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# Neuroinflammation in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection: Pathogenesis and clinical manifestations

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## Abstract

Peripheral inflammation and neuroinflammation are host-mounted to eliminate injury, infection, or toxin to restore homeostasis. However, when inflammation persists, it may promote collateral tissue damage that ultimately culminates in pathological peripheral damage or neurodegeneration.

Since the beginning of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic, responsible of Coronavirus disease 2019 (COVID-19), accumulating evidence describes neurological manifestations and complications worldwide particularly in approximately one-third of patients with COVID-19 particularly in those affected with the severe forms of the disease. Different access routes to the central nervous system have been identified. One immediately used is the entrance by the olfactory and trigeminal nervous affecting olfactory and sensory nerve endings when individuals get the infection by the intranasal route. It can also reach the central nervous system through the choroid plexuses and periventricular areas that lack blood-brain barrier or by its disruption by the exacerbated peripheral inflammation. Until now, the long-term sequelae of SARS-CoV-2 infection is still under research and the post-COVID syndrome.

This review focuses on the consequences of the neuro-inflammatory response in patients with COVID-19 considering its potential relevance in the appearance of neurological sequelae including neurodegenerative disorders.

## Addresses

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## Inflammation overview

Inflammation can be defined as a part of the innate defense system of an organism that is triggered when invading pathogens (through the pathogen-associated molecular patterns, [PAMPs]) or endogenous stress signals (via Damage-associated molecular patterns, [DAMPs]) are recognized by host molecules such as the complement system or through germline-encoded pattern-recognition receptors. The main function of the inflammatory process is to remove the initial cause of injury, either a pathogen or the signal that started the damage, and proceed to the clearance of necrotic cells and tissue repair, to restore homeostasis. In many pathological conditions, the inflammatory response is characterized by the simultaneous participation of immunological, physiological, and molecular processes. Immediately after danger or damage are sensed, inflammatory signs including heat, redness, swelling, pain, and loss of function (known as the cardinal signs of inflammation) are clinically evident. This type of inflammatory response, known as acute inflammation, generally lasts for a few days and involves the release of several well-characterized soluble inflammatory factors, such as anaphylatoxins (C3a, C5a), histamine, prostaglandins, leukotrienes, acute-phase proteins, cytokines (with central and peripheral actions on immune cells and the vascular endothelium), and chemokines, which promote the migration of neutrophils and macrophages to the area of inflammation. In the early phases of the acute immune response, the anaphylatoxins released during complement activation bind receptors on mast cells, which release potent inflammatory mediators such as histamine, proteases, cytokines, chemotactic factors, and arachidonic acid metabolites. The main products of arachidonic acid are prostaglandins and leukotrienes which act on the endothelial cells, smooth muscle, connective tissue, and inflammatory cells. In parallel to the complement activation, PAMPs and DAMPs are recognized by pattern-recognition receptors like toll-like receptors (TLRs) which become activated. TLRs, widely distributed on both immune and other body cells, play a key role in early acute inflammation and are

expressed in tissue-resident and infiltrating macrophages and neutrophils. On TLR activation, several adapter proteins are recruited to initiate specific intracellular signaling cascades that mobilize host defense reactions by synthesizing proinflammatory cytokines (Interleukine-1 $\beta$  [IL- $\beta$ ], Tumor Necrosis Factor- $\alpha$  [TNF $\alpha$ ], and Interleukin-6 [IL-6]) and type-1 interferons. TNF $\alpha$  and mast cell-derived inflammatory factors are potent activators of endothelial cells, and their action leads to deep changes, including chemokine release, the expression of adhesion molecules, and leukocyte transmigration toward injured tissues. TNF $\alpha$  exerts a synergistic effect with IL- $\beta$  and IL-6 on the liver, inducing the production of acute-phase proteins, which in turn induce the production of complement proteins, thus amplifying the inflammatory process. Neutrophils are the most abundant cell type observed in the early phases of acute inflammation; the lytic enzymes (such as lysozyme, myeloperoxidase, and matrix metalloproteinases) in their granules are released on the antigen, leading to its destruction. Neutrophils also phagocytize and destroy the triggering antigen by releasing reactive oxygen and nitrogen species [1].

