Pathology Of Vascular-Platelet And Coagulation Hemostasis In Coronavirus Infection (Literature Review)

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ABSTRACT

The literature review provides the relevance of coronavirus infection, describes in detail the mechanisms of development of endothelial dysfunction, cytokine storm, imbalance in the coagulation system and the development of disseminated intravascular coagulation syndrome in coronavirus infection. It has been analyzed the widely used hemostasiological indicators in general practice, which are important in determining the prognosis of patients with coronavirus infection: platelets, prothrombin time, active partial thromboplastin time, D-dimer and fibrinogen.

Keywords: coronavirus infection, endothelial dysfunction, platelets, prothrombin time, active partial thromboplastin time, D-dimer, fibrinogen

Coronavirus infection (COVID-19) is a new infectious disease that is rapidly spreading around the world, accompanied by severe complications. In December 2019 year observed epidemic outbreak of unknown infection in Wuhan [59], the development of pneumonia in a large number of patients has led to an emergency situation in the Chinese health system. The Chinese Center for Disease Control and prophylaxis has studied the crop made from throat grease for patients and this situation was confirmed by the release of a new type of beta-coronaviruses geltirib [31]. The new virus was called the Severe Acute Respiratory Syndrome Coronavirus SARS-CoV-2 [20, 32].

In COVID 19, severe coagulopathy, arterial and venous thromboses turned out to be the main causes of death. Studies have shown that, SARS-CoV-2 is associated with ACE2 in the vascular endothelium, which leads to an increase in vascular permeability, a violation of microcirculation, the formation of thrombosis in the blood vessels [7]. These changes lead to endothelial dysfunction as well as the development of local or systemic vasculitis [5].

At severe course of any infection, the blood clotting system is disrupted and as a protective system prevents the spread of microorganisms. However, the increase of infammatory cytokines in COVID-19 causes a cytokine storm and this leads to an acute generalized inflammatory reaction, a diffuse jerking of the vascular endothelium endogenous anticoagulants of the coagulation system goes out of control, as a result,develops Acute Disseminated Intravascular Coagulation syndrom (ADIC)[6, 51]. And the "storm of cytokine", which is formed as a result of inflammation, leads to the appearance of inflammatory trombosis-immunotrombosis [3, 4].

Immunotrombosis of microtomy of the lungs is of great importance in the progression of respiratory failure in COVID-19 [10]. In

addition, a sharp increase in the amount of antifospholipid antibodies (anticardiolipine IgA, anti-β2-gli-coprotein1, immunoglobulin A and G) in the blood of patients with a high level of COVID-19, many of which have been identified, can also be evidence of a heavy inflammatory process [57]. In studies of French scientists,out of 25(45%) patients from 56 patients with COVID19 identified lupus anticoagulants [21].

At the same time,in COVID-19, C-reactive protein, erythrocyte sedimentation rate(ESR),ferritin, the procoagulant Von Willebrand factor(vWF) and VIII blood coagulation factor, which are nospesific inflammatory biomarkers increases in the blood [11]. 4-6-times increase in the concentration of the Von Willebrand factor is means of endothelial damage [23, 41].

Endothelium not only controls homeostasis , but also a violation of its integrity leads to circulatory disorders, vasoconstriction of vessels, microcirculation disorders and ischemia of damaged organs [18]. At the same time, the activity and increase in neutrophil leukocytes also contribute to blood clotting and leads to thromboses. The role of leukocytes in the development of immunotrombosis is great. In particular, monocyte and neurophilic leukocytes also produce cytokines, which are activate both chromolytic and coagulation hemostasis [46].

Damaged endothelial cells and monocytes produce tissue thromboplastin (TT). Production of TT activates the blood clotting system in an external way [4.] Hyperinflammatory reactions damage the tissues, as a result in endothelial barrier is disrupts and coagulation is uncontrollable activate [12, 17].

Endothelial dysfunction in COVID-19 was due to the main factors of the pathophysiology of development of thrombotic complications, as a result of which myocardial infarction and stroke develop.Endothelial dysfunction is directly related to the jarring effect of the virus, the inflammatory response reaction of the endothelium, the activity of immune reactions, the production of cytokines [9, 33, 43].

