

A New Hypothesis of Duchenne Muscular Dystrophy

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Abstract: Duchenne Muscular Dystrophy is the product the mutation the gene-dystrophine and appearing defective protein dystrophin. Its function is unclear, suppose protection membranes during the contraction-relax skeletal muscles. The cytoplasmic dystrophin acts as the complexes with different proteins inside and around membranes, which are placing in skeletal muscles, heart, different regions brain, internal organs, their function unclear. The high activity enzyme creatin-kinase in the patients blood is the known fact which is usually explain damage of the process contraction-relax skeletal muscles. The surprising activity enzyme -23 000 M E was found by author at large families with typical pedigree where have some patients and some boys without signs muscle weakness. There were 4 boys 12-22 months life during forming walk, later these boys were diagnosed as Duchenne Muscular Dystrophy patients. Such activity I did not find in literature. Usually the highest activity enzyme 10 000-12 000 ME. This fact testify the simultaneously damage many membranes on large territory, it permits suppose organized damage membranes. Author believe all complexes normal dystrophines may work as one System, beginning learn walk and finishing as age myopathy after 60 years. Suppose the System was ancient and appeared when movements become intensive and one gene utrophine/dystrophine turned out in two genes: utrophin and dystrophin. Dystrophin signal communication is known, but its investigation has begun and showed complex signaling pathways. It is possible to suppose that the first stage of the disease is damage signaling ways. Damage homeostasis and membranes is the second stage. There are deep changes of metabolism: decreasing true muscle proteins, phospholipids, increasing hormones, appearing hyper aminoaciduria. Apoptosis –the three stage of the disease and general destructive factor which turn out pathologic process to the fatal end. Apoptosis hinder all tryings organism to interrupt pathological process and therapeutic trying. Apoptosis can not stop once it began. All three stages have place in preclinical time. The clinic symptoms express destruction more the half skeletal muscles, severe damage metabolism, damage system protection membranes and can not be onset of the disease. The important problem of the disease – studying interaction dystrophin-complexes with membranes during physical stress, signaling ways. Two factors determinate rapid course: damage D-System and apoptosis.

Keywords: Dystrophin, Creatinkinase, Phospholipids, Apoptosis

1. Introduction

At the middle of 19th century Guillaume- Benjamin Duchenne studied a form skeletal muscular pathology in boys named it “ Pseudohypertrophic Paralysis” because the patients looked as athletes, but could not walk and were intellectual be backward. He did not find any pathology the central nervous system, hypertrophies of skeletal muscles turned out pseudohypertrophies and G. B. Duchenn defined it as disease of skeletal muscles. The name of the disease: progressive muscular atrophy or muscular dystrophy determinate for long time the

investigation skeletal muscles and delay studying the disease. Damage brain was ignored.

In 1968 L. Kunkel described the gene-dystrophin. This gene is the longest in the human genome, encompassing 2, 6 million base pairs of DNA and containing 79 exons. The product of the gene –protein-dystrophin (D) was described in 1987 y. E. Hoffman [4]. Now there is much information concerning of D, which don't exist isolated, it forms tightly associated complexes [1-10]. The dystroglycoprotein complex – DGC- the most studying,

plays a mechanical function in stabilizing the sarcolemma against stresses during muscles contraction; role scaffold in neuromuscular junctions; the general function is the connection the cytoskeleton to the extracellular matrix. Other complexes D are studying, its role as mechanical component of cell in signaling function The deficiency D skeletal muscles reduces muscle stiffness, increases sarcolemma deformability, membranes abnormal permeability [10-15]. It is known that D present in the brain among the cortical neurons, hyppocamp, Purkinje cells, astrocytes, blood-brain barrier, but its function is unclear [15-29, 38-47] DMD has three symptoms: damage skeletal muscles, brain, heart, but every symptom is studying apart, the great attention devote the skeletal muscles. The disease has not clear pathogenesis and effective treatment. Based on the analysis the results of

studying DMD and own experience I suggest a new hypothesis for discussion. Before formulate the hypothesis necessary introduce the general facts of the investigation.

2. Material and Infer

The time onset the pathologic process of the disease has the important meaning, because permit to understand essence the disease. Traditionally the appearing clinical symptoms of the muscular weakness of the patients 3-5 years old - the time of onset pathologic process, but the clinic symptoms cannot be criterion because they appear after the loss mass of skeletal muscular and after the large changes of metabolism. I have summarized the results of my biochemical investigation the patients 3-5 years of life as the scheme pathological process. [32]

Table 1. Biochemical parameters the patients with DMD [32].

tissue	increase	decrease
Blood	total lipids, activity of enzymes: creatinkinasa, aldolasa, Hormones: ACTG, cortisol	phospholipides
Muscles	collagen, total lipids	carnosin, myosin, myoglobin, phospholipides
Urine	Hyper aminoaciduria creatinuria	

The table 1 shows the deep changes of metabolism: decreasing true muscle proteins, phospholipids, increasing hormones, enzymes in blood, appearing hyper aminoaciduria. I was shocked when I saw the loss contractility and grey color skeletal muscles the patients 4 years old during biopsy. The presented data shows that this period is not the onset of the disease.