When the acute inflammatory response is not successful in eliminating the initial stimuli, or when regulatory checkpoints fail, it progresses to a chronic inflammatory state, which may last for months or even years. The hallmark of chronic inflammation is the infiltration of immunoinflammatory cells such as macrophages, T helper 1 lymphocytes (Th1, Th2, and Th17), and plasma cells in the injured tissue. The main effector function of these cells is the production of immunoinflammatory cytokines (such as IL-1, TNF- $\alpha$ , Interferon  $\gamma$  [IFN- $\gamma$ ], IL-12, and IL-17), growth factors (such as the epidermal-, insulin-like- fibroblast-, vascular endothelial-, and transforming growth factor), and enzymes that cause a proteolytic cleavage of membrane receptors, leading to the loss of cell functions. All these released factors contribute to the progression of tissue damage and secondary repair, inducing fibrosis and granuloma formation [2]. Chronic inflammation is considered the driving factor of many diseases, including cancer, allergies, vascular diseases, autoimmunity, metabolic disorders, cardiovascular and lung diseases, arthritis, and joint diseases, and neuropathologies [3].

Both acute and chronic exacerbated inflammation disrupt the permeability of the blood brain -barrier (BBB) allowing the recruitment of peripheral inflammatory cells and soluble inflammatory mediators favoring an inflammatory response in the central nervous system (CNS) named neuroinflammation.

## Neuroinflammation

Neuroinflammation is an innate immune response of glial cells, neurons, endothelial cells, and CNS-resident

macrophages that can be triggered by PAMPs to control infections, or by DAMPs after damage by resident cells or misfolded proteins [3]. Neuroinflammation can also be triggered by an exacerbated inflammation in the periphery. A peripheral increase of inflammatory cytokines and chemokines can communicate to the CNS by humoral and/or neurochemical pathways, inducing the activation of resident glial cells, microglia, and astrocytes; along with neurons, these cell types are critical players in the central inflammatory response. Microglia is a major cellular component in neuroinflammation, accounting for 5–20% of all glial cells that continuously sense the CNS microenvironment. Resting, ramified microglia rapidly transform into the amoeboid-activated form when receptors of the innate immunity are activated. Activated cells increase their phagocytic activity and are the main ones responsible for controlling neural apoptosis. Astrocytes also express innate immune receptors, which can trigger their activation and the production of cytokines and chemokines. The secretion of several inflammatory mediators by activated glial cells can modify the blood brain barrier (BBB), favoring the recruitment of peripheral lymphocytes and their activation in the CNS, contributing to the resolution of the original injury and homeostasis restoration [4]. Initially, neuroinflammation plays a protective role in the CNS to restore homeostasis. However, persistent neuroinflammation can result in further damage to neuronal cells [5]. Varying degrees of neuroinflammation, induced by different causes, constitute a common hallmark in infectious and noninfectious neurological diseases [3].

## Neuroinflammation and SARS-CoV-2

Several RNA viruses, including the recently emerging SARS-CoV-2, show a broad tissue tropism, affecting not only peripheral organs (lungs, blood vessels, and so on) but also the CNS. This neurotropism mediates the reported pathogenesis of Coronavirus disease 2019 (COVID-19) in the CNS [6]. The virus enters host cells through interactions between the receptor-binding domain of the viral spike protein (S) and host receptors such as the angiotensin-converting enzyme-2 (ACE2) receptor, neuropilin-1 [7], integrins [8], and the transmembrane proteases serine 2 and serine 4 (TMPRSS2 and TMPRSS4) [9].

