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Biochemical Mechanisms of Progressive Muscle Atrophies: A Comparative Analysis of Clinical Forms and the Experimental Model of Vitamin E Deficiency

Bon EI*, Maksimovich N Ye, Sidzineuskaya AI, Sorokina TS and Zholnerovich MA

Grodno State Medical University, Belarus

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***Corresponding author:** Bon EI, Grodno State Medical University, Belarus

Introduction

Progressive muscle atrophies represent a heterogeneous group of neuromuscular system disorders, traditionally divided into primary myopathies (muscular dystrophies proper) and secondary neurogenic atrophies arising from damage to the spinal cord's motor neurons or their axons. Despite a long history of study, the etiology and pathogenesis of these conditions remain largely unclear, and a unified concept of their origin is absent [1-2]. Clinical practice and pathological anatomy data indicate the heterogeneity of the pathogenetic mechanisms underlying various forms of muscle atrophy. A significant obstacle to studying these diseases for a long time was the lack of adequate experimental models. The situation changed with the discovery that a vitamin E-deficient diet causes changes in animal muscle tissue similar to those seen in human progressive muscular dystrophy [3], making it possible to use an experimental model for in-depth analysis of pathological processes. However, despite the similarity of several morphological and biochemical manifestations, vitamin E deficiency in animals cannot be fully equated with the human disease [4], necessitating a critical approach to interpreting the data obtained. Consequently, a comprehensive biochemical study of both the experimental model and the clinical forms of muscle atrophies become particularly important [5-6]. A detailed analysis of changes in protein, carbohydrate-phosphorus, enzymatic, and mineral metabolism in affected tissues allows us to approach an understanding of the key pathogenetic mechanisms [7]. This work is dedicated to systematizing and analyzing the biochemical shifts identified in various forms of muscle atrophy to identify common patterns and specific features of metabolic disturbances.

Main Body

The diverse forms of progressive muscle atrophies are usually divided into two groups based on pathogenetic criteria:

Primary myopathies (progressive muscular dystrophies), occurring in the absence of functional disorders of the nervous system.

Secondary neurogenic muscle atrophies associated with the loss of function of motor cells in the anterior horns of the spinal cord and their axons. Within the group of neurogenic atrophies, a distinction is made between spinal and neural forms, depending on whether only the motor cells of the anterior horns are affected or the damage also involves the axons of peripheral nerves.

According to S N Davidenkov [1], all types of progressive muscle atrophy can be presented as follows:

- Primary myopathy (progressive muscular dystrophy):
- Pseudohypertrophy (Duchenne form).
- Juvenile myopathy (Erb's juvenile form).
- Scapulohumeral-facial myopathy (Landouzy-Dejerine form).
- Secondary neurogenic muscle atrophy: Spinal form (Werdnig–Hoffmann type).
- Neural form (Roth's peripheral form of muscular tabes, Charcot-Marie amyotrophy).

In addition to the mentioned forms of muscle and neuromuscular pathology, several other clinical variants exist [1-2].

The etiology and pathogenesis of the listed diseases cannot be considered elucidated. The hypothesis of hereditary predisposition, proposed by a number of predominantly foreign authors, faces objections and does not clarify the origin and mechanism of neuromuscular diseases [1-8].

There are strong reasons to believe that the nature of the pathogenetic factors causing various forms of neuromuscular disorders is not the same in all cases. This is evidenced by:

- the clinical picture of the diseases;
- the features of pathomorphological changes in muscles;
- the non-identical nature of biochemical shifts in patients with different forms of pathology.

Attempts to prove the presence of toxic substances in the blood that cause muscle atrophy and paralysis have been unsuccessful [10]. The discovery of endocrine disorders in some cases and the subsequent use of hormonal drugs yielded inconsistent results [2-8]. It appears that in most cases, hormonal disturbances merely accompany the underlying disease, and a significant percentage of patients show no noticeable endocrine abnormalities [8].

A detailed study of biochemical shifts could bring us closer to understanding the pathogenesis of these conditions [5-6]. Of particular importance in this regard is the study of metabolic disturbances in affected tissues. A significant obstacle is the impossibility of reproducing such diseases in animal experiments.

