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Beyond The Lungs: SARS-CoV-2 Pathways to the Nervous System and Its Consequences

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Abstract

Understanding the SARS-CoV-2 pathophysiology regarding neural system contamination and damage is necessary for clinical and therapeutic approaches, which may reduce the damage caused by the disease. In this regard, it is important to highlight that, besides the direct effect on neurons, the inflammatory state caused by a dysregulation of the immune system due to infection are both factors responsible for neurological phenomena of the disease. The presence of the virus in the bloodstream, its ability to directly penetrate the NS through peripheral nerves and the weakening of the blood-brain barrier are added to the tropism of SARS-CoV-2 by ACE-2 receptors, which favours the appearance of brain manifestations, associated with metabolic complications in the autoimmune processes induced by viral clinical condition. It is essential to remember that the cerebrovascular events have been increasingly reported in infected patients and are associated with the hypercoagulability caused by the disease. The activation of the coagulation cascade and deregulation of physiological anticoagulant mechanisms, such as protein C system and the disintegration of fibrin, are possible causes of this hypercoagulable state present in COVID-19. Even though it is still not evident whether the impairment of the nervous system is a result of direct infection by SARS-CoV-2 or of a diffuse inflammatory process affecting various organs and systems generating multiple manifestations, including those of the nervous system, we highlight that the quantity of drugs administered in intensive care units also can interfere with neurological conditions.

Keywords: SARS-COV-2; Nervous system; Neurological conditions; COVID-19

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Introduction

The repercussions and scientific evidence about the involvement of the lungs, heart, kidneys and intestines in COVID-19 is extended to the brain, emphasizing neurological complications and its high rates of morbidity and mortality. In China, at the beginning of the pandemic, 214 hospitalized patients diagnosed with COVID-19 were studied, out of which 78 (36.4%) presented neurological manifestations [1]. Therefore, understanding the SARS-CoV-2 pathophysiology regarding neural system contamination and damage is necessary for clinical and therapeutic approaches, which may reduce the damage caused by the disease. In this regard, it is important to highlight that, besides the direct effect on neurons, the inflammatory state caused by a dysregulation of the immune system due to infection are both factors responsible for neurological phenomena of the disease.

Methodology

Six species of coronaviruses that infect humans were already known, with four of these being associated to cold syndromes and mild upper respiratory tract infections in immunocompetent patients in any age group, and two of these species associated with major respiratory syndromes, the SARS-CoV, etiologic agent of severe acute respiratory syndrome coronavirus, and the

MERS- CoV of Middle East respiratory syndrome coronavirus. The SARS-CoV-2 is the seventh known coronavirus and, among them, neurotropism is not a recent discovery or restricted to SARS-CoV-2. Other members of the family, such as Sars-CoV e Mers-CoV, are also capable of affecting the Nervous System (NS) and causing diseases similar to the ones already reported in patients with COVID- 19, such as encephalitis, strokes, infectious toxic encephalopathy and Guillain-Barre syndrome, in addition to recently reported cases of myelitis [2].

The neurological effects occur by several factors involved in the disease. The presence of the virus in the bloodstream, its ability to directly penetrate the NS through peripheral nerves and the weakening of the blood-brain barrier are added to the tropism of SARS-CoV-2 by ACE-2 receptors, which favours the appearance of brain manifestations, associated with metabolic complications in the autoimmune processes induced by viral clinical condition [3].

Like other infections, SARS-CoV-2 can reach NS through the bloodstream. As much as there is a barrier between blood circulation and neural tissue, this defense is weakened in the presence of the exacerbated inflammatory response generated by the viral infection. The recruitment of white blood cells, such as neutrophils, associated with the known cytokine storm, especially with the release of IL-6, interleukins and other factors, have a crucial role in the activation of metalloproteinases, which are enzymes capable of degrading proteins that comprise the blood-brain barrier and, thus, increasing its permeability [4,5]. The migration of the virus from the endothelium to neuronal cells concomitantly with the presence of viral particles within neural cytoplasmic vacuoles has already been demonstrated in post-mortem microscopic findings in patients with neurological symptoms and positive SARS-CoV-2 RT-PCR [6]. Systemic circulation plays a fundamental role in viral dissemination in the neurological context, with cerebral microcirculation being a facilitating element regarding the coupling of the glycoprotein S (spike) to the functional ACE-2 receptor, as it allows penetration into neurons and glial cells, generating neurological infection [7]. Although ACE-2 receptors are found in greater numbers in the alveolar epithelium of the lungs, brain tissue is recognized as a target for SARS-CoV-2 through these same receptors, allowing the broadening of the symptomatic spectrum of COVID-19 to neurological manifestations [8].

