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CHANGES IN HEMOSTASIS IN PATIENTS WITH POST-COVID SYNDROME

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ABSTRACT

Hemostasis disorders in COVID-19 play an important role in the pathogenesis and clinical manifestations of the disease. The ability to identify factors and risk groups for the development of thrombotic complications, interpret peripheral blood parameters and coagulograms in dynamics, knowledge of diagnostic criteria for possible hemostasis disorders (DIC syndrome, sepsis-induced coagulopathy, antiphospholipid, hemophagocytic, hypercoagulation syndromes, etc.) are necessary to determine the scope of examination, differentiated prescription of adequate therapy (including anticoagulants, blood components, plasmapheresis), which determines the greater effectiveness of complex treatment and the prognosis of patients with COVID-19.

Keywords: Coronavirus-induced coagulopathy, thrombosis risk factors, hypercoagulability syndrome, disseminated intravascular coagulation syndrome.

INTRODUCTION

The most striking clinical manifestation of COVID-19, a new coronavirus infection (NCI), is pulmonary damage. However, with NCI, the blood coagulation system is primarily affected, coagulation disorders occur, which are often hidden and unrecognized, but play an important role in the pathogenesis and clinical manifestations of the disease [1, 2, 3, 4].

MATERIALS AND METHODS

The released cytokines provoke interstitial inflammation, endothelial damage and activation of coagulation, in the pathogenesis of which the tissue factor plays a key role. It is released by monocytes, as well as by endothelial cells damaged or activated due to the action of cytokines. As a result, thrombin is formed, which leads to thrombosis of the alveolar capillaries [5]. In the Western literature, the term “pulmonary intravascular coagulation” has even appeared. This is a process of intravascular coagulation in the capillaries of the lung, which plays an important role in the development of acute respiratory distress syndrome (ARDS). In the development of hypercoagulation in NCI, importance is attached to microvesicles - cytoplasmic microparticles originating from platelets (PLT) and monocytes, which have procoagulant properties [2]. An increase in the number of exosome microparticles in general and in particular due to the number of platelet and leukocyte microparticles can be used as a marker of activation of the hemostasis system and an increased risk of thrombotic complications [3].

RESULTS AND DISCUSSION

Coronavirus-induced coagulopathy (CIC) in the initial stages of the disease is characterized by the development of hypercoagulation without signs of consumption and DIC syndrome. A significant increase in the concentration of D-dimer in the blood is noted. The amount of PLT

is moderately reduced (PLT < 150 * 109 /l is found in 70 - 95% of patients), prothrombin time (PT) is slightly prolonged, fibrinogen (FGN) as an "acute phase protein of inflammation" is increased. The concentration of antithrombin III (AT III) in the blood rarely decreases below 80%, the concentration of protein C does not change significantly. That is, CIC does not have typical signs of FGN and PLT consumption. There is no microangiopathy [4]. Monitoring of PT, D-dimer, the amount of PLT and FGN can help in determining the prognosis of hospitalized patients with CIC [3]. If these parameters are stable or improve against the background of clinical well-being, this provides additional confidence in the gradual cessation of treatment. The frequency of determining D-dimer, PV, FGN and the number of PLTs depends on the severity of the NCI: in hospitalized patients with a mild course, the analysis is taken once every 4-5 days, with a moderate course - once every 2 days, with a severe course - daily, an extraordinary one - if the severity of COVID-19 worsens [4].