In COVID-19, the patient's age serves as one of the risk factors for lethality. While the mortality rate in patients over 85 years of age was 304.9 percent compared to 1000, in patients aged 5-17, this rate was 0.3 percent compared to 1000. COVID-19 the cause of these severe complications in COVID-19 may be a change of the endothelium which is depend on age of patients [54]. NADFN-oxidase and mitochondria produce active forms of oxygen and with age, the active forms of oxygen accumulate [50]. The increase in oxygen-active forms in endothelial cells blocks nitrogen oxide (NO), which has a vasodilator, antiaggregant and cardioprotector effect [53].

As a result of endothelial activity and decay , the Von Willebrand factor is produced [44]. The von Willebrand factor collects in the affected area of the thrombus and faxes them [30]. Spontaneous activated platelets and other blood cells lead to the development of thrombosis [56].

Platelets – short-lived cells without a small nucleus, which are considered to be involved in primary hemostasis[28].But, currently, platelets are complex structures and have fundamental elements for various processes, including autophagy, apoptosis and other. [40]. Platelets also affect other cells, including blood cells, endothelial cells and other vascular cells, leading to a separation of hemostatic and anti-inflammatory mediators. [27].

In COVID-19, hyperactivity of platelets develops and it leads to hypercoagulation and immune response dysfunction [35]. On the surface of active platelets P-selectin and CD40L are exposed, interacting with neutrophils, α-granules, C3 complement component, various cytokines, including CC-hemokin ligand 2 (CCL2), CCL3, CCL7, IL-1β, IL-7, IL-8 and hepatocytes produce growth factor [15,45]. At the same time, the SARS-CoV-2 virus leads to a change in the transcriptome of platelets [34].

SARS-CoV-2 forms immune responses with reactive antibodies in the body, such as H1N1 influenza infection [39].This immune complexes join to the receptor of platelet FcyRIIa and they activate platelets[8]. Viral induced platelets activity increases the amount of platelets and leukocytes conjugates [16].

This is evidenced by the fact that in autopsy of patients who died as a result of COVID-19, increased the amount of platelets, leukocytes in the lung tissue, and developed microthrombes [38].

In vitro and in vivo studies have shown that, in response to viral infection, platelets produse IL-1β and increase endothelial conductivity [24]. At the same time, in COVID-19, platelets accumulate in the vascular net of the neutrophils [38]. The combination of active platelets with neutrophils is of great importance in the development of immunotrombosis, migration of platelets into the alveolar cavity and the development of pulmonary edema [55]. Hypoxia, oxidative stress and other factors disrupt the work of the mitochondria of platelets and lead to apoptosis [37].

Studies have shown that many concomitant disease (for example, diabetes and obesity), which is observed together in COVID-19, leads to oxidative stress and apoptosis of platelets[48].

The development of thrombocytopenia in COVID-19 is associated not only with apoptosis, but also with the expenditure of platelets in the formation of thrombosis, the production of SARS-CoV-2-induced antibodies [58]. Trombocytopenia is a high-lethality Predictor, it was found that in patients with trombocytopenia at COVID-19, the mortality rates were 5 times higher [29].

J.Maquet and other autors studies have shown that 58% of patients diagnosed with COVID-19 and identified trombocytopenia are predisposed to oxygen therapy [35].

9 studies in a meta-analysis of 1779 patients with COVID 19 showed that a decrease in the amount of platelet from 100×109/l serves as a bad prognostic sign, according to the studies examined. In the most severe patients, the amount of platelets is from 35 to 29 × 109/l [29].

However, in patients with COVID-19, thrombocytopenia in rare cases decreases from 100 × 109/l [47], a decrease in the amount of platelets from 100 × 109/l was observed only in patients with 5% of hospitalization [25]. Fan and co-author cited that the average amount of platlets in most patients who were not autonomous to intensive therapy was within the normal [13].

