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A New View on 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 creatinkinase -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.

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 doesn't exist isolated, forming tightly associated complexes with other proteins membrane and plasma The dystroglucoprotein 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 reduce 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 devotes skeletal muscles. The disease has not clear pathogenesis and effective treatment.

Material and Method [20]

The time onset pathologic process disease has the important meaning, because permit understand essence disease. Traditionally

the first criterion onset of the disease was appearing clinical symptoms of the muscular weakness the patients 3-5 years old as difficulties upstairs. Later the high activity some enzymes especially creatinkinasa (CK) become the test for this disease. There is little information of early period 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].

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 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 shows rapid fall activity CK in blood during the disease. 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

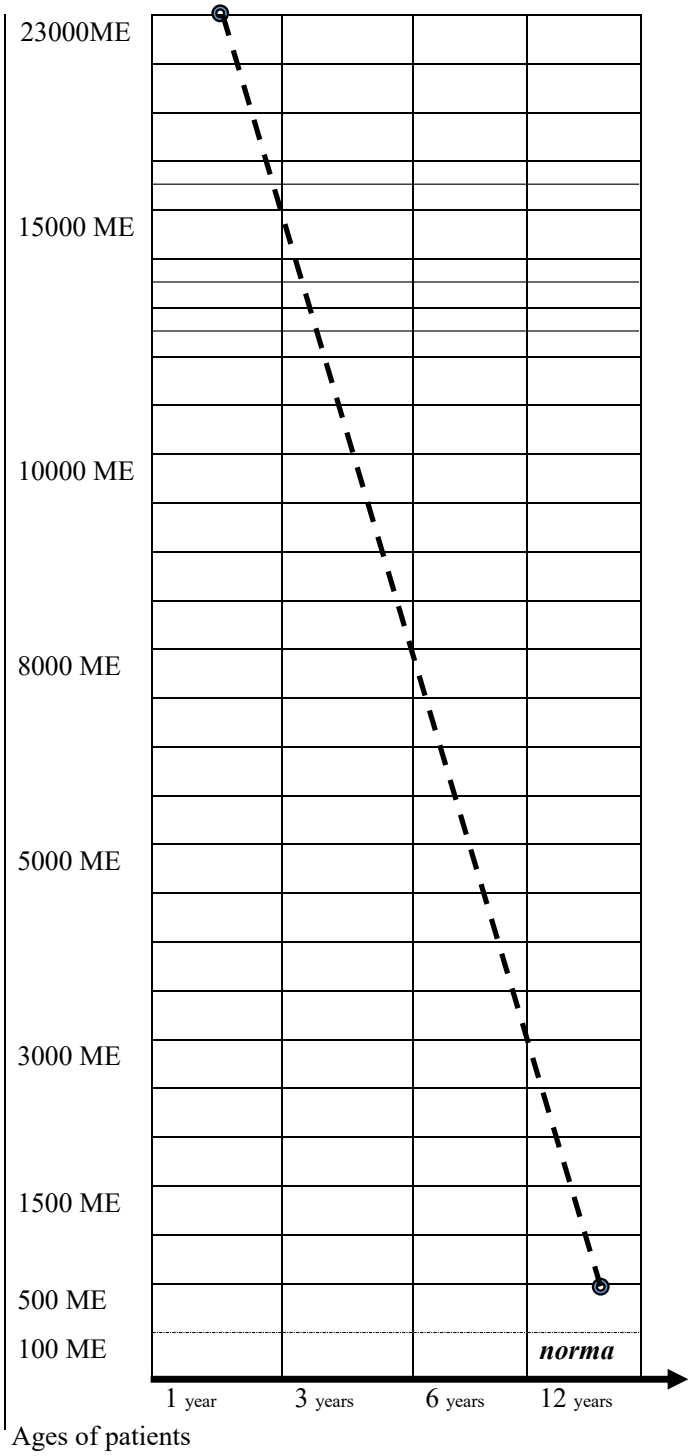
The surprising activity CK must to think of damage many membranes during physical stress, because learning walk is the intensive work patients this age. The calculation done by J. Dreyfus and G. Shapira show that this exponent significant exceed CK which can way out from skeletal muscles. System unites 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 stop movement. The. membranes internal organs as lien, lungs, liver also take apart in physical stress 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 uncrease permeability membranes –destroy metabolism- appear apoptosis. Apoptosis - general factor rapid course the disease, destruction skeletal muscles, System D.

Scheme 2 activity creatinkinasa

The patients with Duchenne Muscular Dystrophy



Discussion

A new view considers 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 in human genome. Suppose role this cover membranes play System Dystrophines (D System).

Two factors: damage D-System and apoptosis base 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 with membranes the most interesting, especially through D-complexes. Complexes D studying in the skeletal muscles, especially DGC, 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 cell, 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 but its role unclear. All three clinical symptoms characterized by absent the full-lengh isomers D [31-37].

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

Nobody considers connection D complexes with phospholipids membranes in spite of the fact that damage lipid metabolism determinate the typical appearance patient with pseudohypertrophy's many skeletal muscles. Patients' blood shows hyperlipidemia, hypercholesterol, increasing correlation fatty acids/glucerol [20,41].

The work with the dipepdites is not finished needs in studying especially the dipeptide carnosin (beta alanyl-L-gistidin). Carnosin is the 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 calls 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 destroyed, 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. Immunohistochemical 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 its origin unclear, possible apoptosis and hypoxia appear simultaneously. There are some factors delay or increase apoptosis, but they not be analyzed. Possible think that Becker form has not apoptosis.
A new conception of pathogenesis connects 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).

Conclusion

Experience and long thinking help to understand role D-complexes in organism. The surprising activity CK in patients consider as simultaneously destroy many membranes and as existence D – System, unite D-complexes placing everywhere. The damage D-System and specific age patient's determinate appearing apoptosis - general factor of rapid course the disease.

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