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MIOPATIYALAR

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Annotasiya

Mazkur maqolada miopatiyalar skelet mushak to‘qimalarining birlamchi zararlanishi bilan kechuvchi kasalliklar guruhi sifatida kompleks tahlil qilinadi. So‘nggi yillarda molekulyar genetika, immunologiya va klinik nevrologiya sohasida erishilgan yutuqlar miopatiyalar etiologiyasi va patogenezini chuqurroq anglash imkonini bermoqda. Tadqiqot doirasida irsiy shakllar, xususan, Duchenne mushak distrofiyasi kabi progressiv kechuvchi kasalliklar, shuningdek yallig‘lanishli miopatiyalar — Polimiyozit va Dermatomiyozit ning klinik-patogenetik xususiyatlari tahlil etilgan. Maqolada mushak tolalarining degenerativ o‘zgarishlari, autoimmun mexanizmlar, fermentativ yetishmovchiliklar hamda metabolik buzilishlarning kasallik rivojlanishidagi o‘rni yoritilgan. Klinik belgilarning proksimal mushak zaifligi, harakat cheklanishi va hayot sifatiga ta’siri ilmiy manbalar asosida baholangan.

Kalit so’z

Kalit so‘zlar: Duchenne mushak distrofiyasi, idiopatik yallig‘lanishli kasalliklar, polimiyozit, dermatomiyozit, mitoxondrial disfunksiya, oksidativ stress, molekulyar diagnostika, autoimmun mexanizmlar.

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Аннотация

В данной статье представлен всесторонний анализ миопатий как группы заболеваний, характеризующихся первичным поражением скелетных мышц. Последние достижения в области молекулярной генетики, иммунологии и клинической неврологии позволили глубже понять этиологию и патогенез

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миопатий. В исследовании проанализированы клинико-патогенетические особенности наследственных форм, в частности, прогрессирующих заболеваний, таких как мышечная дистрофия Дюшенна, а также воспалительных миопатий – полимиозита и дерматомиозита. В статье освещается роль дегенеративных изменений в мышечных волокнах, аутоиммунных механизмов, ферментативной недостаточности и нарушений обмена веществ в развитии заболевания. Влияние клинических симптомов на проксимальную мышечную слабость, ограничения подвижности и качество жизни оценивалось на основе научных источников.

Ключевые слова

Ключевые слова: мышечная дистрофия Дюшенна, идиопатические воспалительные заболевания, полимиозит, дерматомиозит, митохондриальная дисфункция, оксидативный стресс, молекулярная диагностика, аутоиммунные механизмы.

MYOPATHIES

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Annotation

This article provides a comprehensive analysis of myopathies as a group of diseases characterized by primary damage to skeletal muscle tissue. Recent advances in molecular genetics, immunology, and clinical neurology have provided a deeper understanding of the etiology and pathogenesis of myopathies. The study analyzed the clinical and pathogenetic features of hereditary forms, in particular, progressive diseases such as Duchenne muscular dystrophy, as well as inflammatory myopathies - polymyositis and dermatomyositis. The article highlights the role of degenerative changes in muscle fibers, autoimmune mechanisms, enzymatic deficiencies, and metabolic disorders in the development of the disease. The impact of clinical symptoms on proximal muscle weakness, mobility limitations, and quality of life was assessed based on scientific sources.

Keywords

Duchenne muscular dystrophy, idiopathic inflammatory diseases, polymyositis, dermatomyositis, mitochondrial dysfunction, oxidative stress, molecular diagnostics, autoimmune mechanisms.

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INTRODUCTION

Myopathies are diseases characterized by primary damage to skeletal muscle tissue, the etiology and pathogenesis of which have been actively studied in clinical and molecular medicine in recent years. For example, studies analyzing inflammatory myopathies have clearly shown that idiopathic inflammatory myopathies (IIMs) weaken muscles through chronic inflammation and are distinguished by different phenotypes, immunological profiles, and response to treatment, which complicates their classification and treatment strategies [1].

Also, studies focused on the study of genetic myopathies have shown progress in defining the spectrum of hereditary myopathies and strengthening molecular diagnostics, which is important for improving the diagnosis of the disease and developing individualized treatment approaches for patients [2]. Myopathies are a heterogeneous group of diseases, which are based on impaired synthesis of proteins that provide the structure and function of muscle fibers. In particular, mutations in the gene encoding the dystrophin protein disrupt the stability of the muscle cell membrane, which leads to degeneration and fibrosis of the fibers [1]. In inflammatory myopathies, cellular and humoral immune response mechanisms predominate, with T-lymphocyte infiltration and cytokine release leading to impaired necrosis and regeneration processes in muscle tissue [2].