Discussion

Viral penetration into the brain also occurs by way of the cribriform plate of the ethmoid bone by viral infection through the nose that benefits itself from the wide distribution of ACE-2 receptors in the brain, which allows the virus to spread after entering through the olfactory nerve. In addition, the infection pathway through this nerve explains hyposmia as an early symptom described in most infected patients [9]. The olfactory bulb, part of the central nervous system not protected by the dura mater, is undoubtedly a considered route due to the olfactory changes in COVID-19 [10].

In addition to the mechanisms that lead to the direct damage of the brain tissue, it is essential to remember that the cerebrovascular events have been increasingly reported in infected patients and are associated with the hypercoagulability caused by the disease [11]. The pro-thrombotic state seems to be closely related to systemic inflammation caused by the infection, being a dreaded and known complication of situations such as sepsis, which can also be established with the evolution of the disease. The activation of the coagulation cascade and deregulation of physiological anticoagulant mechanisms, such as protein C system and the disintegration of fibrin, are possible causes of this hypercoagulable state present in COVID-19, as well as the presence of pro-inflammatory cytokines and the endothelial lesion. All this imbalance results in the production of thrombin and reduction of endogenous fibrinolysis, which lead to the deposition and maintenance of clots in the microvasculature, which can increase in volume and become important with the evolution of the disease. The development of Disseminated Intravascular Coagulation (DIC) may occur due to the feedback that exists between the process of coagulation and inflammation, since the production of inflammatory mediators induces the process of coagulation and this state promotes the maintenance of the inflammatory process. This vicious cycle accentuates itself from the moment it begins. As a result, it is possible to observe that a lot of patients with COVID-19 show D-dimer concentrations that rise with the severity of the disease, as well as prolonged prothrombin and activated partial thromboplastin times [12]. Changes in these parameters seem to be related with increased risk of cerebrovascular accidents and cerebral venous thrombosis in most critically ill patients with the Severe Acute Respiratory Syndrome (SARS) [7]. This demonstrates that hyper coagulation and the intense inflammatory response generated by the viral presence in the host organism are more frequent in patients with severe infection or various comorbidities.

Moreover, a risk factor for procoagulant state are patients infected with SARS-CoV-2 that have clinical manifestations of peripheral thromboembolic events, digital and lower limb ischemia, associated with laboratory findings of antiphospholipid antibodies, such as anticardiolipin antibodies and anti-beta-2 glycoprotein [13]. These findings may be significant for the possibility of arterial or venous thrombosis, being the basis for the diagnosis of antiphospholipid syndrome and its variant antiphospholipid-like syndrome, which can also develop in other conditions, such as autoimmune diseases, infections, such as tuberculosis, or use of certain drugs.

Furthermore, the occurrence of neurological manifestations associated with autoimmune disorders can also be associated with coronavirus infection. In this condition, the pro-inflammatory state emerges as the likely trigger of these nervous immune-mediated disorders leading to post-infectious complications, including Guillain-Barre syndrome and its variants, such as Miller Fisher syndrome [14].

Even though it is still not evident whether the impairment of the nervous system is a result of direct infection by SARS-CoV-2 or of a diffuse inflammatory process affecting various organs and systems generating multiple manifestation, including those of the nervous system, we highlight that the quantity of drugs administered in intensive care units also can interfere with

neurological conditions, as well as any comorbidities the patient may have [15].

Conclusion

It is crucial to investigate hospitalized patients with neurological characteristics due to COVID 19 in adapt protocols and train health professionals in order to improve the patients' prognosis. Therefore, and with this knowledge of the possible pathways that lead to infection and its repercussions on the nervous system, better therapeutic approaches could be taken and both the morbidity and mortality of neurological disorders and the complications of the infection itself could be reduced.

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