The onset of the disease I revealed during the scientific travel at retired places. Trying to reveal ill boys in the large families with DMD I used the creatin-kinase (CK) test and found the highest activity creatin kinasa 23 000 and 21 000 ME in 4 boys from 14 months to 2 years old, later the genetic analysis confirmed DMD in these boys. One family was the russian, another was the tadjik. This activity CK was surprising, usually the maximal activity CK 10 000- 12 000 ME in the patients 3-5 years old, 3 000-5000 ME 7-9 years old and 1000-500 ME - 12 years old Figure 1.

Index 23 000 ME activity CK point to breaking many membranes because only the skeletal muscles give not such figure., as have shown results of studying enzymes J. Dreyfus and G. Shapira (36). The graphic shows the meaning CK for the diagnosis, prognosis, definition rapid course disease, but the general meaning - opening onset the disease.

The surprising CK, destroy many membranes, connection the onset of the disease and the onset walking permit suppose existence the System unites the whole dystrophines [32]. This System stabilize membranes during stress.

Like symphonic orchestra, where each instrument has own party, different isomers dystrophines have own party, but together they express one idea, one melody, one general aim - cover membranes during physical stress Only all family dystrophines may do this task, like only big orchestra may express idea compositor.

I suppose appearing the System was at early vertebrates,

when one gene utrophin-dystrophin turned out in two genes utrophin and dystrophin, May be the gene-dystrophine is the longest in man genome because regulation D require it. System D has onset one year of life and suppose has the end at 60-70 years old, because manifestations of the myopathy of old ages repeats the same symptoms muscular weakness, damage coordination *and the histologic picture of the skeletal muscles.*

3. Discussion

G. Shapira and J. Dreyfus in 1964 y. wrote in their monography Biochemistry Myopathy: "Muscular dystrophy is a muscular disease, but it is by no means proved that origin of the disease is in the muscles itself [37]. However this disease prize now as muscle pathology.

DMD has three clinic symptoms: damage skeletal muscles, heart, brain. These symptoms are three components of movements, all three has defective D.

My idea of System D help to understand large spreading D, present D at optical and acoustic analysators, which signals can to increase or stop movement. Stress touch many organs as lien, lungs, hepar, which are necessary during stress. [32].

Different age groups the patients with Duchenne Muscular Dystrophy.

Studying role D in skeletal muscles show the part in mechanical stability costamer, protect process contraction-relax and estimate D as the structure protein but don't explain rapid course the disease.[32-37]

The question –what determinate the rapid pathological temp the disease is unclear.[60-77]

I suppose hypoxia and apoptosis the cause of rapid temp of the pathological process. For the classic variant DMD the rapid course of the disease is typical, but there are some

variants with mild course and late onset, possible organism can delay development of apoptosis.