MAIN PART

To understand the pathogenesis of myopathies in depth, it is necessary to analyze them from a molecular and biochemical perspective. The functional integrity of skeletal muscle fibers depends on the balance between cytoskeletal proteins, ion channels, mitochondrial bioenergetics and immune-regulatory mechanisms. When this balance is disturbed, degenerative-dystrophic processes begin in muscle fibers.

As an example, let's consider biochemical disorders in Duchenne muscular dystrophy.

The main role in the pathogenesis of Duchenne muscular dystrophy (DMD) is associated with the deficiency of the dystrophin protein. Dystrophin acts as a mechanical link between the sarcolemma and the cytoskeleton. Its absence reduces the mechanical stability of the muscle cell membrane and leads to uncontrolled entry of calcium ions into the cell [10]. An increase in calcium concentration activates Ca^{2+}-dependent proteases, such as calpains, which enhance the breakdown of myofibrillar proteins and accelerate the processes of necrosis [12].

In addition, disruption of the nNOS (neuronal nitric oxide synthase) signaling pathway associated with the dystrophin complex reduces muscle perfusion and

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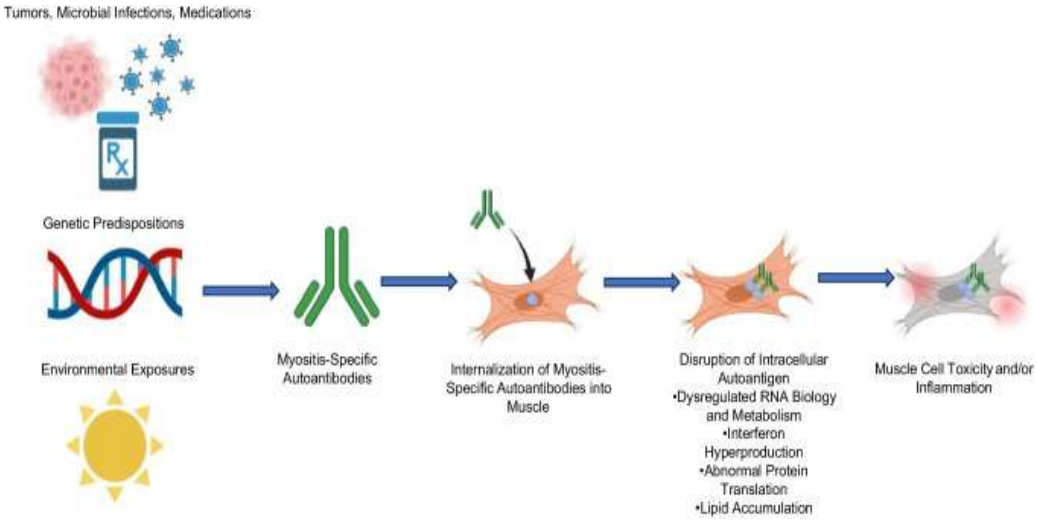
creates local ischemic conditions. As a result, oxidative stress increases and lipid peroxidation increases [10]. Oxidative stress leads to a decrease in mitochondrial membrane potential, cytochrome c release, and activation of apoptotic cascades. As noted by Emery, the regeneration cycle of muscle fibers is also disrupted and the exchange with fibrotic tissue increases [10]. Bushby et al. analyzed the clinical progression of DMD and showed that the level of creatine phosphokinase (CPK) is significantly increased in the early stages of the disease, which is considered a biochemical marker of myofibrillar breakdown [12]. At the same time, impaired sarcoplasmic reticulum function further disrupts Ca^{2+} homeostasis and increases the energy demand of the contractile apparatus. Immune-metabolic mechanisms in inflammatory myopathies. T-lymphocyte infiltration, macrophage activation, and cytokine imbalance are important in the pathogenesis of idiopathic inflammatory myopathies (IIM). As described by Dalakas, CD8+ T cells directly damage muscle fibers through MHC-I and induce myofibrillar necrosis through cytotoxic mechanisms [11].



