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Rheological Parameters in Patients with Brain Infarct During COVID-19

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Abstract

In the description of the analytical clinical data of the patients with COVID-19 from difference country. In article shows detailed description of the rheological situation in patients with neuropathic during COVID-19. This data was compared with results of rheological study in analogical disease group patients without COVID-19. The article describes the effect of various anticoagulants on blood rheology, also describing protocols. In vivo, in vitro experiments, that studied a range of rheological parameters different anticoagulants. Measurement of RBC aggregation, RBC deformities, plasma viscosity were study with innovative technologies, quantitative methods. The work presents a scientific focus, after deep and increase research area is able to transport the newest conclusion to the clinical practice to treatment management of COVID-19.

KEY WORDS. COVID-19, brain infarct, neurological problems, brain infarct

Introduction

Coronavirus infection is an acute viral disease with upper respiratory tract infection caused by a virus of the genus Betacoronavirus of the Coronaviridae family. The official names are: Disease coronavirus disease (COVID-19); Virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) [1] is a family that includes as of April 2020 40 types of RNA-containing complex viruses that have supercapsids. Combined into two subfamilies that affect humans and animals. The name is associated with the structure of the virus: from supercapsid come large spiky processes in the form of clubs, which have resemble the crown. Virions measuring 80-220 nm. A nucleocapsid is a flexible helix, which consists of a genomic plus RNA strand and a large number of nucleoprotein N molecules. It has the largest genome among RNA genomic viruses. A supercapsid is secreted in its structure, in which glycoprotein trimeric spikes (peplomer), membrane glycoprotein, small membrane glycoprotein, hemagglutinin esterase are embedded. Coronaviruses penetrate the cell membrane by simulating molecules to which transmembrane cell receptors respond. Until December 2019, it is believed that HCoV-229E, -OC43, -NL63, -HKU1 circulated among the population, which are year-round in the structure of acute respiratory viral infections, and, as a rule, cause damage to the upper respiratory tract of mild to moderate severity. Until 2002, coronaviruses were considered as agents causing mild diseases of the upper respiratory tract with virtually no fatal outcome. At the end of 2002, SARS-CoV appeared, the causative agent of SARS, which caused severe acute respiratory syndrome (SARS). This virus belongs to the genus Betacoronavirus. The natural reservoir of SARS-CoV is bats, intermediate hosts are camels and Himalayan civet. In total, over the period of the epidemic in 37 countries of the world, more than 8 thousand cases were recorded and 10% of them were fatal. In 2012, the world faced a new coronavirus (MERS-CoV), a causative agent of the Middle East respiratory syndrome, belonging to the genus Betacoronavirus. The main natural reservoir of MERS-CoV coronaviruses are bats and one-humped camels (dromedaries). Since 2012, 2,519 cases of coronavirus infection caused by the MERS-CoV virus have been registered, of which more than 30% have been fatal. All cases are geographically associated with the Arabian Peninsula. On February 11, 2020, the World Health Organization assigned the official name of the infection caused by the new coronavirus, COVID-19 (“Coronavirus disease 2019”) [2]. On February 11, 2020, the International Committee on Virus Taxonomy assigned its own name to the causative agent of COVID-19 infection, SARS-CoV-2. The new SARS-CoV-2 coronavirus is a single-stranded RNA-containing virus, belongs to the Coronaviruses family, belongs to the Beta-CoV B line. The virus is assigned to pathogenicity group II, like some other representatives of this family (SARS-CoV virus, MERS-CoV virus). Coronavirus SARS-CoV-2 is believed to be a recombinant virus between bat coronavirus and a coronavirus of unknown origin. The genetic sequence of SARS-CoV-2 is similar to the sequence of SARS-CoV [3].

