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ПОРАЖЕНИЕ МЫШЕЧНОЙ СИСТЕМЫ ПРИ COVID-19

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Damage of the Muscle System in Covid-19

Резюме

Статья посвящена поражению мышечной системы при новой коронавирусной инфекции (COVID-19) . Проведен анализ литературы российских и иностранных исследователей по внелегочным проявлениям COVID-19. Главной мишенью COVID-19 (Corona Virus Disease 2019) является эндотелий сосудов. Для проникновения в клетки вирус использует рецептор — ангиотензинпревращающий фермент 2 (АПФ2). Показано, что к одной мишени могут присоединиться до трех вирусов. В скелетной мускулатуре также имеется АПФ2. При COVID-19 вовлечение в патологический процесс мышечной системы является предиктором неблагоприятного прогноза. В 20% случаев среди госпитализированных пациентов COVID-19 выявляются лабораторные признаки повреждения сердечной мышцы. К основным механизмам повреждения мышечной системы при COVID-19 относятся АПФ2-зависимый механизм, степень вирусной нагрузки, цитокиновый шторм, острая гипоксемия и лекарственная токсичность. Поражение мышечной системы при COVID-19 служит дополнительным фактором риска смерти. В представленной работе приводятся сведения о возможных патогенетических механизмах развития миопатии, а также мышечной слабости при COVID-19, протекающие с повышением содержания креатинкиназы крови.

Ключевые слова: *коронавирус, инвазия, эндотелий, мышечная система, креатинкиназа, лактатдегидрогеназа, миопатия*

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Abstract

The article is devoted to the lesion of the muscular system in the new coronavirus disease — 2019. The analysis of the literature of Russian and foreign researchers on the extrapulmonary manifestations of COVID-19 is carried out. The main target of COVID-19 (CoronaVIrus Disease 2019) is the vascular endothelium. To enter cells, the virus uses a receptor — angiotensin-converting enzyme 2 (ACE2). It has been shown that up to three viruses can attach to one target. Skeletal muscles also have ACE2. In COVID-19, involvement of the muscular system in the pathological process is a predictor of a poor prognosis. In 20% of hospitalized COVID 19 patients, laboratory signs of heart muscle damage are found. The main mechanisms of muscle damage in COVID 19 include ACE2-dependent, viral load, cytokine storm, acute hypoxemia, and drug toxicity. Damage to the muscular system in COVID 19 is an additional risk factor for death. The presented work provides information on the possible pathogenetic mechanisms of the development of myopathy, as well as muscle weakness in COVID-19, occurring with an increase in blood creatine kinase.

Key words: *coronavirus, invasion, endothelium, muscular system, creatinkinase, myopathy, lactate dehydrogenase*

Conflict of interests

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ACE2 — angiotensin-converting enzyme

Introduction

For more than one year, the novel coronavirus disease 2019 (COVID-19) claimed the lives of more than 1.95 million people, and the number of cases has exceeded 91 million worldwide [1]. This determines the high medical and social significance of COVID-19 worldwide. Currently, the attention of researchers and clinicians is focused on extrapulmonary manifestations of COVID-19 [2, 3]. Periodicals contain active discussions of issues related to coronavirus damage to organs other than the pulmonary system, including the skin and visible mucosae, nervous system, gastrointestinal tract, endocrine and cardiovascular systems [4, 5–7]. It is due to that the vascular endothelium is the main target of COVID-19. The virus uses the angiotensin-converting enzyme 2 (ACE2) receptor to penetrate the cells. It was noted in many studies that up to three viruses can attach to one target (ACE2) [1, 8]. ACE2 and TMPRSS2 (Transmembrane protease, serine 2 — membrane-bound serine protease) are also unevenly distributed among patients of European and Asian origin, which can also have an effect on the intensity of infection and the severity of COVID-19 [8]. As discussed above, the key point in the pathogenesis of internal organ damage by COVID-19 is the interaction of the virus with vascular endothelial cells, development of hyperpermeability and endothelial dysfunction, as well as impaired microcirculation. The accumulated data indicate that ACE2 is also present in skeletal muscles [9]. In case of COVID-19, the involvement of the muscular system in the pathological process is a predictor of poor prognosis. Recent review studies showed that approximately 20% of patients hospitalized with COVID-19 demonstrated signs of damage to the heart muscle, which may be an additional risk factor for death [10]. According to numerous data, basic mechanisms of damage to the muscular system by COVID-19 include ACE2-dependent mechanism, level of viral load, cytokine storm, acute hypoxemia and drug toxicity [10].