1-rasm

Proposed pathogenesis of idiopathic inflammatory myopathies. The development of myositis is influenced by a complex interaction of pre-existing diseases, microbial infections, drugs, genetic predisposition, and environmental influences. These factors may contribute to the production of myositis-specific autoantibodies, which have been found to accumulate in the muscle tissue of patients. Recent studies have linked the pathogenesis of myositis to the intracellular action of these autoantibodies, which disrupt the function of their specific autoantigens. This disruption may contribute to muscle cell toxicity and inflammation. [19]

The clinical features of IIM include muscle atrophy and necrosis, mainly caused by persistent inflammation, which culminates in muscle regeneration, increased expression of specific antibodies, and severe pain. The first phase of

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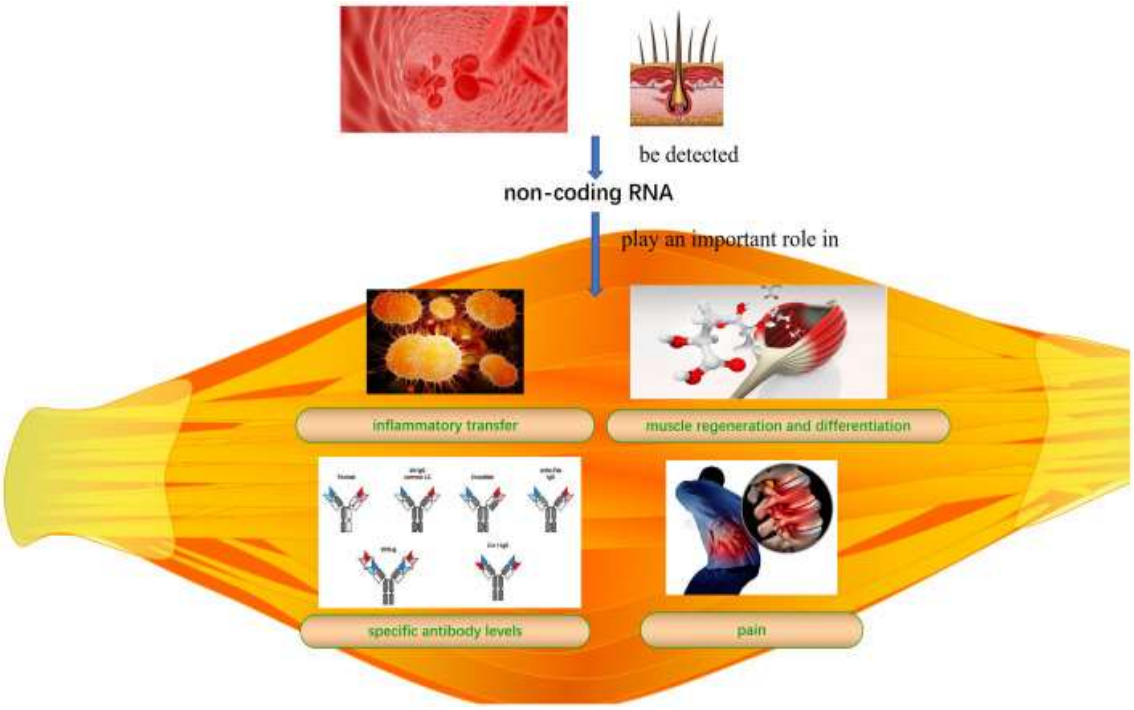
muscle regeneration is an inflammatory response, in which macrophages and lymphocytes infiltrate the injury site, engulf necrotic debris, and stimulate a myogenic response. The second phase involves the activation and differentiation of satellite cells (SCs), and the third phase involves the growth of new muscle fibers and the remodeling and differentiation of regenerative muscles. All phases are closely associated with myogenic regulatory factors (MRFs), such as myogenic factor (Myf)5, Myf6, myostatin, and myogenic cell assay proteins. MiRNAs can regulate MRFs through TNF-α and IL-1β, which inhibit NF-κB, MAPK p2, and other important pathways that inhibit myogenic differentiation into myoblasts/myotubes. Therefore, identifying ncRNAs that effectively regulate the inflammatory response, SC activation and differentiation, myophil maturation and differentiation, specific antibody expression, and muscle pain inhibition may be important in the treatment of IIMs with different subtypes of therapies. (Figure 2)[18]



2-rasm

Lundberg et al. have shown that in dermatomyositis, microvascular damage and the deposition of the complement system C5b-9 complex in capillaries cause ischemic processes in muscle fibers [13]. Ischemic conditions exacerbate mitochondrial dysfunction, which leads to reduced ATP production and muscle weakness.

In recent years, it has been shown that mitochondrial DNA fragments are released into the cytoplasm and that they trigger an immune response as DAMPs (damage-associated molecular patterns). This process enhances the activation of the

NLRP3 inflammasome and leads to the release of the cytokines IL-1β and IL-18. As a result, a chronic inflammatory cycle is formed.

Danieli et al. have shown that oxidative stress markers and respiratory chain enzyme activities are reduced in inflammatory myopathies [15]. This is manifested by a decrease in the activity of NADH dehydrogenase and cytochrome oxidase, which disrupts muscle energy balance.

