides the implementation of all conventional diagnostic methods it is necessary:

a). to raise awareness of the general population with the aim of explaining the importance of visiting genetic counseling, even if only a single case exists among the family members;

b). to inform probands who are in a risk group that besides creatine phosphokinase determination in blood serum they must undergo biopsy of pelvic and shoulder skeletal muscles. We think, the indubitable fact that the striated muscles have so called stem cells (satellite cells) makes this investigation necessary. These cells have oval shape with large bubbled nuclei situated under sarcolemma of muscle fibers or in between them. They become active under destruction of muscle fibers, transform into myoblasts, and then in myotubules stimulating reparative myogenesis (Figure 2).

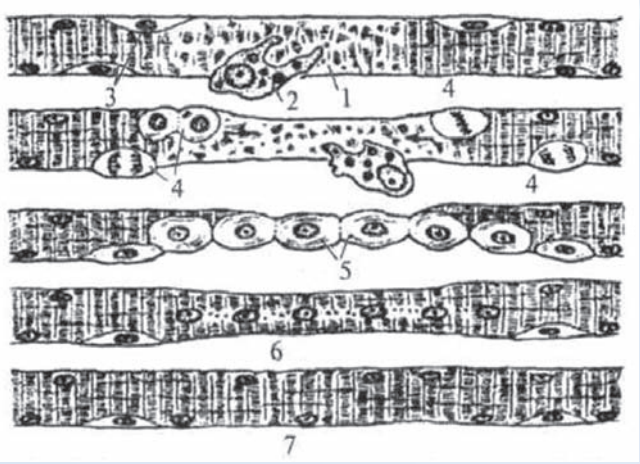

Figure 2. *Schematic picture of muscular fiber regeneration:1) damaged lesion; 2) macrophage; 3)myosattelite; 4) dividing sattelite; 5) young myoblasts; 6) myotubule; 7) regenerated myofibrille.*

Currently at examination of the muscle biopsy material specialists mainly focus research on destruction of contractile and mitochondrial elements of muscular framework, edema, and other destructive processes occurring in muscular dystrophy. All mentioned destructive processes affect the whole muscle. Changes of contractile apparatus, lipid dystrophy and activation of regenerative elements in the contractive row are revealed. Hence, we should not speak about the specificity of the changes typical for progressing muscular dystrophy.

In our opinion, besides atrophic and pseudoatrophic processes the investigation of the character of reparative myogenesis in dystrophic changes of muscular fibers not only in the dystrophy focus but also in remote site might provide information about the presence of myodystrophy. It can serve worthwhile information not only about muscle reactivity, but also about regeneration intensity, direction and the form of muscle damage.

If a doctor has any difficulty making differential diagnostics of myodystrophy using the above mentioned methods, he can use the method of genetic diagnosis as well. n