Since 1928, when it was established that a vitamin E-deficient diet causes changes in animal muscle tissue (rabbits, guinea pigs, hamsters, rats, etc.) similar to those observed in progressive muscular dystrophy [3], the possibility of studying this disease experimentally emerged. The most complete and systematic study of biochemical shifts during vitamin E deficiency in animals was conducted by D. L. Ferdman and his colleagues [11].

However, in terms of origin and disease course (duration, localization), vitamin E deficiency in animals cannot be equated with progressive muscular dystrophy in humans [4-12]. The etiology and specific details of pathogenesis for both conditions remain unknown. It is known that vitamin E plays a significant role in biological oxidation reactions: α-tocopherol and its derivatives accelerate the redox process between cytochromes b and c [4-12]. However, this data is insufficient to explain the polymorphic clinical picture and biochemical shifts observed with vitamin E deficiency [4-12]. Nevertheless, experimental muscular dystrophy in animals, sharing many common features with the clinical form of this disease, can be used, with some justification, as its closest model [3-4].

Biochemical Changes in Progressive Muscle Atrophies

The following outlines the results of biochemical studies of various muscle and neuromuscular diseases, mainly the experimental and clinical forms of progressive muscular dystrophy [2-5-11].

Quantitative Changes in Muscle Proteins. During the development of the atrophic process in vitamin E-deficient animals, total muscle mass decreases, and some muscle fibers undergo necrosis [3-4]. Simultaneously, the content of connective tissue proteins (collagen) increases, while the amount of true muscle proteins decreases: myosin content drops by approximately half, and the fraction of water-soluble proteins also decreases [11]. The decrease in contractile protein content has been confirmed by other researchers [13].

Study of protein fractional composition using electrophoresis showed that in extracts from atrophic muscles, the areas of peaks corresponding to actomyosin and myogen group proteins decrease, while the myoalbumin peak increases. Similar changes were found in atrophy following polio and in other forms of muscle pathology. These shifts are not specific to vitamin E deficiency or progressive muscular dystrophy [13].

Rumery, Mauer, and Mason studied the effect of vitamin E deficiency in pregnant females on the muscle tissue of offspring. In rat pups born from females on a vitamin E-deficient diet, by day 21 of life, there was a decrease in total, protein, and residual nitrogen, a reduction in the actomyosin fraction, and an increase in the number of stromal proteins. Subsequently, some pups died, while the survivors recovered spontaneously, and by day 30, their muscle protein content returned to normal [11].

Qualitative Changes in Muscle Proteins. In vitamin E deficiency, qualitative changes in muscle proteins are observed [11]. A decrease in myosin solubility and a weakening of actin's ability to polymerize are noted [11]. The ATPase activity of purified myosin from dystrophic muscles is slightly reduced [14-15]. Modern studies using cryo-electron microscopy confirm the structural disruptions in the dystrophin-glycoprotein complex underlying these functional changes [16].

In vitamin E-deficient animals, a higher content of free actin was found, indicating lower stability of the actomyosin complex and likely playing a role in the impairment of contractile function [11]. The spectral properties of myosin change insignificantly [10]. Thus, both quantitative and qualitative changes in the proteins of the actomyosin complex play a significant role in the impairment of contractile function in atrophied musculature [13-16].

Turnover Rate of Muscle Proteins. In vitamin E-deficient animals, an increased turnover rate of water-soluble proteins and actin is observed, likely associated with enhanced proteolysis in muscle tissue [11]. The proteolytic activity of muscle homogenates towards denatured hemoglobin is significantly above normal. Conversely, in cardiac muscle, the rate of protein turnover is reduced. Current data highlight the key role of the ubiquitin-proteasome system and autophagy in these processes [2-7].

Nitrogenous Extractives. In muscles during vitamin E deficiency, the content of creatine, carnosine, and anserine decreases, while the content of ammonia, glutamine, and glutamic acid increases.

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Creatinuria is a typical sign of primary myopathies [12-18]. In children aged 4-7 years with progressive muscular dystrophy, urinary creatine excretion is lower than in healthy children, whereas in children aged 8–16 years, it is higher, which is explained by metabolic reorganization under the influence of sex hormones. Using labeled glycine (N^{15}), it was shown that creatine in the urine of myopathy patients is not of muscular origin but is synthesized in the liver and not utilized by muscles [6]. It has been suggested that the cause of creatinuria may not be reduced creatine phosphorylation but rather a slowdown in its penetration from the blood into the dystrophic muscle [6-12]. Modern studies confirm that the creatine/creatinine ratio is a reliable biomarker of muscle function in Duchenne dystrophy [18].