Bioenergetic derangement in metabolic and mitochondrial myopathies. The main pathogenetic mechanism in metabolic myopathies is a violation of the oxidative phosphorylation system. As noted by Cohen, if complexes I–V of the electron transport chain are defective, ATP synthesis is sharply reduced and muscle fibers experience energy deficiency [14]. This process is manifested by rapid fatigue and lactate accumulation during exercise.

Sharp and Haller emphasize that in metabolic myopathies, enzyme deficiencies in glycogenolysis and fatty acid oxidation lead to substrate accumulation in the muscle [15]. For example, carnitine palmitoyltransferase II deficiency limits the entry of fatty acids into mitochondria and reduces energy production.

A study published in the journal EMBO Molecular Medicine identified a multi-organ metabolic response mechanism in mitochondrial myopathies, in which muscle energy stress triggers metabolic reprogramming in the liver and adipose tissue [16]. This indicates that the disease has a systemic nature.

Also, a clinical genomic study involving 207 patients confirmed the genetic spectrum and the importance of molecular diagnostics in hereditary myopathies [9]. These results indicate that metabolic disorders are often multigenic and complex in nature.

Ca^{2+} – ROS – Mitochondria Interaction. Although the various forms of myopathies differ in etiology, a central mechanism that unites them is a disruption of calcium homeostasis and mitochondrial bioenergetic dysfunction. In dystrophin deficiency, increased sarcolemmal permeability enhances Ca^{2+} influx and leads to Ca^{2+} accumulation in mitochondria [10]. Increased mitochondrial Ca^{2+} overloads the electron transport chain, increasing the production of reactive oxygen species (ROS) [14].

Increased ROS levels lead to lipid peroxidation, protein oxidation, and mtDNA damage. Danieli et al. have found decreased activity of respiratory chain complexes I and IV in inflammatory myopathies, suggesting a direct link to oxidative stress [1]. Oxidative stress, in turn, activates the NF-κB signaling pathway and increases the synthesis of inflammatory mediators [11].

Under these conditions, the mitochondrial permeability transition pore (mPTP) is more likely to open, leading to cytochrome c release and activation of caspase cascades. Cohen suggests that apoptotic mechanisms in mitochondrial myopathies directly contribute to the reduction in muscle fiber number [14].

In idiopathic inflammatory myopathies, mitochondrial fragments and mtDNA are released into the cytoplasm and activate the immune system as DAMP molecules [13]. This process increases the production of IL-1β and IL-18 cytokines through the activation of the NLRP3 inflammasome complex [8].

According to Dalakas, CD8+ T-lymphocytes directly damage muscle fibers with increased MHC-I expression through a cytotoxic mechanism [11]. This process is accompanied by ATP deficiency and mitochondrial dysfunction, limiting cell regeneration.

Lundberg et al. have shown that in dermatomyositis, the complement system C5b-9 complex is deposited in the capillary endothelium, which exacerbates microvascular ischemia and energy deficiency [13]. As a result, muscle fiber atrophy and fibrosis develop.

A study published in the journal EMBO Molecular Medicine has shown that in mitochondrial myopathies, muscle energy stress induces metabolic reprogramming in the liver and adipose tissue. Mitokines such as FGF21 and GDF15 are released as systemic biomarkers, which activate metabolic adaptation mechanisms [16].

Sharp and Haller have shown that in metabolic myopathies, an imbalance between the glycolytic and fatty acid oxidation pathways leads to substrate accumulation in the muscle [15]. This is manifested by lactate accumulation and exercise intolerance.

Chakravorty et al., in a genomic study of 207 patients, confirmed the broad spectrum of inherited myopathies and the importance of molecular diagnostics [9]. They reported that many metabolic myopathies are associated with multigene mutations, and that there is a direct correlation between the clinical phenotype and the biochemical profile.

Creatine phosphokinase (CPK) levels are significantly elevated in Duchenne muscular dystrophy and have been used as biomarkers of myofibrillar breakdown [12]. In addition, FGF21 and GDF15 have been proposed as biomarkers of mitochondrial dysfunction [16].

Mercuri and Muntoni have shown a correlation between muscle MRI images and biochemical processes; fibrosis and fatty infiltration parallel mitochondrial dysfunction [17].

CONCLUSION

Diseases accompanied by primary damage to skeletal muscle tissue develop on the basis of complex genetic, immune and metabolic mechanisms. Dystrophin deficiency, impaired calcium homeostasis and oxidative stress lead to degeneration of muscle fibers in hereditary forms. In inflammatory forms, immune processes mediated by T-lymphocytes and cytokines disrupt the balance of muscle necrosis and regeneration. Mitochondrial dysfunction and bioenergetic deficiency are manifested as a common pathogenetic link of diseases. Modern molecular diagnostic methods and biomarkers play an important role in early diagnosis and choosing an individual treatment strategy.

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