The natural reservoir of the SARS-CoV-2 virus is bats. The genomic sequences of viruses found in bats are identical to those in patients with COVID-19. Currently, the main source of infection is an infected person, including those at the end of the incubation, prodromal period (the beginning of virus isolation from target cells) and during clinical

manifestations. The transmission mechanism is aspiration. Transmission: airborne and, according to many authors, contact: through water, food and objects. In fecal samples from patients infected with SARS-CoV-2, a pathogen was detected. The fact of the implementation of the artificial mechanism of SARS-CoV-2 transmission has been established. Susceptibility to the pathogen is high in all population groups. The risk groups for severe disease and the risk of death include people aged 60-70 years, patients with chronic diseases. Mortality in different countries is different and varies in different age groups. This may depend on the health system and the health of the nation in a particular age range in one particular country. SARS-CoV-2 virus is characterized by low environmental stability. Dies under the influence of ultraviolet, disinfectants, when heated to 40°C for 1 hour, to 5°C – in 30 minutes. Clinical picture. The incubation period with COVID-19: from 2 to 14 days, On average 5-7 days. Among the first symptoms of COVID-19, an increase in body temperature (90%), cough – dry or with a small amount of sputum (80%), shortness of breath (55%), myalgia and fatigue (44%), compression of the chest (20%), headaches similar to migraine (8%), hemoptysis (5%), diarrhea and nausea (3%). These symptoms are observed in the absence of an increase in body temperature [2]. Clinical options and manifestations of COVID-19: acute respiratory viral infection of the lung; pneumonia without respiratory failure; pneumonia with acute respiratory failure; ARDS; sepsis; septic (infectious toxic) shock. Hypoxemia develops in more than 30% of patients. Most patients with severe COVID-19 develop pneumonia in the first week of illness. However, it must be pointed out that in most of the literature COVID-19 is associated with pneumonia, even in the case of a middle course of the disease.

The diagnosis is established on the basis of an epidemiological history, clinical examination and laboratory results. When collecting an epidemiological history, it is necessary to take into account the patient's visits during the previous 14 days to COVID-19 countries and regions, close contacts during this time with people who arrived from endemic areas, as well as contacts with people whose diagnosis has been confirmed by laboratory tests.

General Laboratory Diagnostics: general (clinical) blood test; blood chemistry; study of the level of C-reactive protein (CRP) in blood serum; pulse oximetry with SpO_2 measurement to detect respiratory failure and assess the severity of hypoxemia (pulse oximetry is a screening method that allows you to identify patients with hypoxemia who need respiratory support and evaluate its effectiveness); for patients with Spo2 less than 90%, according to pulse oximetry, a study of arterial blood gases with the determination of PaO_2, $PaCO_2$, pH, bicarbonates, lactate is recommended; coagulogram.

Instrumental Diagnostics: computed tomography (CT) of the lungs is recommended for all patients with suspected pneumonia. CT of the lungs is a more sensitive method for diagnosing viral pneumonia. The main findings in pneumonia are bilateral infiltrates in the form of "frosted glass" or consolidations, which are predominantly distributed in the lower and middle zones of the lungs; in the absence of the ability to perform CT, a panoramic radiography of the chest organs is performed in the anterior direct and lateral projections. An X-ray of the chest reveals bilateral confluent infiltrative blackouts. Most often, the most pronounced changes are localized in the basal parts of the lungs. A small pleural effusion may also be present; electrocardiography in standard leads. Specific laboratory Diagnostics: detection of SARS-CoV-2 RNA by PCR in a smear from a nose, nasopharynx and /

or oropharynx. Also, samples can be water, which is used to wash the bronchi during fibro bronchoscopy (bronchoalveolar lavage), sputum, biopsy or autopsy lung material, whole blood, serum, and urine. Besides for differential diagnosis, PCR studies are carried out on pathogens of respiratory infections: influenza viruses of type A and B, rhinoviruses, respiratory syncytial viruses, parainfluenza viruses, adenoviruses, human metapneumoviruses, MERS-CoV. Microbiological diagnosis for Hemophilus influenzae type B, Streptococcus pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae. About disease in target groups.