Anatomy and Physiology of Muscular System

According to current data, the human muscular system includes approximately 500 (400–600) muscles (40% of body weight) that provide movement of the body in space, maintaining posture, breathing, chewing, swallowing, and speech, are involved in the work of internal organs, blood circulation, heat regulation metabolism. They also play an important role in human perception of the position of the body and its parts in space [11]. Three muscle groups are distinguished according to their morphological characteristics:

1) striated muscles (skeletal muscles);
2) smooth muscles;
3) heart muscle (or myocardium).

It is important to keep in mind that the muscular system is characterized by intensive metabolism. Therefore, it has well-developed blood circulation for delivering oxygen, nutrients and biologically active substances to muscles and removing metabolic products and carbon dioxide [11]. Blood flow in a muscle is continuous, but its activity depends on the nature and intensity of work. With no muscle load, about a third of all capillaries are functioning; when the load increases, the number of capillaries increases significantly. During physical activity, up to 2,500 capillaries open per 1 mm of muscle cross-section versus 30–80 at rest, which is accompanied by an increase in the rate of oxygen utilization.

Therefore, 1 g of hemoglobin (Hb) can bind 1.34 ml of oxygen, and the average oxygen capacity in an adult is about 200 ml/l of blood [12]. If we take into account the fact that, on average, an adult consumes 250 ml of oxygen per minute, then COVID-19 significantly reduces this figure leading to systemic hypoxia. Skeletal muscles have the following physiological properties: excitability, conductivity, contractility and elasticity. Muscle strength increases with age, especially in adolescence. From the age of 18, the growth of muscle strength slows down, and ends by the age of 25–26. After the age of 40, muscle strength gradually decreases, and its most significant decrease is observed after the age of 50. The intensity of muscle strength development also depends on gender. Muscle fiber of a skeletal muscle, as in cardiac muscle, consists of myofibrils that, in turn, are divided into units — sarcomeres formed by actin and myosin, which causes cross-striation. Depressions of actin filaments are filled with troponin. Unlike skeletal muscles, a smooth muscle has no cross-striation and contains less myosin than actin. It also contains calmodullin that binds to Ca^{2+} ions and activates myosin light chain kinase.

It should be noted that one of the important differences between skeletal and cardiac muscles is that the cardiac muscle requires extracellular calcium for its normal contraction. The entire amount of Ca^{2+} in skeletal muscles is located in the sarcoplasmic reticulum, which is not enough for the heart muscle. First, extracellular Ca^{2+} enters the cell through T-tubules and then triggers the release of even more Ca^{2+} from the sarcoplasmic reticulum. That is why Ca^{2+} channel blockers can change the contractility of heart muscle but have no pronounced effect on skeletal muscles. After muscle contraction, free Ca^{2+} ions actively move back into the sarcoplasmic reticulum, and the muscle relaxes, i.e., myosin heads do not form a bond with actin [13]. Inflammatory myopathies in cases of COVID-19 represent a heterogeneous group of curable pathologies of the muscular system. Myopathies are conventionally divided into five subtypes depending on their clinical and pathological features: dermatomyositis, polymyositis, necrotizing autoimmune myositis, inclusion body myositis, and overlap myositis [14, 15]. Damage to the muscular system by COVID-19 is observed mainly in adults and can be found at any stage of disease, either with acute manifestations, reaching its peak within a few days or weeks, or with subacute manifestations, progressing steadily and causing severe symmetrical weakness and a very high level of creatine kinase.

In order to detect myositis-associated lung lesions in cases of COVID-19, computed tomography should be performed, which, depending on lesion degree, reveals irregular linear shadows, cystic enlightenments, foci of ground glass attenuation, thickening of bronchial walls and formation of "honeycomb lung" [16]. The most pronounced changes are found in basal and subpleural areas. If the muscular system is involved in the pathological process, as already noted, an increased level of creatine kinase in blood is very often observed.