Monitoring of the amount of PT, APTT, D-dimer and fibrinogen calculated by coagulation hemostasis indicators is important in determining the prognosis of patients with COVID-19 [4]. Coronavirus-induced coagulopathy (CIC) initially leads to the development of hypercoagulation. D-dimer concentration increases sharply, prothrombin time (PT) decreases, fibrinogen increases. The concentration of antithromycin III (AT III) in the blood decreases by 80% in rare cases, the concentration of protein C does not change. At the same time, in COVID-19, the time of acute partial thromboplastin time (APTT) decreases, the VIII clotting factor increases [11].

An increase in the concentration of D-dimer is a prognostic indicator of patient's bad condition [22], which indicates a craving for intensive therapy [19, 25, 47]. According to the recommendations of the ISTH, it is mandatory to check the concentration of D-dimer, prothrombin time, the number of platelets in order to determine the extiogenesis of hospitalization in all patients with SARS-CoV-2 [49].

Studies have shown that when 4103 patients condition evaluated as critical, the amount of D dimer is more than 2500 ng/ml, oxygen saturation is less than 88%, ferritin content is more than 2500 ng/ml, and C-reactive protein is more than 200 mg/l [42]. Even without clinical signs, when the amount of D dimer increases 3-4 times, hospitalization is necessary, since this indicator indicates an increase in the production of trombin [1, 4]. High prevalence of mortality in patients with high D-dimer [36].

Hyperfibrinogenemia is marker of COVID-associated coagulopathy [2]. N. Tang and co-author identified an increase in fibrinogen in all patients who were hospitalized with COVID-19. In comparison with the control group, patients with COVID-19 had a higher fibrin content: 5,02 g/l in patients, while in the control group 2.9 g / l [47].

In patients with COVID-19, fibrinogen is high in the middle of the blood and its decrease

is indicative of the development of (ADIC)if it is associated with the inflammatory process [3].

The development of ADIC in COVID-19 leads to secondary coagulopathy and worsens the prognosis. In autopsy, when examined 71.4% of patients with 183 deaths were diagnosed with ADIC [47].

In the case of patients with COVID-19, and the course of the disease depends on the indicators of the hemostasis system, initially the concentration of fibrinogen increases, while when ADIC progressive develops, the amount of fibrinogen and antithrombin decreases [29, 49].

A sharp decrease in the amount of fibrinogen from the blockade to 1,0 g/l was observed before death [47]. Nevertheless, ISTH experts estimate that patients with COVID-19 do not need to measure the concentration of fibrinogen when they arrive at the hospital [49]. However, given the fact that fibrinogen is easy to check, is widely used, is very much in favor of the hemostasis system, other authors consider it to be an inspection [14].

According to some authors, changes in hemostasis in COVID-19 are different from hemostasiological silences in normal sepsis. Thrombositopenia and hypofibrinogenemia in sepsis are stronger, but the amount of D-dimer is several times lower. At the same time, there are practically no hemorrhagic complications at ADIC in COVID-19 [26].

In patients with COVID-19, as a result of DTIs, diffuse damage to the microtomy of the lungs, as a result of which acute respiratory distress syndrome develops, which leads to death [52].. If ADIC in recovered patients suffered by 0.6%, in patients who died, this indicator is 71.4% [47].

The fact that patients with acute partial thromboplastin time(APTT) COVID-19 should be examined when treated in stationary conditions is a favorable indicator [14]. APTT is one of the indicators of coagulation hemostasis, which is considered important in assessing the internal (XII, XI, IX and VIII clotting factors) and general (X, V, II and I clotting factors) pathways of blood clotting, and is sharply reduced in patients with COVID-19 [47].

An increase in the isolation cytokines in COVID-19 causes a cytokine storm, which leads to an acute generalized isolation reaction, dysfunction of the vascular endothelium. Damaged endothelial cells and monocytes produce tissue chromboplast, as a result of which the blood clotting system is disrupted by an external pathway. Monitoring of the amount of PT, APTT, D-dimer and fibrinogen calculated by coagulation hemostasis indicators is important in determining the prognosis of patients with COVID-19, the concentration of bunda D-dimer and fibrinogen increases sharply, the time of prothrombin (PT) and the time of acute partial thromboplastin decreases. And hypercoagulation leads to thrombotic complications.An increase in the concentration of D-dimers and a decrease in the amount of fibrinogen indicates the patient's craving for intensive therapy.

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