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Letter to the Editor

PATHOPHYSIOLOGY AND NEUROINFLAMMATION IN COVID-19

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INTRODUCTION

COVID-19, the disease caused by the coronavirus-19 infection, has caused more than five million deaths worldwide. In addition, infection with SARS-CoV-2, a positive-sense, single-stranded RNA genome, has been associated with numerous symptoms (1) (Table I).

Table I. *Some of the numerous symptoms associated with SARS-CoV-2 infection.*

• Muscle pain	• dizziness	• impaired consciousness
• fever	• psychiatric symptoms	• neuromuscular disorders
• anosmia	• seizures	• myocarditis
• hyposmia	• stroke	• fatigue
• loss of taste	• chills	• delirium
• anxiety	• shortness of breath	• depression

In addition, a critical neurological symptom of COVID-19 is brain fog, a pathological state represented by cognitive dysfunction and fatigue. It has also been observed that in COVID-19, individuals experienced increased depressive phenomena and states of anxiety when compared to healthy subjects, symptoms that occurred, above all, after the clinical signs of COVID-19 were no longer evident (2). In COVID-19 survivors, psychological and neural dysfunction is seen during and after viral infection (2). These effects were more evident in women, even though they showed lower inflammatory parameters than men (3).

SARS-CoV-2 enters the nervous system through the nasal (olfactory bulb) and oral routes, binds to a converting enzyme called angiotensin-2 (ACE-2), and is mainly conveyed through neurons and blood circulation (4). The virus invades the central nervous system (CNS) and can cause long-term damage, a significant effect that should be considered. The spike protein S in the S1 and S2 sub-units allows the entry of the virus in the cytosol and binds to ACE-2 expressed in many body cells, including brain endothelial cells (4); this induces CNS inflammation and brain damage, which are mediated by pro-inflammatory cytokines produced by the immune system. The ACE-2 enzyme is also expressed in the

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brain in the cerebellum, thalamus, and inferior olivary nuclei (5). Therefore, COVID-19 is not only a lung disease but is also a brain disease, with long-term effects following the obvious symptoms of the disease. CNS disturbances in COVID-19 can range from quickly reversible mild symptoms to more complex and severe longer-lasting symptoms that devastate brain tissue (such as stroke) (6).

Induction of stroke by SARS-CoV-2 infection

Stroke is one of the most frequent symptoms of COVID-19 and often occurs in outpatients, demonstrating the severity of the disease. The activation of immune cells by the virus leads to the secretion of various cytokines and chemokines, which can cause cerebral hyperinflammation, detectable by electroencephalogram (7). In COVID-19, immune cells, including monocytes/macrophages and mast cells (MCs), are recruited and release inflammatory cytokines by activating the extrinsic coagulation pathway, resulting in a thrombotic state and ischemic stroke.

Women are more protected from SARS-CoV-2, as estrogen secretion stimulates immune cells, which inhibit coronavirus-19 replication (8). In fact, in women, 17β-estradiol inhibits adhesion molecules, such as ICAM-1, which are pro-inflammatory molecules (9). It also appears that females infected with the virus have fewer inflammatory cells in their lungs and, therefore, a lower level of inflammatory cytokines than males; this is why women are less vulnerable to COVID-19 than men. The release of pro-inflammatory cytokines causes the "cytokine storm" with thrombotic effects and brain damage.

Pro-inflammatory cytokines such as IL-1, TNF, and IL-6, as well as type I interferon (IFN), associated with some chemokines, cause endothelial cell dysfunction, provoking coagulopathy with increased prothrombin, which causes thrombosis, respiratory failure, and acute renal failure, mechanisms that are still under study (10). The neurologic impairments in COVID-19 can also be due to the passage of inflammatory cytokines from the bloodstream through the blood-brain barrier (BBB) (11). In addition, there is a poor oxygen supply since malfunctioning of the lung can occur. The virus can cause encephalopathy with changes in the brain's structure and/or functions, a condition that can be improved with pharmacological treatment (such as steroids) and ventilation (12); this demonstrates that SARS-CoV-2 affects mental health with neuropsychiatric complications due to inflammatory mediators activated by the virus through tissue colonization of immune cells in COVID-19 (13).

However, rare adverse events have occurred after vaccination, but most of these were resolved in the short term and with nonspecific therapy. The anti-COVID-19 vaccination is essential for immunity against coronavirus-19, although thrombosis with bilateral facial paralysis and encephalitis have occurred after vaccination and are considered side effects with a low incidence (14).

Myocarditis after anti-COVID-19 vaccination

Another rare side effect ff mRNA vaccination is myocarditis, mainly in young adult males between approximately 20 and 30 years of age and in adolescents (about 50 cases per million vaccinated) (15). Myocarditis is an inflammation of the myocardium that can cause cell and tissue death. It can be caused by many ailments, including viral infections, and can cause chest pain, shortness of breath, and sometimes death. Myopericarditis occurs if the inflammation involves the pericardium that surrounds the heart. However, future studies are needed to resolve these problems that may present after COVID-19 vaccination.

CONCLUSIONS

The above studies show that SARS-CoV-2 affects mental health with neuropsychiatric complications due to inflammatory mediators activated by the virus through tissue colonization of immune cells in COVID-19.

Conflict of interest

The authors declare that they have no conflict of interest.

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