Case Report No. 1

Patient N., 38, at the end of November 2020 felt malaise, low-grade fever, symmetrical muscle weakness and fatigue. The next day, an unproductive cough appeared. He took antipyretic agents. In connection with the onset of dyspnea, computed tomography of thoracic organs was performed; it revealed polysegmental pneumonia (Fig. 1). Physical examination results: a patient with hypersthenic constitution, height 172 cm, weight 110 kg, body mass index (BMI) 37.2 kg/m^2. General condition at admission is evaluated as moderate: body temperature 37.8 °C, blood pressure (BP) 120/90 mm Hg, pulse 103 beats per minute, rhythmic, respiratory rate — 24 breaths per minute, percentage of blood oxygen saturation 87%. Sclerae are not injected, no conjunctival or eyelid hyperemia found. Oral mucosa is moist and clean. Peripheral lymph nodes are not palpable. Borders of relative cardiac dullness are not extended. Heart rhythm is regular, sonorous tones, no abnormal breath sounds. On percussion: clear pulmonary sound over lung fields; on auscultation — decreased vesicular breathing over both lungs. Abdomen is enlarged due to the thickness of subcutaneous fat, with soft, painless palpation. Parts of the colon within normal on palpation. Liver edge of soft-elastic consistency, on palpation — along the costal margin along right mid-clavicular line. Spleen is not palpable, no peripheral edemas. Computed tomography (Fig. 1) revealed multiple, separate and confluent areas of ground glass compaction, with peribronchovascular location through all lung fields. Confluent lesions are also visible in posterior-basal segments of both lungs. In connection with the lesions, a reticular component and linear cord-like thickening were found.

Laboratory tests: Hb — 158 g/l, RBC — 5.39 x 10^{12}/l, WBC — 4.78 x 10^9/l, neutrophils — 2.96 x 10^9/l, platelets — 179.6 x 10^9/l, lymphocytes — 26.34%, monocytes — 8.99%, erythrocyte sedimentation rate (ESR) — 10 mm/h. Clinical urinalysis: protein — 0.15 g/l, RBC — 8.8 cells/μl. Blood biochemistry: uric acid — 5.6 mg/dl (3.5–7.2), glucose — 5.76 mmol/l, glycosylated hemoglobin (HbA1c) — 5.9% (it is important that HbA1c level is not influenced by random factors, in particular, physical activity (decomposition of glycogen from muscle tissue)).

Lipid profile: total cholesterol (TC) — 3.57 mmol/l, low-density lipoprotein cholesterol (LDL-C) — 2.42 mmol/l, high-density lipoprotein cholesterol — 0.79 mmol/l, triglycerides — 0.99 mmol/l. Blood electrolytes: magnesium — 0.74 mmol/l (0.77 — 1.03), sodium — 140 mmol/l (136–145), blood calcium — 2.16 mmol/l (2.11–2.55), potassium — 4.2 mmol/l (3.4–5.5), inorganic phosphorus — 1.25 mmol/l (0.87–1.45). C-reactive protein (CRP) — 26 mg/l (up to 5). Given CRP correlation with the nature of inflammation, as well as confirmed COVID-19 and pneumonia, cytokine status, vascular endothelial growth factor, procalcitonin and D-dimer in the blood were additionally checked. So, interleukin-6 (IL-6) concentration was 6.768 pg/ml (up to 10), tumor necrosis factor