Ischemic Brain Infarct. Ischemic stroke is a violation of cerebral circulation with damage to brain tissue, a violation of its functions due to difficulty or stopping the flow of blood to the place(s). It may be due to insufficient blood supply to the area of the brain due to a decrease in cerebral blood flow, thrombosis or embolism associated with diseases of blood vessels, heart or blood [3]. It is one of the main causes of death among people [4]. In recent years, mortality from diseases of the circulatory system takes first place. Mortality from stroke is in second place, second only to mortality from coronary heart disease. Total stroke morbidity and mortality rates in many countries of the world tend to increase. Ischemic strokes account for 70-85% of all cases of stroke, cerebral hemorrhage – 20-25%, subarachnoid hemorrhage – 5%. The ratio of the frequency of ischemic and hemorrhagic types of stroke is 4:1 [5]. There are various classifications of ischemic strokes, depending on the etiopathogenetic and clinical aspects, the localization of the infarction zone. By the rate of formation of the neurological deficit and its duration: transient ischemic attacks (TIA); “Minor stroke” – prolonged ischemic attack with a reverse neurological defect[eleven]; progressive ischemic stroke – characterized by the gradual development of cerebral and focal symptoms over several hours or 2-3 days with subsequent incomplete restoration of functions; completed (total) ischemic stroke is a formed cerebral infarction with stable or incompletely regressing deficiency. According to the severity of the condition of patients mild severity; moderate severity – the predominance of focal neurological symptoms over the cerebral, there are no disorders of consciousness; severe stroke – occurs with severe cerebral impairment, depression of consciousness, gross focal neurological deficit, often with dislocation symptoms.

Pathogenetic: stroke (including arterial-arterial embolism) – occurs against the background of atherosclerosis of cerebral arteries of large or medium caliber. This type of stroke develops stepwise, with an increase in symptoms over several hours or days, often debuts in a dream. Often an atherothrombotic stroke is preceded by transient ischemic attacks. Cardioembolic stroke (22%) – occurs when the embolism of the brain artery is completely or partially blocked. The onset of cardioembolic stroke is usually sudden, awake. At the onset of the disease, the neurological deficit is most pronounced. More often, a stroke is localized in the area of blood supply to the middle cerebral artery, the size of the focus of ischemic damage is medium or large, a hemorrhagic component is characteristic. A history of thromboembolism of other organs is possible. Hemodynamic stroke (15%) – due to hemodynamic factors – a decrease in blood pressure (physiological, for example, during sleep; orthostatic, iatrogenic arterial hypotension, hypovolemia) or a decrease in cardiac output (due to myocardial ischemia, severe bradycardia, etc.). The sizes of heart attacks are different, localization is usually in the zone of adjacent blood supply (cortical,

periventricular, etc.). Hemodynamic strokes occur against the background of the pathology of extra – and / or intracranial arteries (atherosclerosis, septal artery stenosis, abnormalities of the vascular system of the brain). Lacunar stroke (20%) – due to the defeat of small perforating arteries. As a rule, it occurs against the background of high blood pressure. It develops gradually over several hours. They are localized in the subcortical and stem structures (basal ganglia, inner capsule, white matter of the semi-oval center, the base of the bridge), the size of the foci does not exceed 1.5 cm. There are no general cerebral and meningeal symptoms, focal symptoms corresponding to the affected structure. In 9% of cases, a stroke develops according to the type of hemorheological micro occlusion (9%) (in some sources the term “rheological stroke” is also used [6]). Such a stroke occurs against the background of the absence of any vascular or hematological disease of established etiology. The cause of the stroke is pronounced hemorheological changes, disorders in the hemostatic system and fibrinolysis. Scanty neurological symptoms combined with significant hemorheological disorders are characteristic [7]. Patients with suspected hemorheological stroke (retrospective conclusion) participated in our studies. We tried to describe briefly cause-effect relationship between the virus and the pandemic, which claimed an incredible number of lives in these 4 months, infected almost 2 million people, endangered the economy of the whole world, also the health care system, health of world population. However, only a narrative of facts and a review are no enough. In our international collaboration, we set ourselves to find out what is the relationship between blood rheology and the course of the disease. In our international collaboration, we set ourselves the goal – to draw the attention of scientific generation to those aspects that need further study. Our scientific group consists of representatives of different specialties, different institutions of different countries, so we can describe the problems in different prisms. We will present you with unpublished data for discussion so far, we think that may be useful in terms of diagnosing and preventing complications of diseases against the backdrop of COVID-19 surveillance, and have a different health model.

