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# A New View Duchenne Muscular Dystrophy

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*Abstract-* Duchenne Muscular Dystrophy is the result of mutation gene-dystrophine, product - protein-dystrophin presents in organism as the complexes proteins placing everywhere, their role unclear. Suppose all dystrophine complexes work as one functional System D, thanks signal ability complexes. Suppose the System D the ancient and appeared when the gene dystrophin-utrophin divided into two genes dystrophin and utrophin at early vertebrates. Perfect this System made the gene the longest in human genome. The surprising activity creat inkinase-21-23 000 ME, found by author, make to think of the damage much membranes-damage System. Destroy System D is beginning of the disease, finishing apoptosis-general destructive factor. Two factors determinate the disease–damage the system D and apoptosis.

*Keywords: dystrophin, creatine kinase, metabolism, apoptosis.*

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## I. Introduction

At the middle of 19th century Guillaume- Benjamin Duchenne studied an unusual form skeletal muscular pathology in boys and named it "Pseudohypertrophic Paralysis" because the patients looked as athletes , but could not walk and were intellectual be backward. He did not find pathology the central nervous system, hypertrophies of skeletal muscles turned out pseudohypertrophies skeletal muscles and G.B. Duchenn called disease as pathology skeletal muscles , later name of the disease progressive muscular atrophy or muscular dystrophy. Consider the disease as the pathology skeletal muscles delay its studying.

In 1968 L.Kunkel (1) described the gene-dystrophin. This gene 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) described in 1987 y. E. Hoffman(2). There are much information D, it don't exist isolated, forming tightly associated complexes with other proteins membrane and plasma The dystrogluco protein complex – DGC- the most studying, its plays a mechanical function in stabilizing the sarcolemma during muscles contraction; role scaffold in neuromuscular junctions. The general function DGC in skeletal muscles - the connection the cytoskeleton to the extracellular matrix. There are the popular scheme DGC through laminin has connection with sarcolemma and links with contractile apparatus. DGC forming numerous proteins including syntrophin, sarcoglucan, sarcospan, dystrobrevin find in skeletal muscles and brain. The deficiency D skeletal muscles reduces muscle stiffness, increases sarcolemma deformability, membranes abnormal permeability.(3-13) It is known that DGC present in the brain among the cortical neurons, hyppocamp, Purkinje cells, astrocytes, blood-brain barrier, choroid plexus, glial but its function is unclear.D-complexes found in internal organs (kidney, liver, lungs), periphery nerves, acustic and optic analyzators (14-19 ).

The function D repeat Utrophin (U) which encoded by the UTRN- autosomal gene. Studying the models DMD show complexes with U instead DGC, the same changes observed in patients.DMD has three clinical symptoms: damage skeletal muscles, brain, heart, but every symptom is studying apart, the great attention devote skeletal muscles. The disease has not clear pathogenesis and effective treatment.

## II. Material and Method (20)

The time onset pathologic process disease has the important meaning, because permit understand essence a disease. Traditionally the first criterion onset of the disease was appearing clinical symptoms of the muscular weakness of the patients 3-5 years old as difficulties up stairs.Later the high activity some enzymes, especially creat inkinasa(CK), become the test for this disease. There are little information of early period the disease because the most patients in clinic loss walking and the parents of the patients rarely early address. Summarized the results biochemical investigation 34 patients 3-5 years of life present scheme 1 (20,21).

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*Schema 1:* Biochemical parameters the patients 3-5 years old with DMD (20)

| Tissue | Increase | Decrease |
|---|---|---|
| Blood | total lipids, activity of enzymes: creatinkinasa, aldolasa, Hormones: ACTG, cortisol | phospholipides |
| Muscles | collagen, total lipids | carnosin, myosin, myoglobin, phospholipides |
| Urine | hyperaminoaciduria creatinuria | |

The scheme shows the deep changes of metabolism: decreasing true muscle proteins, phospholipids, increasing hormones, enzymes in blood, appearing hyperaminoaciduria. I was shocked when I saw the loss contractility muscles, grey color during biopsy at patient 4 age old. The presented data shows that this period is not the onset of the disease, these changes are typical for destruction metabolism.

The onset of the disease revealed during my scientific travel at retired places. Trying to reveal ill boys in the large families with DMD I used CK test and found the highest activity 23 000 and 21 000 ME in 4 boys 14-24,months old; later the genetic analysis confirmed DMD in these boys. One family is russian, another tadjik See scheme 2. which shows rapid fall activity CK in blood during the disease.

The presented facts point to the time of the onset the disease and rapid course pathologic process in preclinical period. Activity CK was defined by standard spectrophotometric method (norma 100 ME) This exponent was surprising, because usually the maximal activity CK 10 000.- 15 000 ME in the patients 3-5 years old, 3 000-5000 ME - 7-9 years old and 1000-500 ME - 12 years old. The onset of the disease is in preclinical period.