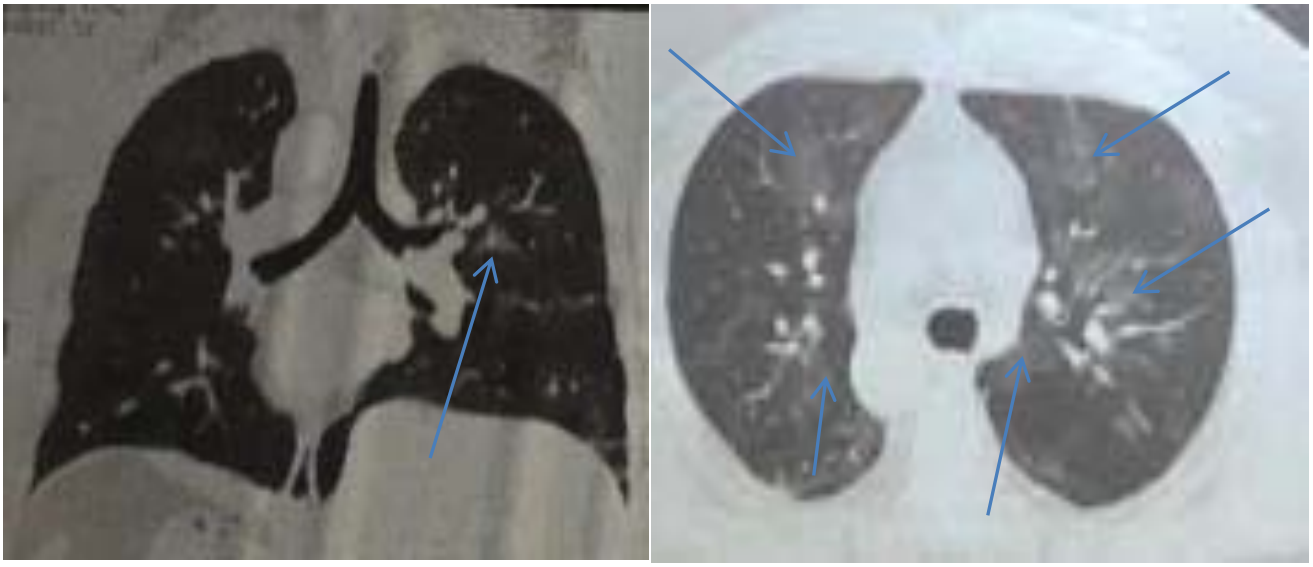

Figure 1. *CT of patient N., 38 years old*

alpha (TNF-alpha) — 3.269 pg/ml (up to 6), vascular endothelial growth factor — (220.27 pg/ml) , procalcitonin — 0.095 ng/ml (0–0.1), ferritin — 1069 ng/ml (28–365), and D-dimer — 0.288 mg FEU/ml (0–0.55) of blood. Patients with COVID-19 may develop liver and kidney damage. Liver and kidney functional tests in our patient showed the following results: total bilirubin — 13.4 μmol/l, alanine aminotransferase (ALT) — 39 U/l, aspartate aminotransferase (AST) — 27 U/l, folic acid — 5.3 ng/ml (3.1–20.5 ng/ml), fibrinogen — 4.7 g/l, blood creatinine — 77.8 μmol/l. Estimated glomerular filtration rate (GFR) according to CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) was 109 ml /min/1.73 m^2. According to some scientific literature data, it was found that the earliest laboratory marker of kidney damage is increased cystatin C level [17]. In our patient, the level of cystatin C was 1.37 mg/l (0.31–0.79), estimated GFR — 56 ml/min/1.73 m^2 (CKD-EPI formula with cystatin C) [17, 18], blood homocysteine — 8.98 μmol/l (5.46–16.2). Prothrombin index was 76.7%, prothrombin time — 12.4%, and international normalized ratio (INR) — 1.14. Symptoms of severe symmetrical muscle weakness and limitation of movement raised the need to test for markers of myopathy. Creatine kinase level exceeded 4 upper normal limits — 847 U/l (30–200). Considering obesity and muscle complaints, thyroid function was checked: thyroid-stimulating hormone concentration — 2.1447 mIU/l (0.35–4.94), thyroxine — 106.23 nmol/l (62.67 — 150.8), and triiodothyronine — 0.99 nmol/l (0.89 — 2.44) were within reference range. It should be noted that the patient's levels of lactate dehydrogenase, rheumatoid factor, complements C3 and C4 were within normal. Based on clinical, epidemiological, and laboratory results, the following diagnosis was established: Bilateral polysegmental pneumonia, RF grade 2. Myositis, acute course, moderate, of viral etiology. Obesity grade II (BMI 37.2 kg/m^2). Low-flow oxygen therapy and drug treatment (antibacterial agents, anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs)) improved the patient's condition: muscle weakness and fatigue decreased, motor activity increased, cough stopped. Laboratory tests over time revealed complete normalization of creatine kinase, CRP, ESR levels, and disappearance of proteinuria.