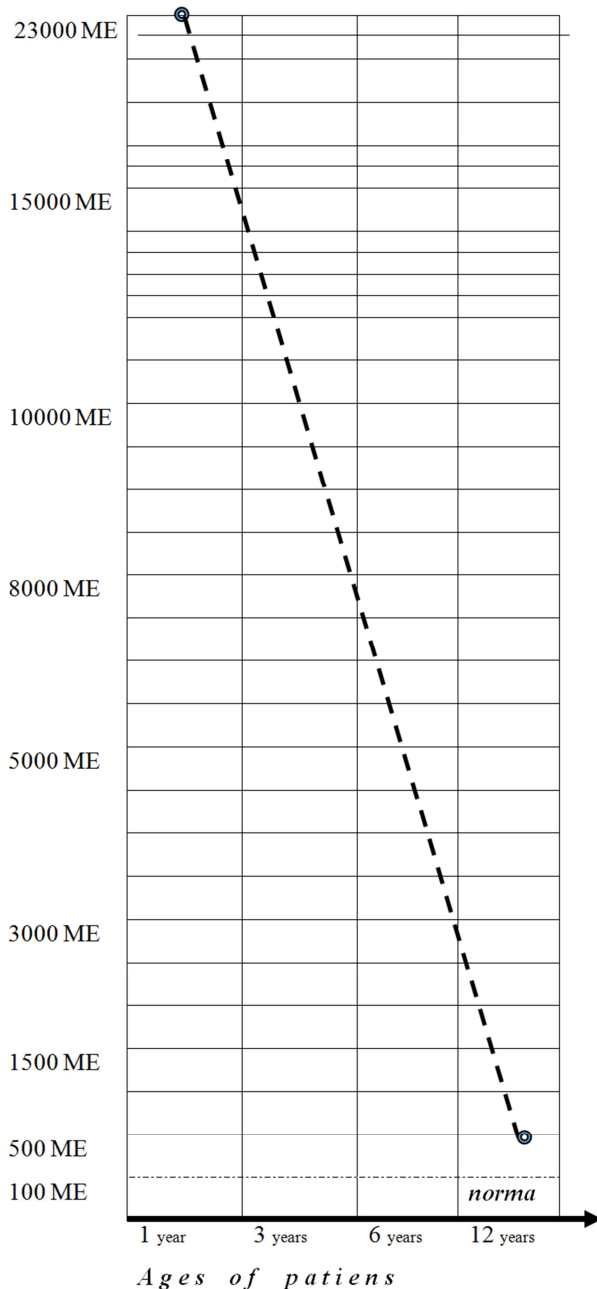


Figure 1. Activity Creatinkinasa (32)

I suppose, that the role the pathology of the lipid metabolism did not prize, though changes this metabolism are expressed; the appearance of the patients, the deposit lipids as pseudohypertrophies in many skeletal muscles, tongue, internal organs. May be conflict the complex beta-dystroglycan with phospholipids membrane is a key component of the pathologic process [32].

Apoptosis is the programm death of cells itself or from cells of the immune system. Apoptosis occurs when cells existence uselessly for organism. The initiative of apoptosis is regulated intracellular signal when cells in stress.

Apoptosis is the highly regulated process and cannot stop once it has begun. [47-51] Apoptotic markers: DNA fragmentation, caspases activation, cytochrome c release, mRNA decay are revealed at model mdx, at the patients with DMD. The morphologic investigation the skeletal muscles of the patients show the typical changes: cells decreased, round of, condensation chromatin The question of apoptosis or necrosis is discussed, but necessary take into consideration the stage of the disease - the onset of the disease accompany the signs of apoptosis, the late stage the necrosis. [52-60]

So, pathological process DMD has. some stages, see schema 2.

4. Conclusion Hypothesis

Duchenne disease begins as destroy the System Dystrophines. This System unite all dystrophines placing everywhere. Normal work System - stabilize membranes during stress. Defective dystrophines damage work System, membranes. Breaking membranes excites disbalans metabolism, appear hypoxia. Dangerous situation excite apoptosis. Apoptosis - the general factor destroy metabolism which lead organism to fatal end.

Two factors determinate the disease-damage System D and apoptosis.

In the future is necessary: 1 studying apoptosis and possibilities organism delay it. 2- studying the dysrophine complexes in brain, heart. 3- studying connection phospholipids membranes and dystrophine.

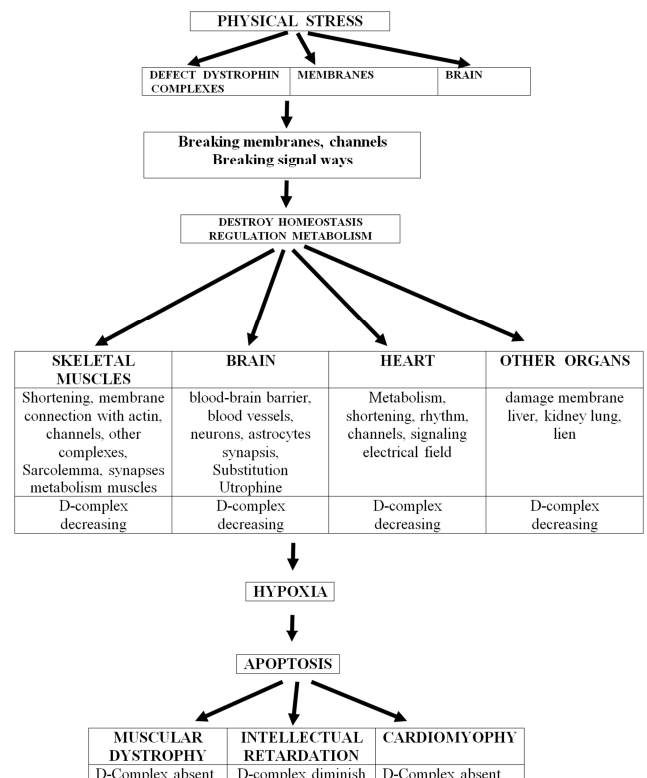


Figure 2. Pathogenesis Duchenne Disease.

5. Resume

Duchenne Muscular Dystrophy - a neuromuscular disease- has three clinical symptoms: damage skeletal muscles, heart and brain, the last symptom was marked Duchenn. The symptoms are three components of movements. The onset of the disease reveals by the creatinkinasa-test (23 000ME) during beginning walking. The test testify damage membranes on large territory because only skeletal muscles cant do it. Author believe the damage membranes connect with destroy System, units the whole dysrophines. System stabilize membranes during physical stress. Defective dystrophines destroy work System and membranes. This situation not dangerous but appear apoptosis, which is the general factor leading organism to fatal end.

Two factors determinate course the disease: damage system dystrophines and apoptosis.

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