LETTER TO THE EDITOR

Post-COVID-19 sequelae: an imbricate network between neuroinflammation and dysbiosis

Secuelas post-COVID-19: una imbricada red entre la neuroinflamación y la disbiosis

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The coronavirus disease 2019 (COVID-19) still affects millions of people worldwide. Like other respiratory viruses, the main entry route for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is through the nasal passages, from where it can directly reach the respiratory system and the central nervous system (CNS). Both systems have cells that express the ACE2 receptor, among others, which mediate the virus entry into cells. Therefore, besides predominantly causing respiratory issues, the virus can affect the CNS. By expressing signals associated with the virus *per se* and damage signals, the pathogen can promote both systemic inflammation and CNS inflammation (central inflammation or neuroinflammation). In its acute phase, these exacerbated inflammatory phenomena aim to control the infection, but when sustained or persistent (chronic inflammation), they can amplify the damage. It is estimated that this chronic inflammation scenario is observed in 10% up to 30% of non-hospitalized infected patients and 50% up to 70% of hospitalized patients. This exacerbated peripheral and central inflammation promotes the development of post-COVID sequelae or post-COVID syndrome (PCS)[1]. In this context, PCS is already an emerging global health problem. Clinically, this condition is heterogeneous and multisystemic, with signs and symptoms that can persist beyond 12 weeks post-acute infection. The described signs can occur regardless of age and the clinical form of COVID-19 the infected person had.

One of the best-characterized clinical signs with the greatest impact on morbidity is neuropsychiatric, including neurocognitive alterations, fatigue, headache, anosmia/hyposmia, dizziness, diffuse pain, anxiety, or depression, which occur in more than 80% of those who have experienced severe COVID-19. Although the causes of PCS are unknown, various pathophysiological mechanisms may be involved; among these, immune system dysregulation with or without reactivation of underlying pathogens and intestinal dysbiosis seem to be determining factors. The outlook looks grim in Mexico, considering the high prevalence in the general population of conditions such as diabetes, hypertension, obesity, and periodontal disease, among others, which are characterized by a state of chronic inflammation closely related to dysbiosis and, consequently, neuroinflammation.

Those affected by PCS share clinical features with other post-viral syndromes, including changes to the immune response, both innate (activation of innate cells such as macrophages, neutrophils, and NK cells) and adaptive. In the latter, the number of several T cell subtypes is affected, including fewer effector memory CD4+ T cells, as well as markers of exhaustion (increased programmed death ligand 1 [PD-1], an immunoregulatory protein) in both CD4+ and CD8+ T cells, which persists for more than 12 months[1,2]. Interestingly, it has been reported that even 8 months after having had COVID-19, there is a loss of naive B and T cells, along with increased expression of type I

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interferons (IFN-α and IFN-β) and III (IFN-λ)[1,3]. These findings could be potentially useful for confirming the clinical diagnosis of PCS through flow cytometry tests.

Other alterations in the immune profile include the elevation of pro-inflammatory cytokines such as interleukin [IL] 1β, IL-6, tumor necrosis factor-alpha, and chemokines such as IFN-λ inducible protein-10 and eotaxin 1 (CCL11); the latter has been closely associated with cognitive dysfunction and microglial activation at the hippocampal level, as well as inhibition of neurogenesis in a murine model of SARS-CoV-2 infection[1,4].

Magnetic resonance imaging studies have shown a decrease in the cortical volume of gray matter, particularly in the orbitofrontal cortex and parahippocampal gyrus (regions functionally connected to the primary olfactory cortex) and a significant reduction in overall brain size in individuals with PCS[5]. Additionally, alterations in the gut microbiota have been reported since the acute phase of COVID-19, with fewer species such as *Faecalibacterium prausnitzii* and *Eubacterium rectale*, which have immunoregulatory properties, and more species such as *Ruminococcus gnavus* and *Bacteroides vulgatus*. These changes during the acute phase have been associated with the development of the pro-inflammatory cytokine storm but can persist chronically, even a year after the infection. Their persistence leads to changes such as the reduction of anti-inflammatory bacterial products like short-chain fatty acids, particularly butyrate (a metabolite derived from the fermentation of polymeric carbohydrates, like starch), increased intestinal permeability, and translocation of toxic microbiota components (bacterial like lipopolysaccharide [LPS] or fungal like galactomannan and β-D-glucan) into the blood, which strongly contributes to systemic inflammation and neuroinflammation[1]. The causal role of microbiota alterations in inflammation is supported by data on the transfer of microbiota from human individuals with PCS to healthy mice, which promotes various pathological changes such as impaired pulmonary defense mechanisms against bacteria and cognitive impairment, phenomena that collectively simulate the neurocognitive manifestations of PCS[6].

The persistence of systemic/neuroinflammatory phenomena induces deleterious effects on the brain, particularly due to sustained microglial and astrocyte activation (astrogliosis) and neuron loss, which could precipitate the development of neurodegenerative diseases. In this context, a scenario that warrants short-term attention is presented, particularly considering the ongoing circulation of SARS-CoV-2, which promotes the generation of new variants, the high prevalence of low-intensity chronic inflammatory states combined with an aging population, and the increase in neurocognitive and psychiatric signs in PCS. Early recognition of PCS may be important for proper treatment planning and preventive measures that could potentially help reduce the risk of neurodegeneration, such as regular nasal washes with saline solution, routine aerobic exercise, consumption of prebiotic polyphenols (coumarin, tannins, phenolic acids, flavonoids) through diet combined with probiotics, and cognitive therapy that could impact the homeostasis of the gut and nasal microbiome.

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