Case Report No. 2

Patient T., 24. In mid-November 2020, the patient noted febrile body temperature, muscle weakness, fatigue, lack of muscle strength in limbs (Fig. 2), more on the right. Three days later, a productive cough appeared. He took non-steroidal anti-inflammatory drugs on his own. In connection with the onset of dyspnea, computed tomography of the chest organs was recommended; it revealed polysegmental pneumonia. Physical examination results: a patient of normosthenic constitution, height 185 cm, weight 85 kg, BMI — 24.8 kg/m^2. General condition of the patient was evaluated as mild: body temperature 38.3 °C, BP 120/80 mm Hg, pulse 100 beats per minute, rhythmic, respiratory rate — 23 breaths per minute, blood saturation 95%. Sclerae are not injected, no conjunctival or eyelid hyperemia found. Oral mucosa is moist and clean. Peripheral lymph nodes are not palpable. There was a change in skin pigmentation on lower extremities (lower legs, feet) (Fig. 2). According to the patient, these changes in skin color appeared along with the increased body temperature. Borders of relative cardiac dullness are not extended. Heart rhythm is regular, sonorous tones, no abnormal breath sounds. On percussion: clear pulmonary sound over lung fields; on auscultation — decreased vesicular breathing over both lungs. Abdomen was not enlarged, soft and non-tender on palpation. Parts of the colon within normal on palpation. Liver edge of soft-elastic consistency, on palpation — along the costal

