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Disorder of Iron Metabolism as a Universal Pathogenetic Factor in Damage to Organs and Systems in COVID-19

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RELEVANCE The pathogenesis of COVID-19 remains one of the most pressing. The literature discusses the role of iron as a factor supporting inflammatory processes, hypercoagulability and microcirculation crisis in severe COVID-19.

THE AIM OF STUDY was to identify changes in iron metabolism in patients with severe COVID-19 and hyperferritinemia.

MATERIAL AND METHODS In this study, we used a content analysis of available scientific publications and our own observations of the peculiarities of the clinical picture and laboratory parameters in patients with a severe course of COVID-19 who had hyperferretinemia at the height of the disease. The main group consisted of 30 patients hospitalized in the Department of Anesthesiology, Resuscitation and Intensive Care of N.A. Semashko City clinical Hospital No. 38 with the diagnosis COVID-19, bilateral polysegmental pneumonia, severe course and hyperferritinemia. The diagnosis of a new coronavirus infection was confirmed by visualization of bilateral viral lung lesions with chest CT-scan, positive PCR test for SARS-CoV-2 and the presence of immunoglobulins to SARS-CoV-2. The control group consisted of 20 healthy volunteers. The study evaluated the biochemical parameters of iron metabolism, fibrinolysis and markers of inflammation. Changes associated with impaired iron metabolism were assessed by the level of serum iron, transferrin, daily and induced iron excretion in the urine. Statistical processing was carried out using nonparametric methods.

RESULTS All patients with severe COVID-19 and hyperferritinemia showed signs of impaired iron metabolism, inflammation and fibrinolysis — a decrease in the level of transferrin ($p<0.001$), serum iron ($p<0.005$), albumin ($p<0.001$), lymphocytes ($p<0.001$) and an increase in leukocytes ($p<0.001$), neutrophils ($p<0.001$), CRP ($p<0.005$), IL-6 ($p<0.001$), D-dimer ($p<0.005$), daily urinary iron excretion ($p<0.005$) and induced urinary iron excretion ($p<0.001$).

CONCLUSIONS The study showed that in the pathogenesis of the severe course of COVID-19, there is a violation of iron metabolism and the presence of a free iron fraction. The appearance of free iron can be caused by damage to cells with the "release" of iron from cytochromes, myoglobin, hemoglobin, or violation of the binding of iron to transferrin, which may be the result of a change in the protein structure or violation of the oxidation of iron to the trivalent state. When assessing the degree of viral effect on the body, one should take into account the effect of various regulators of iron metabolism, as well as an assessment of the level of free iron not associated with transferrin.

Keywords: new coronavirus infection, COVID-19, SARS-CoV-2, iron metabolism, free iron, ferritin, transferrin, NTBI, nontransferrin bound iron
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BP – blood pressure
CRP – C-reactive protein
HF – hyperferritinemia
MV – mechanical ventilation

INTRODUCTION

The success of the treatment of any disease is determined by the full understanding of the entire chain of the pathological process. Recent scientific publications indicate a possible connection between the severe course of *COVID*-19 and impaired metabolism of endogenous iron. A high level of serum ferritin, which physiological function is deposition (sequestration) of iron in tissues, was reported already in the first publications devoted to the severe course of *COVID*-19 [1]. *G. Bolondi et al*. pointed to a number of important signs in addition to hyperferritinemia (HF) indicating a change in iron metabolism in severe patients with *COVID*-19: low level of serum iron, transferrin and a decrease in transferrin saturation with iron [2]. In other studies, it was noted that patients with severe hypoxemia have significantly lower serum iron levels, and the severity of the disease and mortality in *COVID*-19 are closely correlated with the level of serum iron [3, 4]. It was also found that increased concentrations of ferritin and hepcidin in the serum of patients are associated with the severity of *COVID*-19 [5]. The physiological role of hepcidin is to inhibit the export of iron from cells to the blood, and its synthesis is induced by iron and cytokines [6, 7].

Several pathophysiological hypotheses of the effect of *SARS-CoV*- 2 on iron metabolism are considered. One of the first was the hypothesis of virus-induced hemoglobinopathy caused by the displacement of iron from the heme molecule, which leads to disturbed oxygen transport function of the blood and explains the significant hypoxia in patients [8]. Later, a theory was put forward about the hepcidin-like action of *SARS-CoV*- 2, based on the distant similarity of amino acid sequences between the spike protein of the coronavirus and human hepcidin [9]. The hepcidin-like action of the virus can provoke a violation of iron metabolism and lead to hyperferritinemia.