To identify hemostasis disorders and an increased risk of thrombotic complications (the incidence of VTEC in patients with NCI reaches 27–69% [8]) or hemorrhagic complications, as well as the development of microcirculation thrombosis and multiple organ failure, it is important to monitor such indicators as D-dimer, FGN and the amount of PLT, PV, ESR, C-reactive protein (CRP), lactate dehydrogenase, triglycerides, and ferritin [1]. If secondary activation of blood coagulation that occurs during severe infection gets out of the control of endogenous anticoagulant mechanisms, and an acute generalized inflammatory reaction leads to extensive damage to the vascular endothelium, a complication may be acute DIC syndrome with subsequent tissue ischemia, leading to the development of multiple organ failure [3]. If in surviving patients with NCI, DIC was recorded only in 0.6% of cases, then in those who died - already in 71.4% of cases [4]. The presence of coagulopathy, arterial and venous thrombosis in NCI is associated with the risk of death [2]. Analysis of autopsy data of patients who died from NCI indicates the presence of, in addition to diffuse damage to the alveoli, multiple thromboses of small vessels of the lungs and associated multiple hemorrhages in the alveoli [5]. Megakaryocytes are involved in the thrombotic process in the lungs, the resulting thrombi are rich not only in fibrin, but also in PLT. Signs of thrombotic microangiopathy in the lungs are noted. Electron microscopy data indicate the presence of significant damage to endothelial cells associated with the penetration of SARS-CoV-2 into cells, widespread thrombosis of small vessels, microangiopathy, occlusion of alveolar capillaries and signs of neoangiogenesis [4].

The pathogenesis of DIC in NCI is represented by three interconnected processes: the cytopathic damaging effect of the virus on vascular endothelial cells, a “cytokine storm” with the release of high-molecular von Willebrand factor (VWF), stimulating the activation of both plasma and platelet blood coagulation pathways, and the development of systemic vasculitis with damage to small and medium-sized vessels [2].

Determination of the D-dimer level is decisive for the diagnosis of CIC. A relationship has been identified between an increase in D-dimer levels and the severity of patients’ disease, the need for more intensive therapy, and the prognosis of the disease [5].

Tang et al. [2] showed that significantly elevated D-dimer levels were one of the predictors of death: in those who died, the mean value was 2.12 μg/mL (range 0.77–5.27 μg/mL), while in survivors it was 0.61 μg/mL (range 0.35–1.29 mg/mL) with a normal value of less than 0.5 μg/mL. D-dimer levels > 2500 ng/mL were an independent risk factor for disease severity to

critical in 4103 patients with confirmed CCI, along with oxygen saturation < 88%, ferritin levels > 2500 ng/mL, and CRP > 200 mg/L [4]. Patients with a 3-4-fold increase in D-dimer levels should be hospitalized even in the absence of other symptoms of severity, since this clearly indicates an increase in thrombin production [1, 3, 4].

Another marker of coagulation and fibrinolysis activation, fibrin degradation products (FDP), has the same significance. In patients with NCI, the average plasma FDP concentration was 7.6 μg/ml, while in survivors it was 4.0 μg/ml ($p < 0.001$), with normal values < 5.0 μg/ml [3].

In NCI, an increase in the PT indicator is associated with the severity of the condition and is a risk factor for the development of ARDS [3].

Another significant diagnostic test is the amount of PLT.

The potential for significant drug-drug interactions should be considered when antivirals are co-administered with statins, antiplatelet agents and DOACs [4]. Data on the clinical significance of antithrombotic drug-drug interactions for COVID-19 are presented in tables published by the University of Liverpool Drug Interaction Group and discussed in documents prepared by international expert groups [5]. In patients without symptoms of NCI in the presence of contacts or with minimal symptoms of NCI, the use of antiplatelet agents and heparinoids can be considered without a significant increase in the risk of bleeding. Dipyridamole (75 mg 3 times a day, according to the instructions), being an antiplatelet agent and vasodilator, inhibits phosphodiesterase, blocks the reuptake of adenosine (which acts on platelet A2 receptors and activates adenylate cyclase), inhibits the synthesis of thromboxane A2, reduces viral replication, suppresses excessive reactivity and adhesion of PLT to the endothelium, and enhances the effects of type I interferon [2].

CONCLUSION

Coagulation disorders not only lead to the development of clinically significant thrombotic complications, but also play a role in the pathogenesis of NCI, including lung damage. Therefore, CIC treatment is an integral and necessary part of the complex treatment of NCI. The effectiveness of CIC therapy affects the severity and prognosis of patients with COVID-19

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