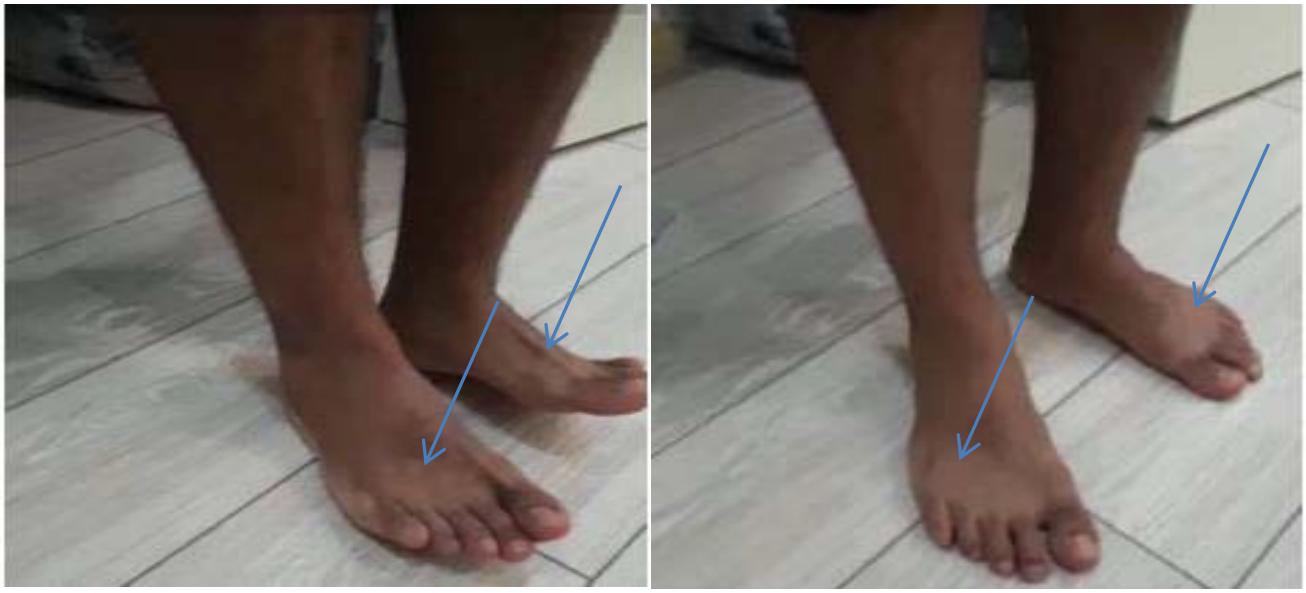

Figure 2. *Changes in skin color on the lower limbs*

margin along right mid-clavicular line. Spleen is not palpable, no peripheral edemas. Laboratory tests: Hb — 154 g/l, RBC — 5.28 × 10^{12}/l, WBC — 5.95 × 10^{9}/l, neutrophils — 3.11 × 10^{9}/l, platelets — 225.4 × 10^{9}/l, lymphocytes — 30.36%, monocytes — 14.90%, ESR — 5 mm/h, CRP — 7.3 mg/l. Clinical urinalysis: protein — 0.15 g/l, RBC — 1.8 cells/μl. Blood biochemistry: glucose — 4.11 mmol/l, total cholesterol — 4.42 mmol/l, LDL-C — 2.95 mmol/l, blood calcium — 2.14 mmol/l (2.11–2.55), potassium — 4.8 mmol/l (3.4–5.5), inorganic phosphorus — 0.97 mmol/l (0.87–1.45), lactate dehydrogenase — 188 IU/l (125–220), creatine kinase — 1,266 U/l (30–200), cystatin C — 1.16 mg/l (0.31–0.79), vascular endothelial growth factor — 99.37 pg/ml (10–700 pg/ml), IL-6 — 0.560 pg/ml (up to 10), TNF-alpha — 2.656 pg/ml (up to 6), gamma glutamine transpeptidase — 58 U/l (12–64), AST — 48 U/l (5–34), ALT — 25 U/l (0–55). Levels of thyroid hormones were within reference range. Prothrombin index — 85.7%, prothrombin time — 12.9%, INR — 1.12, fibrinogen — 4.5 g/l. GFR (CKD-EPI, 2011) was 124 ml /min/1.73 m^2. Given clinical and epidemiological data and laboratory parameters, the following diagnosis was established: Bilateral polysegmental pneumonia. Myositis, acute course, severe, of viral etiology. Treatment performed (glucocorticoids, antibacterial agents, anticoagulants, NSAIDs) improved the patient's condition: manifestations of muscle weakness and fatigue decreased, motor activity in limbs fully recovered, cough stopped. Concentration of creatine kinase decreased to reference range in three weeks. Changes in the patient's skin associated with myositis and indicating the severity of inflammatory changes completely disappeared during follow-up.

Creatine kinase (creatine phosphokinase) is an enzyme that catalyzes the formation of the high-energy compound creatine phosphate from adenosine triphosphoric acid (ATP) and creatine; this compound is required for increased physical activity. It should be emphasized that the activity of creatine kinase in women is slightly lower than in men. Target (reference) values of creatine kinase in women are 24–170 IU/l and in men 24–195 IU/l [20]. According to current data, the creatine kinase molecule consists of two subunits — M (from "muscle") and B (from "brain"). Combinations of these subunits form three different isoenzymes: MM — is contained in skeletal muscle, BB — in brain, and hybrid MB — in heart muscle. Normal content of CK isoenzymes in blood serum is as follows: CK-MM — 94–96%, CK-MB — 4–6%, CK-BB is absent or is found in trace amounts. In clinical practice, a combination of muscle weakness and increased creatine kinase levels tend to be the signs of myositis [20, 21].

Creatine kinase is found mainly in skeletal muscles, myocardium, as well as in smooth muscles and the brain [20]. It should be noted that creatine kinase activity is inhibited by thyroid hormones, in particular, by thyroxine. Therefore, in clinical practice, increased creatine kinase level requires the exclusion of thyroid dysfunction. Activity of creatine kinase in children is higher than in adults, which is associated with intensive growth and participation in this process of muscle and nervous tissues that are rich in CK. It is equally important that increased creatine kinase levels can be found in cases of statin-induced myopathy, HIV infection, obstruction of the biliary tract, diabetes mellitus, hypertriglyceridemia, renal failure, and use of certain medications: prednisolone, phenobarbital, thiopental, and tolvaptan [22, 23]. The onset of muscle symptoms or increased creatine kinase level in patients taking statins requires the exclusion of other causes, such as increased physical activity, injuries, cramps, hypothyroidism, infections, carbon monoxide poisoning, alcohol abuse, and drug use [19]. According to the regulation of the