Recently, the role of transferrin in the development of the disease has been discussed, in particular, its involvement in coagulopathy associated with *COVID*-19 [10]. Transferrin is an iron carrier protein that circulates in the blood and delivers iron to cells through receptor-mediated endocytosis [11]. It is important to note that the affinity of iron for transferrin is very high ($10^{23} M^{-1}$ at *pH* 7.4), but it progressively decreases with decreasing *pH*. It is found that transferrin enhances the enzymatic activity of thrombin and XII*a* factor and blocks the action of antithrombin inactivating, rendering procoagulant action [12]. This point is important, since the severity of the *COVID*-19 disease is currently associated with thrombus formation, which mechanisms have not been fully understood yet. Although transferrin was not included in the list of proteins interacting with *SARS-CoV*- 2, it seems appropriate to study its role in the pathogenesis of the disease [13].

The study of the participation of free iron in the pathogenesis of *COVID*-19 deserves special attention. It is known that the binding (neutralization) of free iron reduces the production of interleukin-6 (IL-6) and reduces the manifestations of the inflammatory response syndrome [14]. Free iron is highly reactive and potentially highly toxic due to the formation of reactive oxygen species [15]. This mechanism can play a role in lung damage due to the high activity of free radical processes. Normally, the protection of the lungs from the toxic effects of iron is provided by a multilevel system, which includes transferrin, lactoferrin, ferritin, iron transporter protein in macrophages (*Natural resistance-associated macrophage protein* 1- *Nramp* 1), ferroportin. Non-integrity of this defense causes severe inflammatory damage to the lungs [16]. Iron also has a multifactorial damaging effect on the cardiovascular system. It was found that free iron enhances the expression of cell adhesion molecules (*Vascular Cell Adhesion Molecule* 1- *VCAM*-1, *CD* 106) in endothelial cells, which provokes dysfunction of the microvasculature [17]. Iron may play a leading role in the hypercoagulability found in patients with severe *COVID*-19. According to the concept of *B. Lipinski* (2013), free blood iron generates hydroxyl radicals that convert circulating fibrinogen into an insoluble fibrin-like material (or parafibrin) that is completely resistant to enzymatic proteolysis. Parafibrin attracts macrophages, contributing to the formation of the inflammatory process [18]. Analysis of numerous data has shown that iron is a fundamental factor in many aspects of pathological thrombosis [19]. In the experiment, iron (Fe^{2+}) dose-dependently induces platelet aggregation [20]. Also, iron can have a direct cardiotoxic effect due to increased production of reactive oxygen species, changes in the membrane potential of mitochondria, and disruption of the cytosolic dynamics of calcium [21–23].

A review of the available literature data showed the relevance of the study of iron metabolism in patients with severe *COVID*-19, which may further determine the improvement of the therapeutic approach.

The material of the present study is based on survey data of 30 patients hospitalized in the Department of Anesthesiology and Intensive Care Unit of N.A. Semashko St. Petersburg City Hospital No. 38 with a diagnosis *"COVID*-19, bilateral polysegmental pneumonia, severe course", who had increased level of ferritin in the blood. The diagnosis was confirmed by visualization of bilateral viral pneumonia on computed tomography of the lungs. Twelve out of 30 patients had a positive PCR test for *SARS-CoV*-2 ribonucleic acids, and 25 patients had antibodies to *SARS-CoV*-2 of the *IgM* and *IgG* classes. The control group consisted of 20 healthy volunteers. In 6 patients from the study group and in 6 volunteers, the daily urinary iron excretion was determined. In 6 patients from the study group, the induced daily urinary iron excretion was determined after intramuscular administration of 500 mg of deferoxamine.

In all patients, the following parameters were examined: hematologic- hemoglobin, RBC, WBC, neutrophils, lymphocytes, monocytes, platelets (*Sysmex XN* 1000, *Sysmex Corporation*, Japan), biochemical parameters- serum iron, albumin, transferrin, *C*- reactive protein (CRP) (*Cobas c*501, *Roche Diagnostics*, Switzerland); indicators of gas and acid-base state of blood (CBS) (*Cobas b*221, *Roche Diagnostics*, Switzerland); fibrinogen content (*Sta Compact*, *Stago Diagnostica* France); concentration of IL-6, *D*- dimer (JSC "Vector-Best", Russia), ferritin (LLC "Company Alkor Bio", Russia) in the blood with enzyme-linked immunosorbent assay (ELISA) (*ELx* 800, *BioTek Instruments,* USA). Antibodies *IgM* and *IgG* to *SARS-CoV*-2 were semiquantitatively determined and evaluated by the positivity ratio according to a set of instructions «*SARS-CoV*-2-*IgM*-ELISA-Best" and « *SARS-CoV*-2-*IgG*- ELISA-Best (JSC "Vector-Best", Russia). Iron concentration was also determined in urine collected within 24 hours by inductively coupled plasma mass spectrometry (*Agilent* 6850 *Ser*. II, USA).