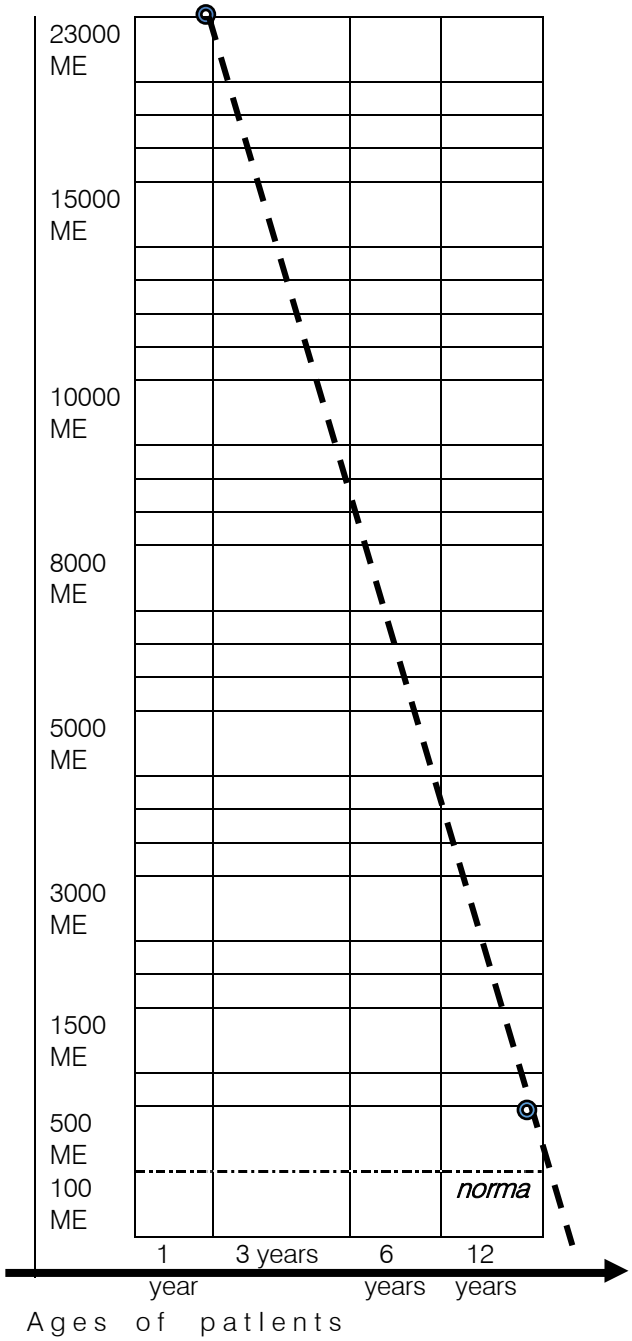
*A new hypothesis*

The surprising activity CK must to think of damage many membranes during physical stress, because learning walk is the intensive work patients this age. The calculation done by J. Dreyfus and G. Shapira show that exponent significant exceed CK which can way out from skeletal muscles. System unites all D complexes thanks its signal abilities.

Existence System D help to understand present D at optical and acoustic analyzators, which signals can to increase or stopmovement, touch internal organs as lien, lungs, liver. D-system has onset one year of life and suppose the end 60-70 years old because manifestations of the myopathy of old ages repeat the same symptoms muscular weakness and damage coordination.

Damage System D determinates permeability membranes–destroy metabolism- appear apoptosis. Apoptosis - general factor rapid course the disease, destruction skeletal muscles, System D. Studying the disease by the stages help to reveal the logic biochemical changes. The most important the first stage – time damage System D and appearing apoptosis.

*Scheme 2:* ACTIVITY CREATINKINASA( )the patients with Duchenne Muscular Dystrophy




## III. Discussion

A new view consider DMD as the neuromuscular pathology with damage brain, skeletal muscles, heart - three general factors of movement. Intensive movements crease overload physical stress which hearts membranes. Nature produced cover membranes from early vertebrates million years ago. Complicated regulation this cover made the gene the longest human genome. Suppose role this cover membranes play System Dystrophines (DSystem).

*Two factors:* damage D-System and apoptosisbase a new hypothesis.

D System unites all complexes D placing everywhere. Existence System D help to understand present D at optical and acoustic analyzators, which signals can to increase or stop movement. Like symphonic orchestra, where each instrument has own party, different isomers dystrophines complexes have own party, but together they express one idea, one melody, one general aim - cover membranes during physical stress. Only all family dystrophines do this task, like only orchestra may express idea compositor. How System save membranes is unclear: limit time for intensive movements, for example high speed for short distance or another measures.

Contact D System withmembranes the most interesting, especially through D-complexes.

