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CYTOKINES STORM AND SEPSIS: PREVALENCE IN THE COVID–19

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ABSTRACT

In December 2019, a new betacoronavirus (SARS-CoV-2) was identified as the source of COVID-19. This viral infection with systemic repercussions requires hospitalization of a huge number of patients with high mortality. In many cases, there is a dysregulated inflammatory response triggered by a phenomenon called a cytokine storm, which leads to life-threatening multiple organ dysfunctions, known as sepsis. Respiratory, cardiac and tissue perfusion functions are severely impaired in these individuals. The loss of those vital functions is related to the pathophysiology of this syndrome with tragical morbidity and mortality.

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INTRODUCTION

In December 2019, a new betacoronavirus (SARS-CoV-2) was identified as the source of COVID-19. Phylogenetically similar to SARS-CoV and MERS-CoV, it triggers a primary viral pneumonia (COVID-19), which can lead to Severe Acute Respiratory Syndrome (SARS). About 80% of the cases are asymptomatic or mild symptomatic and present with dry cough, fever, fatigue and dyspnea. The other 20% exhibit more severe forms of the disease, 15% require hospitalization in wards due to the need of complementary oxygen therapy and 5% develop critical forms of the disease, along with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation and ICU admission (López-Colazzo *et al.,* 2020). The pathophysiological picture of severe forms of the disease begins with a phenomenon called "cytokine storm" , characterized by a high production of these immune response mediators, with the absence of adequate action of regulatory mechanisms, causing an exacerbated inflammatory process that leads to complications, mainly respiratory, and may evolve with systemic repercussions, such as damage of cardiac function, caused by attacks on the myocardium and the elevation of injury such as troponin C (Wang *et al.,* 2020). Pro-thrombotic changes can also occur, which are evidenced by elevated D-dimers and tissue hypoperfusion. In this hyperinflammatory response, changes in mitochondrial functions are observed with systemic repercussions and viral infectious processes, like COVID-19, can trigger sepsis, which is a multiple organ dysfunction with a high risk of death. Sepsis shows tragical morbidity and mortality in these cases (ZICK, 2020). The purpose of this review is to describe the predisposing mechanisms and factors listed in the medical literature by which SARS-CoV-2 is believed to cause the cytokine storm that leads to sepsis in patients affected by COVID-19 and the occurrence of septic shock in individuals with the severe forms of this disease.

METHODOLOGY

An integrative bibliographic review was carried out and developed online using the Scielo, MedLine (PubMed), Cochrane Library and LILACS databases. Inclusion criteria were research and papers published in 2020, in English or Portuguese that included the keywords: COVID-19, betacoronavirus, SARS-CoV-2, cytokine storm, sepsis and septic shock and that addressed the pathological mechanism by which SARS-CoV-2 can trigger the cytokine storm and its relation with cases of sepsis and septic shock existing in patients with COVID-19. Duplicate articles that did not match the inclusion criteria were excluded. The research was adapted and 15 articles were used. The process of choosing the articles started with a reading and descriptive evaluation of each study with the subsequent collection of data and information necessary for the preparation of this review. After selecting the appropriate studies for the descriptive criteria, a review of the basic bibliography was carried out, the data of the studies were then evaluated and a discussion was held regarding the association of sepsis and septic shock with COVID-19, an integrative

review was prepared for appraisal and possible explanation of the results.