Statistical processing was carried out using *Microsoft Excel* and *Statistica* 10. Elementary statistical indicators were calculated (*Me* [25%; 75%]). To assess the statistical significance of the differences between independent samples, nonparametric tests were used. The differences between the signs were considered statistically significant at a confidence level of $p < 0.05$.

The aim of the study is to identify changes in iron metabolism in patients with severe *COVID*-19 and HF.

Based on the purpose of the study, the following tasks were set:

1. To investigate clinical and laboratory parameters of inflammation, coagulation and iron metabolism in patients with severe *COVID*-19 and HF.

2. To assess the daily urinary iron excretion and the induced daily urinary iron excretion in patients with severe *COVID*-19 and GF.

3. To determine the main directions for further research of disorders of iron metabolism as a factor in the pathogenesis of *COVID*-19.

RESEARCH RESULTS

All patients included in the study (18 men, 12 women) were urgently hospitalized. The age of the patients was 65 [58.3; 69.8] years. The main complaints upon admission: a long-term increase in temperature over 38° C, weakness, dry cough, lack of effect from treatment for 6 [5; 7] days. Upon admission to the hospital, a decrease in blood oxygen saturation to 90 was noted [82; 93.5]%. Computed tomography revealed pneumonia with a lung lesion volume ranging from 35% to 95% in all patients. On the 10^{th} [6; 12.5] day of illness the progression of respiratory failure and a decrease in blood oxygen saturation to 75 [52.5; 80]% were observed, so the patients were transferred to the Department of Anesthesiology, Resuscitation and Intensive Care. The treatment was carried out in accordance with the protocols of the Temporary Guidelines approved by the Ministry of Health of the Russian Federation. Fatal outcomes were noted in 19 patients (63.3%). The main clinical and laboratory data of patients are presented in Table 1.

At the time of the study all patients underwent respiratory support under the control of the gas and ABB arterial blood: in 6 patients mechanical ventilation (MV) was performed in *SIMV-PC* mode with FiO_2 from 90% to 100%, 24 patients underwent noninvasive mechanical ventilation with FiO_2 from 40% to 100%. Severe lung damage was confirmed by low values of the oxygenation index- 93.6 [70.9; 119]. When assessing the parameters of the systemic hemodynamics of patients, a tendency for hypertension was noted: the mean blood pressure (BP) of patients was 94.3 [81.3; 106] mm Hg. (Table 2).

All patients had neutrophilic leukocytosis and severe lymphocytopenia. The indices of red blood and the number of platelets in patients did not differ from the values of the control group (Table 3).

The high level of ferritin in patients was accompanied by a significant decrease in the content of transferrin, albumin and iron in the blood serum. At the same time, the patients were characterized by a significant increase in the content of *C*RP and IL-6. In the blood of patients the significant increase in the concentration of *D*-dimer and moderate increase of fibrinogen (Table 4) were obderved.

Iron in urine was determined in patients without azotemia, hematuria, proteinuria, and hemoglobinuria (Table 5). Since the excretion of iron in the urine changes significantly during the day, it was decided to evaluate the daily excretion of iron. Normally, a small amount of iron is excreted in the urine- 100–300 μg/day [24]. In patients with severe *COVID*-19 and HF, the daily urinary iron excretion was significantly increased and amounted to 650 [452; 798] μg/day, which was statistically significantly higher than the values of the control group (p=0.004). The daily deferoxamine-induced urinary iron excretion in patients was 1962 [1232; 2568] μg/day. In previous studies, it was found that in healthy people, the daily excretion of iron after administration of deferoxamine averaged 800 μg/day [25, 26]. It is known that deferoxamine binds iron, forming a stable non-toxic compound feroxamine, which is excreted by the kidneys. It is important to note that deferoxamine chelates only free iron in blood and tissues, not affecting the iron of transferrin, hemoglobin, and cytochromes [27]. In this regard, an increase in the content of iron in urine after the administration of deferoxamine may indicate the presence of free iron in patients with severe *COVID*-19 and HF.