Material and Methods

Our protocol and studies are fully consistent with the Ethical principles for medical research involving human subjects [8]. We used “Georgian methods” [9,10].

Results

Our results showed that in all cases when a patient with COVID-19 developed neurological changes (rheology ischemic brain infarct), a violation of the rheological status of the blood was uniform, i.e. RBC aggregation index, RBC deformability index, blood plasma

viscosity changed. Changes in this group corresponded and were 10-15% different from those from the same group of patients with a similar diagnosis without COVID-19. RBC aggregation index was 58,0 ± 6,2%; RBC deformability index was 2,70 ± 0,05 RBC deformability index, Plasma viscosity 1,60 ± 0,05 sP in patients with neuroscience problems (without COVID-19). RBC aggregation index was 63,8 ± 5,2%; RBC deformability index was 2,90 ± 0,05%; RBC deformability index; Plasma viscosity 1,75 ± 0,05 sP in patients with neuroscience problems (without COVID-19).

Discussion and Conclusions

Although a study was conducted in China on almost 60,000 thousand patients with COVID-19, the list of symptoms did not include heart attacks, strokes, hemorrhages, as manifestation and display of infection, but death in some cases was associated precisely with these diseases.

Over the past month, medical reports, scientific articles with arguments about the causal relationship of COVID-19 with neurological syndromes appeared (by the time this article is published, the amount of information will probably increase), but much remains unknown at this point in time. We began to become interested and monitor how many people in our countries have neurological problems

Here we make a reservation that in the results section of this article we did not include data from patients with hyposmia and anosmia during COVID-19. Here we announce that we will publish these data in the next publication, which is now being done by this expanded research group.

Our train of thought provoked the fact that neurological diagnoses, despite their absolute pathophysiological autonomy, have one very important similarity. This is the presence of a rheological mechanism. More commonly, COVID-19 always or almost always entails pneumonia. And pneumonia is a vivid example of such a pathophysiological state as an inflammation with all stages inherent in inflammation.

Despite the fact that the tissues of which organ are inflamed, inflammation always as a pathophysiological process comes with a mandatory violation at the level of microcirculation.

Thus, we hypothesized that violations of blood hemorheology lead to disturbances in microcirculation, which in turn disables the main arteries. In confirming our thoughts, the anatomical structure of the virus helped us. As you know, the virus has a very large size and is not particularly elastic. Thus, the physical movement of the virus, in addition to other effects on the blood flow, can cause the destruction of blood flow not only in the small arteries, but also in the large arteries, since the parabolic equilibrium of the blood profile will leave the stationary-laminar state due to loss erythrocytes impulse in the array near the virus. Rheology is one of the most priority systems of the body, which primarily ensures blood flow (together with the coagulation / anticoagulation system), provides trophic function, oxygenation of the body. In addition, the rheological system of the body includes not