*Complexes D* are well studying in the skeletal muscles, especially DGC. Suppose it stabilizes the sarcolemma; takes a part as scaffold neuromuscular junctions; connects the cytoskeleton to the extracellular matrix. The popular scheme shows connection Dystrophin associated complex with proteins (DPC) trough beta-dystroglucan-laminin with sarcolemma. Disassociation complex lead to disrubtion of cell signaling, loss connection with contractile elements (22-30).

In brain isomers D syntrophin, dystroglucan, dystrobrevin are in glial, blood-brain barrier, cells Purkinje, astrocytes, hyppocamp, vascular cells.

All three clinical symptoms characterized by absent the full-lengh isomers D.(31 -37).

The couple-D and proteins, did not analysed: who determinate general role, who has contact with membrane? May be D only staffold for signal and transport, contact with membrane have different proteins, possible the cause in bad contact or damage signal ?

Nobody consider connection D complexes with phospholipids membranes in spite of the fact that damage lipid metabolism determinate the typical appearance patient with pseudo hypertrophiesmany skeletal muscles. Patients blood shows hyperlipidemia, hypercholesterol, increasing correlation fatty acids/ glucerol.(20,41).

The work with the dipepdites is not finished, its meaning needs in studying especially the dipeptide carnosin (beta alanyl-L-gistidin). Carnosin hasthe high concentration in the skeletal muscles, has close connect with synapsis, its early disappearance make think of its role in pathogenesis, especially comparison with other forms myopathies.

The great interest call the conflict between the intensive breaking metabolism at the patients and absent reaction organism. The blood circulation overcrowded proteins, lipids, membranes ,channels are breaking, the work heart is destroy, but don't call complaints; creasing impression "remedy" in blood like narcotic.

Damage D-System destroy metabolism and homeostasis which lead to apoptosis - programmed cells death from cells immune system.

*Apoptosis*– is a form of programmed cell death or cell "suicide" which observed in multicellular organism. Unlike necrosis apoptosis produces cell fragments called apoptic bodies that fagocytes are able to engulf and remove before contents of the cell. Apoptosis begins the nucleus of the cell begins to shrink. After it plasma membrane blebs and folds around different organells and move away from one another. Immuno histochemical studies describe the signs apoptosis in the patients; DNA fragmentation, caspases activation, cytochrome c release, mRNA decay; in skeletal muscles the typical changes: cells decreased, round of, condensation chromatin (38-42). Take away half of the mass of skeletal muscles during 1-2 years can do only apoptosis. Shock apoptosis on immature brain patient excites the deep retardation delay intellectual development,. cognitive difficulties are revealed during learning. (17,42). Some authors connect cognitive troubles with pathology definite D-complex.

Hypoxia play the general role in the pathogenesis increasing destroy metabolism , but it origin unclear, possible apoptosis and hypoxia appear simultaneously. There are some factors delay or increase apoptosis, but they not be analysed. Possible think that Becker form has not apoptosis.

A new conception of pathogenesis connect the onset of the disease with destroy work System, rapid course with apoptosis, the total dystrophy with serious damage metabolism. The presented facts show how much information of pathological process we have at late period and little of early period; how much is known about skeletal muscles and how little of brain.(43-48).

Using non-mammalian model, especially drosophila melanogaster, show connection D with movements. Suppose D-System is a part of the complex locomotor system. A new view offer the first attempt explain role D-complexes in organism.

*The title Duchenne Muscular Dystrophy* necessary be replaced Duchenne"s Disease or Duchenne Dystropathia (DD).

## IV. Results

The existence D - System basis on 1 – the highest activity CK which shows simultaneusly damage many membranes-damage system. 2-full-lengh isomers D distinguish heart, skeletal muscles, brain as the general components System. 3 D- System is the ancient from early vertebrates, its perfect made the gene the longest in man genome.

Damage D-System begins pathologic process of the disease. Destroy metabolism and the specific features age patients excite apoptosis Apoptosis – the general factor rapid course of the disease, loss walking, destruction skeletal muscles, brain, heart, D-System. two events are in preclinical period of the disease.

## V. Conclusion

System D unit all complexes dystrophines - the first attempt to explain the role D complexes in organism. The role System D-defence membranes during physical stress. Destroy System D lead to destruction membranes, metabolism, appearing

apoptosis – the general factor rapid course of the disease. The onset of the disease and apoptosis have place in preclinical stage

## Resume

Duchenne Muscular Dystrophy - neuromuscular disease- has three clinical symptoms: damage skeletal muscles, heart and brain – threecomponents of movements. Intensive forming walk accompany the physical stress, which damage work of membranes.. The activity CK - 23 000 ME point to damage mass membranes on large territory- damage system. Such System D units the whole dystrophines for work as functional system., thanks signal communication complexes. Destroy System excite damage membranes, metabolism. This factor and specific features age patients call apoptosis, which is the general destructive factor leading organism to fatal end. Two factors determinate course the classic type DD: damage System D and apoptosis in preclinical stage.

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