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Covid-19: Effect on Hemostasis

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Since December 2019, the first cases of coronavirus infection began to be registered, by now there is enough data accumulated to analyze the pathogenesis of the disease, as well as to develop etiopathogenetic treatment. The cytokine storm and coronaviral induced coagulopathy are considered to be the main pathogenesis link, which made possible to develop an etiopathogenic treatment. Cytokine Storm destroys precursor cells and reduces platelet production. The further formation of autoimmune complexes leads to thrombocytic destruction and induces damage to the endothelial cells of lung capillaries. Recommended direct parenteral anticoagulants treatment with low-molecular weight heparin forms (LMHs).

Introduction

In December 2019, the WHO office in China first reported an epidemic of unexplained lower respiratory tract infections in Wuhan. The disease, which belongs to the coronavirus family, is called Coronavirus Disease 2019 (COVID-19). The exponential growth of coronavirus infection has led to an increase in infections worldwide and significant mortality in a number of countries.

The pathogenesis of a new coronaviral infection is not fully investigated. The main target of the virus are type II lung alveolar cells with receptors of type II angiotensin converting enzyme. It is believed that the receptor CD147 (Basing (CD147, EMMPRIN)), a multifunctional glycoprotein in the cellular membrane, is one of the ways the virus penetrates the cell. Currently only little information is available about the interaction of the virus with erythrocyte porphyrin, leading to impaired hemoglobin-oxygen binding and hyperferritinemia. However, SARS-Cov_2-infection has been shown to be associated with coagulopathy, a complication linked to an overreaction of the immune-system.

Cytokine Storm

Much attention is paid to the “cytokine storm”, an umbrella term for an overproduction of cytokines triggered by infections, faulty genes or autoimmune disorders, through which patients with COVID-19 show high levels of neutrophils, linked to a high risk of development of acute respiratory distress syndrome (ARDS). The severity of pulmonary infiltration depends on the degree of pulmonary invasion by neutrophils and monocytes/macrophages as well as their quantity in peripheral blood. Neutrophils produce cytokines and chemokines [1]. Thus, lymphopenia and neutrophilia are considered as blood born severity markers in patients with COVID-19, as they are

predicators for a rather malign course of the infectious process [2].

COVID-19 induced coagulopathy

Along with clinical manifestations of symtoms similar to those observed with common cold, a number of specialists consider the development of coagulopathy to be an adverse outcome factor of the disease. Pulmonary tissue autopsies of patients who died from severe acute acute respiratory infections show microvascular lesions, occlusions and micro thrombosis mediated by complement activation and associated procoagulant status. Damage to endothelial capillary cells of lung tissue by cytokines leads to platelet activation and clotting, micro thrombosis and fibrin deposition. In some cases also skin lesions with confirmed inflammatory thrombogenic vasculopathy have been reported [3]. Hypoxia further promotes thrombosis by increasing blood viscosity and by transmitting signals to hypoxia-induced factors (HIFs) [4].

Coagulation is further promoted by treatment, as patients with severe forms of COVID-19 infection requiring artificial lung ventilation are immobilized, which can cause stagnation of blood flow. Additionally, intensive therapy requires catheterization of vessels (both mainline and peripheral), which is a cause of endothelial damage. Thrombocytopenia is generally not an indicator of increased severity, but it must be differentiated from pseudotrombocytopenia. In-vitro, anticoagulant induced auto-antibody production (by application of EDTA, ethylenediaminetetraacetic acid) induces artificial platelet coagulation, leading to incorrect thrombozyte counts. The frequency of this phenomenon is about 2%, so if pseudo thrombocytopenia is suspected, blood samples are taken in tubes containing citrates or heparin as anticoagulant, and platelet count is performed manually [5].

COVID-19 patients typically do not display significant level of true thrombocytopenia. The Yang X. et al. study included 1476 patients, of whom 238 (16.1%) died. Thrombocytopenia was observed in 306 (20.7%) patients with platelet count as the lower limit of the normal range 125 × 109 /l [6].

The mechanisms of thrombocytopenia in patients with new coronaviral infection consist in the infection of hemopoietic cells of the bone marrow resulting in dysfuctional hemopoiesis. Cytokine Storm destroys precursor cells and reduces platelet production. The further formation of autoimmune complexes leads to thrombocytic destruction and induces damage to the endothelial cells of lung capillaries, triggering platelet activation, aggregation and reduction of circulating blood platelets [7].

Diagnostic aspects

Decrease in thrombocyte numbers can be a sign of organ dysfunction, sepsis, and the development of a dissimulated intravascular clotting syndrome (ICA). Monitoring of platelet count during hospitalization is thus very important for prognosis in patients with COVID-19. Intra-hospital lethality is tripled in patients with thrombocytopenia. The lower the platelet count, the higher the mortality rate [6].

The state of hypercoagulation is confirmed by coagulogram data. The given components of Virkhov’s triad testify to the propensity of this group of patients for thrombosis. One of the most common laboratory indicators studied in COVID-19 patients is the coagulogram, indicating thrombocytopenia, hyperfibrinogenemia and D-dimer increase.

Changes in coagulogram screening tests (ACTV; PV) are insignificant. Increased values of D-dimer, PDF, fibrinogen, decrease of antithrombin and PT levels measured by Quicktest were found in lethal COVID-19 patients [8]. Additional laboratory studies show an increase in the activity of anti-

hemophilic factor VIII, which belongs to the proteins of the inflammatory phase, as well as an increase in von Willebrand factor, which confirms the damage of glycocalyx of endothelial cells by cytokines [9].

A number of studies have shown efficacy of bedside methods like thromboelastography (TEG) in diagnostics of hypercoagulation [10]. However, the clinical value of TEG in COVID-19 has not yet been established [11]. In contrast, the efficacy of anticoagulant heparin therapy in patients with extra-hospital pneumonia was proven even before the pandemic of a new coronavirus infection.

Treatment of COVID-19 induced hypercoagulation

When direct parenteral anticoagulants are chosen, low-molecular weight heparin forms (LMHs) should be preferred, which have a lower molecular weight (4000 - 5000 kD) than unfractionated heparin and block factor Ha to a greater extent while less frequently causing complications such as heparin-induced thrombocytopenia and osteoporosis. Accordingly, a reduction of treatment duration in patients on artificial lung ventilation using LMH has been observed [12]. The synthetic medication fondaparinux also showed its effectiveness in reducing the total mortality and frequency of pulmonary artery thromboembolism in patients with extra-hospital pneumonia in comparison with placebo [13].

Pharmacological prevention of thromboembolic complications is required for all patients with severe COVID-19. LMH and fondaparinux do not interact with other drugs that are used in the treatment of new coronaviral infection. At present, anticoagulant dosing solutions must be specifically tailored to optimize treatment as drugs with antithrombotic effects represent also risk factors for thromboembolic complications, or bleeding [14].

Thus, in all patients with COVID-19 it is necessary to evaluate the coagulation status in dynamics by determining the level of D-dimers, prothrombin time, platelet count, fibrinogen content, as well as to prescribe low-molecular heparins for preventive purposes.

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