Aminoaciduria. In various forms of neuromuscular pathology, increased urinary excretion of amino acids (methionine, valine, leucine, arginine, taurine, etc.) has been observed, linked to enhanced proteolysis [2-7]. The severity of aminoaciduria correlates with the localization of the process: it is pronounced in pelvic girdle dystrophy and absent in the humeral form.

Enzymes. Changes in enzyme activity play a key role in the energetics of muscle activity [5-11]. In vitamin E deficiency and myopathies, the activity of glycolysis and glycogenolysis enzymes in muscle tissue is reduced: phosphorylase, phosphoglucomutase, aldolase, phosphohexose isomerase [11].

Concurrently with the decrease in enzyme activity in muscles, their activity in the blood serum increases [17]. Hyperaldolasemia (increased aldolase activity) is observed in the vast majority of patients with primary muscular dystrophy and is a valuable diagnostic sign [9]. In atrophies of neural origin, serum aldolase activity remains normal [17]. In children, aldolase activity can exceed the norm by up to 6 times but decreases with disease duration [5-9]. Similar changes have been described for lactic dehydrogenase, aminopherase, nucleotidase, and acid phosphatase [1; 5; 6]. Modern proteomic studies have enabled the identification of more specific biomarkers of muscle damage, such as fragments of titin, myosin-binding protein C, and carbonic anhydrase III [6-9-15].

Carbohydrate-Phosphorus Metabolism. In the early period of experimental dystrophy, glycogen content in muscles decreases, correlating with a drop-in phosphorylase activity and glycolytic activity [11]. At the same time, oxygen consumption by muscle tissue during vitamin E deficiency is increased [12], although data on human myopathies are less consistent [1].

In the muscles of vitamin E-deficient animals, the content of phosphocreatine, ATP, and ADP is reduced, but the turnover rate of phosphorus compounds (acid-soluble phosphorus, ATP, creatine phosphate) is significantly increased [3-11], refuting the hypothesis of uncoupling of respiration and phosphorylation [12]. Modern studies confirm the presence of mitochondrial dysfunction in muscular dystrophies; however, the focus has shifted towards the phenomenon of mitohormesis and redox-sensitive pathways regulating energy metabolism [12].

Pentosuria. In patients with muscular dystrophy, the content of aldopentoses, predominantly ribose, is increased in the urine, which may indicate a change in carbohydrate metabolism [2]. However, the data are heterogeneous; other researchers have not found significant differences [2].

Mineral Metabolism. In muscular dystrophy, muscle tissue shows a decrease in intracellular potassium content and an increase in sodium content; total and intracellular water are reduced [19]. The turnover rate of potassium in dystrophic muscles does not differ from normal. Similar changes (decreased potassium, increased calcium and sodium) are observed in vitamin E-deficient animals [3-19].

Features of iron metabolism in myopathies include a slower disappearance of radioactive iron from the serum and its faster incorporation into myoglobin, with an overall decrease in iron content in muscles [11]. In light of current understanding, disturbances in iron metabolism are considered in the context of ferroptosis-a regulated form of cell death that plays a significant role in the pathogenesis of muscular dystrophies [7-20].

Conclusion

Progressive muscle atrophies are characterized by profound disturbances in protein, carbohydrate-phosphorus, and enzymatic metabolism, including a decrease in contractile proteins and macroergic compounds in muscles [1-13]. Hyperaldolasemia and creatinuria hold the greatest diagnostic value, allowing differentiation between primary myopathies and neurogenic forms [5-9]. The experimental model of vitamin E deficiency in animals reproduces many biochemical changes but cannot be fully equated with the human disease [3-4]. The etiology and primary pathogenetic mechanisms remain unclear; endocrine and hereditary factors have not been convincingly confirmed [1-8]. Further research should focus on identifying the molecular mechanisms initiating the atrophic process and developing pathogenetically sound therapeutic approaches [2-16-19].

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