RESULTS

The most frequent symptoms of critically ill hospitalized patients are: fever, severe dyspnea with a drop in oxygen saturation below 94%, and a dry cough. The most common laboratory alterations were leukopenia, elevation of inflammatory tests such as C-reactive protein and ferritin, in addition to suggestive alterations of prothrombotic phenomena with elevation of D-dimers (Zhang e*t al.,* 2020). Among the hospitalized patients with COVID-19, 26% were treated in Intensive Care Units (ICU), of whom 60% presented respiratory failure and 31% developed septic shock (ZICK, 2020). According to the data obtained in this review, these severe forms of COVID-19 could be associated with the systemic phenomenon known as cytokine storm, a situation in which the host's immune system has an exaggerated inflammatory response to the SARS-CoV2 infection and triggers an increase in the erythrocyte sedimentation rates (or erythrocyte sedimentation rate - ESR), C-reactive protein (CRP), tumor necrosis factor (TNF-α), interleukins such as: IL-2, IL-1RA (LI H et al., 2020) and IL-6, IL-7, IL-8, IL-9, IL-10 (Zhang *et al.,* 2020). This cytokine storm would be associated with the systemic effects of SARS-Cov-2, generating mitochondrial changes that would favor survival and viral replication. In patients with decompensated comorbidities and impaired organic response due to chronic diseases, such as the elderly, diabetics, patients with autoimmune and hematological diseases, immunosuppressed and cardiac patients, have a high rate of clinical conditions with unfavorable outcomes and high mortality. In these patients, changes in cardiac output, tissue hypoperfusion, hypoxemia and pro-thrombotic phenomena can be triggered by the hyperinflammatory response unleashed by sepsis, which can progress to shock, circulatory collapse and death. Changes such as, marked elevation of inflammatory phase proteins in inflammatory tests, hypoxemia and alteration of coagulation parameters - evidenced by the elevation of D-dimers - are associated with severe cases, even in the absence of hypotension. Also, there are often signs of shock with delayed capillary filling time, common weak peripheral pulses and pale extremities. In this scenario, the exacerbated increase in cytokines, caused by an infectious condition related to SARS-CoV-2 and the changes in the patient's humoral and innate immune responses, may promote a rise in the microvascular permeability, along with endothelium activation, leading to an intravascular hypercoagulation with the embolization of different organs, such as the lungs, brain and heart (Colantuoni *et al.,* 2020).

DISCUSSION

According to the data from the studies analyzed in this review, there is evidence that SARS-CoV-2 infection causes hyperinflammation in some individuals, which leads to endothelial dysfunction, prothrombotic phenomena, tissue hypoperfusion and hypoxemia. These events could be associated with a cytokine storm that causes an uncontrolled and exacerbated activation of neutrophils, monocytes and macrophages. Upon activation**,** specific cell types - such as neutrophils and monocytes - release free radicals, which promote a rise of reactive oxygen species (ROS), resulting in endothelial damage and compromise of mitochondrial function. Patients with decompensated comorbidities and impaired organic response due to chronic diseases such as, the elderly, diabetics, patients with autoimmune and hematological diseases, immunosuppressed and cardiac patients, have a worse prognosis when infected by SARS-CoV-2, because in these groups changes in mitochondrial function are already observed and some cells are senescent and possibly dysfunctional. These individuals may be unable to meet the hypermetabolic demands and deregulation caused by sepsis. Mitochondrial proteins can also serve as damage-associated molecular patterns (DAMP), activating innate immunity. The growth in oxygen reactive species (ROS) and viral-mitochondrial interaction seem to be necessary for replication and increased viral load, evidencing a possible rise in the virus survivability and the prevalence of sepsis in patients with impaired mitochondrial function. Thus, the hyperinflammatory state, the change in mitochondrial capacity and the high viral load associated with decompensated underlying diseases contribute to the increase in mortality associated with COVID-19 sepsis.

Conclusion

It is considered that in patients with severe forms of COVID-19, hyperinflammation occurs due to the cytokine storm and as a consequence of this process, endothelial dysfunction, prothrombotic phenomena, tissue hypoperfusion and hypoxemia are observed. These changes in homeostasis caused by SARS-CoV-2 infection may result in sepsis with life-threatening multiple systemic organ dysfunctions. Elderly patients, immunosuppressed and with decompensated chronic comorbidities are unable to provide an adequate organic response, and in many cases, the mitochondrial response may be senescent and ineffective to meet the high metabolic demand characteristic of septic conditions. Therefore, they have a worse prognosis in this scenario of inflammatory dysregulation of the immune response and high rates of hospitalization and mortality occur. However, more complex and detailed studies are still required to fully understand the mechanisms of how SARS-Cov-2 can trigger the phenomenon of sepsis and septic shock in patients with COVID-19. The decline in mitochondrial function may be associated with the high mortality observed in these specific groups mentioned that evolve to sepsis in severe cases of COVID-19.

Conflict of interest: There was no conflict of interest by any of the authors reported in the work or by their educational institution.

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