only the issues of macro and microcirculation, I provide the movement of other biological fluids and gases through various systems and organs, including in the intercellular space, in the alveoli, etc. Rheology is, on the one hand, a separate system that, regardless of various factors, is leading in connection with blood circulation, but on the other hand, rheology plays a special role in microcirculation. this is due to the fact that in rheology is mainly regulated by formed elements, in particular RBC. RBC often have larger sizes than the capillaries themselves, so it is necessary to cram the elasticity, normal aggregation and other factors so that they do not have obstacles for penetration into the microvessels. In our studies, we saw that for any disease with COVID-19, the rheological status is violated due to a strong change in the aggregation of erythrocytes. In the last century, it was believed that rheological studies are only priced in the microvasculature, when the size of the red blood cell is several times larger than the diameter of the capillaries where the red blood cell must pass. In this approach, there is common sense when it comes to erythrocyte deformability and plasma viscosity, but if you pay attention to the aggregation of red blood cells, this is a very valuable descriptive physical argument and diagnostic parameter both in macro and micro circulation. Why did erythrocyte aggregation always be disturbed with COVID-19 even when in a similar situation without COVID-19 patients did not have an increased erythrocyte aggregation coefficient? The virus can get into macrocirculation in the following ways, either the virus enters the large vessel from the smaller vessel, which is at an acute angle, with great force, or it is pushed for a long time due to its roughness and non-elasticity and is thus ejected into the blood stream, or the virus enters the laminar blood stream at right angles. All other cases are a mathematical approximation and the vector sum of these cases. Some types of movement come down to rotary, oscillating, linear and reciprocating, irregular motion. Each one moves in a slightly different way and each type of achieved different. any movement of the virus can be determined by a combination of different types of movements, precisely because of this there are violations of the velocity vector of red blood cells, their impulses and angular momentum. All this happens due to a collision with the virus, or the fact that red blood cells have to accelerate and move along the “path broken by the virus”. This causes an unexpected collision of red blood cells in the plasma, which, in turn, moves with glides at different times near the parietal layer of blood vessels. This contributes to the bonding, monetization and, most importantly, the aggregation of red blood cells. Thus, the presence of a new coronavirus promotes the formation of aggregates not only immediately during erythropoiesis, not only in the microvasculature, as usual, but also in macrocirculation. All this causes an explosion of rheological disturbances in COVID-19. In terms of blood circulation, the rheological system is completely self-sufficient. But with regard to turnover, necessary here fusion and interaction of two different systems: rheological and coagulation/anticoagulation. A very interesting fact is that the coagulation and anticoagulation systems usually balance each other being mutually exclusive and interconnected at the same time. But even with physiological processes, the anticoagulation system is depleted faster than the coagulation system. This imbalance is enhanced in parallel with the consumption of the adaptive energy of the body, despite this physiological process (for example, pregnancy, aging) or pathophysiological (inflammation and any disease). As for the rheological system of the body, there is no antipode, which for example (reduced aggregation, increased deformability, etc.). There is

no so-called “anti-rheological” compensatory reactions. But the modern clinical approach and treatment tactics are aimed at ensuring that exogenous therapy helps and determines optimal conditions for normal blood flow, regardless of the factors that disrupt this normal current. There is some recommendation that application of heparin in COVID-19 has good answer reaction because of the risk of disseminated intravascular coagulation and venous thromboembolism. However, its efficacy remains to be validated.

Coagulation results, medications, and outcomes of consecutive patients being classified as having severe COVID-19 in China were analyzed. The mortality between patients who given heparin and patients who did not heparin, as was a different risk of coagulopathy, which was stratified by the sepsis-induced coagulopathy (SIC) score or D-dimer result.

This result shows that in patients with severe COVID-19 who took for 7 days or longer heparin, their D-dimer and prothrombin time were better, change of platelet count was negatively, correlated with monthly mortality in multivariate analysis. No difference in monthly mortality was found between heparin users and nonusers. But if patients have D-dimer was very more than limit of normal and they took heparin, these patients monthly mortality have low. Also, anticoagulant therapy mainly with low molecular weight heparin appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer. However, as we studied the marker of thromboembolism, it became clear that it can be used to determine neurological conditions (stroke, subarachnoid hemorrhage). The results of studying the correlation of serum D-dimer levels with the results of intracerebral hemorrhage (spontaneous or after rupture of cerebral artery aneurysm) are reliable [11].

A high level of peripheral blood serum D-dimer in patients shortly before admission to the hospital after cerebral hemorrhage or rupture of aneurysm is a statistically significant harbinger of the development of early severe neurological disorders, adverse outcomes or deaths. Reassessing D-dimer levels can help identify patients at high risk for adverse outcomes and make adjustments to treatment tactics [12,13]. All this speaks in defense of these and other studies of these factors for the purpose of forecasting.

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