DISCUSSION

The study showed that HF in patients with severe *COVID*-19 was accompanied by a decrease in serum transferrin and albumin, which may be associated with impaired protein-synthetic liver function. Increased urinary iron excretion after the administration of deferoxamine indicated the presence of readily mobilized free iron in the blood of patients, which may be a trigger for multi-*organ* damage in severe *COVID*-19. Increased CRP, IL-6, *D*-dimer and lymphocytopenia and in combination with a neutrophil leukocytosis showed pronounced inflammation, thrombogenesis and fibrinolysis in these patients. Analysis of scientific data has shown that free iron is a fundamental factor in the inflammatory process and pathological thrombus formation, which suggests the active participation of free iron in the pathogenesis of severe *COVID*-19 [28].

Considering the pathophysiological processes underlying the appearance of free iron in *COVID*-19, several hypotheses can be made. The first hypothesis is based on the mechanisms of alteration- the release of iron from cells damaged by a viral particle. In this case, the content of the cytoplasm and organelles enters the extracellular matrix, where it undergoes phagocytosis and destruction by specific enzymes, for example, proteases. After that, iron is in the extracellular matrix, if we are talking about tissue, or in blood plasma, if we are talking about endothelial cells or erythrocytes. In addition, any cell of the body contains a sufficient amount of cytochrome iron, which can also be released in the "virus-matrix-protease" chain. As a result, a "chain reaction" occurs, namely: a viral particle leads to the destruction of the cell with the release of iron, which, being, in fact, a "secondary radical" and possessing powerful oxidizing properties, causes further avalanche-like destruction of cell membranes. In this case, the main defense mechanism is the binding of free iron to transferrin. There is a hypothesis of the second *modus operandi* of the *SARS-CoV*-2 virus – damaging the transferrin protein or transferrin gene. Given that damage to a single protein by a virus is impossible, the most likely theory is that protein synthesis is impaired. It can be assumed that *SARS-CoV*-2 inserts a particle of its genetic material into the hepatocyte genome responsible for the replication of the transferrin gene. The structure of the gene changes so the structure of the protein changes. Defective transferrin does not bind the iron molecule, and secondary free radicals continue to destroy cell membranes. In addition, the dysregulation of the ionic state of iron-oxidation of Fe^{2+} to Fe^{3+}, a process regulated by blood ferroxidase - ceruloplasmin, can hinder the process of including iron in transferrin . One way or another, these hypotheses require further detailed study with an interdisciplinary approach.

CONCLUSION

The study revealed a change in several indicators of iron metabolism in patients with *COVID*-19, which confirms the high probability of the participation of free iron in the pathogenesis of the severe course of *COVID*-19. Comparison of the available literature data on the toxic effect of free iron with the picture of the severe course of *COVID*-19 allows us to make an assumption about the similarity of these pathological processes. A number of authors consider the use of iron-binding therapy as a promising component of prevention and intensive therapy for severe *COVID*-19 [29–31].

The appearance of free iron in the blood or tissues could be caused by damage to cells with the release of iron from cytochromes, myoglobin, hemoglobin, or disturbed binding of iron to transferrin, which is possibly associated with a change in the structure of the protein or a violation of the process of transferring the iron ion to the trivalent state.

When assessing the degree of viral influence on iron metabolism, one should take into account the influence of various regulators - hepcidin, cerruloplasmin, iron-regulating proteins *(IRE-BP),* bivalent metal transporters (*DMT* 1), hefestin, ferroportin, as well as transferrin receptors *(sTfR)* and the level of non transferrin bound free iron *(NTBI)* .

In the pathogenesis of the severe course of *COVID*-19, there is a violation of iron metabolism, which is confirmed by the presence of hyperferritinemia (1263 [718; 1663] ng/ml; p <0.01), hypotransferrinemia (1.38 [1.17; 1.58] g/L; p <0.01), decreased serum iron levels (14.23 [9.2; 16.23] µmol/L; p <0.05) and increased urinary iron excretion (650 [452; 798] µg/day; p <0.01). The high values of induced urinary iron excretion are most likely associated with the presence of free iron in the blood or tissues.

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Editorial commentary

Since the advent of COVID-19, we have begun to better understand the pathogenetic mechanisms of this disease. However, there is certainly no need to talk about a clear understanding of all the details of the pathogenesis of COVID-19. In this regard, studies devoted to the study of its various mechanisms are of extremely high interest and are of great practical importance. The presented study is devoted to the study of an extremely interesting pathophysiological mechanism of the pathogenesis of COVID-19, namely, disorders of iron metabolism. The article presents literature data showing the obvious significance of these violations in COVID-19.

At the same time, we would like to get acquainted in more detail with the treatment tactics used by the authors: the peculiarities of the logistics of patients, in particular, the most severe category; the possibility of extracorporeal membrane oxygenation and its results. It would be desirable if the authors would devote more space to describing the design and discussing their own research results in the next article.

We would be glad to see the continuation of this work in the publication.