National Lipid Association Muscle Safety Expert Panel (USA, 2014), statin-induced muscle symptoms include the following [24, 25]:

1) «Myalgia» (muscle pain);
2) «Myopathy» (muscle weakness);
3) «Myositis» (muscle inflammation diagnosed based on intravital morphological examination of muscle tissue and/ or according to MRI results);
4) «Myonecrosis» (muscle damage diagnosed based on a significant increase in serum creatine kinase level);
5) «Rhabdomyolysis» with myoglobulinuria and/or acute kidney damage with increased serum creatinine level.

Issues relating to statin-induced myopathy are described in detail in the publication by O. M. Drapkina et al. (2012) [26].

In a review study, T. A. Ruzhentsova et al. (2018) demonstrated that muscle cell damage is accompanied by the release of various intracellular components into the bloodstream which forms the basis for laboratory diagnosis of a large number of pathological processes (for example, dermatomyositis, progressive muscle dystrophy tetanus, as well as brain diseases (schizophrenia, manic depressive disorder, epilepsy, head injuries), after surgery, for any type of shock) [22, 27]. Muscle damage in cases of COVID-19 is based on various pathogenetic mechanisms. Hyperimmune inflammation associated with the production of proinflammatory cytokines, activation of apoptosis, development of vasculopathy and accompanied by inflammatory skeletal muscle infiltration is of the greatest importance in cases of COVID-19 [28]. Scientific literature sources show a high prevalence of muscle symptoms [29]. According to the authors, this is due to the damage to skeletal muscles, with the corresponding manifestation in the form of increased creatine phosphokinase and lactate dehydrogenase levels. Such changes can be associated with ATP 2 in skeletal muscles [9]. Hsueh S. J. et al. (2020) described a case of severe myopathy in a 51-year-old woman with COVID-19 and significantly increased level of creatine kinase [30]. It should be noted that creatine kinase level in hospitalized patients with COVID-19 can be influenced by bed rest, frequent medical procedures, injections and intake of medications [31]. However, patients with COVID-19 also demonstrated myalgias in combination with increased creatine kinase level at the pre-hospital stage [32]. Severe damage to the muscular system, i.e., rhabdomyolysis as a possible late complication associated with COVID-19 was described by M. Jin and Q. Tong in a 88-year-old man with bilateral pneumonia and severe weakness: tests showed increased creatine kinase to 13,581 U/l and lactate dehydrogenase to 364 U/l [33]. The publication by H. Zhang, et al. (2020) presented a case of COVID-19 associated with skeletal muscle damage; with manifestations in the form of generalized muscle weakness, dysphagia and respiratory symptoms in a 58-year-old woman; her creatine kinase level reached 700 U/l [34]. It should be noted that muscle biopsy revealed perivascular inflammatory infiltration and increased expression of HLA (Human leukocyte antigen) of class I (A, B, C) on non-necrotic fibers [34]. It is worth bearing in mind that in clinical practice, increased creatine kinase levels can be found in patients with myopathies, dermatomyositis, poliomyelitis, acute cerebrovascular event, and traumatic brain injuries [19, 35].

When dealing with problems of muscle damage in cases of COVID-19, it should be noted that issues concerning classification, severity criteria, and approaches to the management of myosites and myopathies associated with coronavirus disease are still poorly understood due to insufficient data. Management of myositis and myopathy in actual clinical practice is based on NSAIDs. Glucocorticoids may be used for severe myositis [36, 37].

Conclusion

In clinical practice, it is important to conduct additional tests to assess the level of creatine kinase in comorbid patients — in addition to defining changes that are typical for COVID-19. In cases of increased creatine kinase level, it is recommended to exclude hypothyroidism, muscle injuries, liver and kidney abnormalities, as well as taking statins. Presented clinical cases demonstrate the need for comprehensive careful assessment of all available clinical and medical information, as well as the results of laboratory and diagnostic tests. In the context of the ongoing COVID-19 pandemic, creatine kinase and lactate dehydrogenase levels should be monitored to verify damage to the muscular system and prevent virus-induced myositis.

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