The ACE2 receptor is highly expressed in several tissues and organs, such as the endothelium, lung, heart, pancreas, liver, and CNS [10]. ACE receptors are broadly distributed in the CNS, in circumventricular organs, the subfornical organ, paraventricular nucleus, nucleus of the tractus solitarius, the rostral ventrolateral medulla, and regions associated with the cardiovascular system [11,12]. TMPRSS2 is expressed in the liver, pancreas, microvasculature, and the nervous system (both central and peripheral) [13], TMPRSS4 is expressed in lung, kidney, pancreatic, colonic, and

gastric tissues [14]; finally, neuropilin-1 is expressed in the brain, eyes, lung, pancreas, kidney, endocrine tissues, and even in immune cells [7].

In the CNS, SARS-CoV-2 can infect neurons as well as glial cells (astrocytes and microglia), triggering an exacerbated innate response. Astrocytic involvement has been related to increased levels of the serum protein S100b, and a higher BBB permeability is correlated with COVID-19 severity and organ damage [15].

Simultaneously, an exacerbated systemic infection leads to a massive release of inflammatory mediators, including cytokines, chemokines, interleukins, and antibodies [16] that result in an increased BBB permeability. Thus, cells of the acquired immunity can be recruited to the CNS, favoring the clearance of infected cells. On the other hand, this exacerbated neuro-inflammatory response can promote neural damage that, if chronic, may favor the occurrence of neurological sequelae [6].

Various preclinical studies have suggested that SARS-CoV-2 could enter the CNS via transsynaptic neurons (including olfactory, trigeminal, glossopharyngeal, and vagus nerves), by a hematogenous (BBB), immunological (through mucosal immune cells), or meningeal route, via Cerebral Spinal Fluid (CSF) through the choroid plexus or circumventricular organs, or by an enteric route [17–20]. Supporting the hematogenous route, some reports indicate that SARS-CoV-2 can propagate from the lower respiratory tract to the cardiovascular and respiratory centers of the brainstem [21].

Several neurological manifestations of SARS-CoV-2 infection (particularly in severe patients with COVID-19) have been found in clinical series at rates ranging from 35% to 80% [22–26]. These clinical manifestations have been classified into three main groups: 1) CNS involvement signs, including headache, altered consciousness, encephalitis, cerebrovascular disease, seizures, and ataxia; 2) peripheral nervous system involvement signs, such as anosmia/hyposmia, dysgeusia, visual alterations, neuralgia, and Guillain-Barré syndrome; and 3) musculoskeletal involvement signs, such as myopathy, myalgia, and fatigue [23,24,27–30]. Some works have also reported postinfection neurological symptoms [31,32]. The increased relevance of neurological clinical symptoms in COVID-19 has promoted the coining of the term neuroCOVID for its diagnosis, management, and treatment [33]. In this context, Fotuhi *et al.* proposed a conceptual framework of neuroCOVID staging, as NeuroCOVID stage I, from the SARS-CoV-2 virus binding to host receptors of nasal and gustatory epithelial cells. Patients developed smell

and taste complaints. In this stage, cytokine storm remains low and under control. For NeuroCOVID stage II, the virus activates the immune response with increased levels of cytokines, ferritin, C-reactive protein, and D-dimer, this last may result in hypercoagulable state, at which patients are prone to strokes or venous thrombosis. The increased immune response also may cause vasculitis affecting muscles and nerves. Finally, for NeuroCOVID stage III, the cytokine storm damages the BBB which allows the infiltration of peripheral inflammatory factors and viral particles into the cerebral milieu. All these pathogenic processes are related to brain injury (edema, delirium, encephalopathy, seizures, and so on) [34].

## Evidence of neuroinflammation in SARS-CoV-2

### Transgenic murine model

Considering the neurological complications associated with SARS-CoV-2 infection, animal models have been used to deepen into the pathophysiology of the disease. Although murine models are usually not appropriate because mouse ACE2 cell surface protein does not successfully bind viral S protein, some strategies have allowed us to overcome this issue, like using transgenic mice expressing the human angiotensin-converting enzyme 2 under the cytokeratin 18 promoter (K18-human angiotensin-converting enzyme 2). In this model, SARS-CoV-2 intranasal inoculation results in a fatal respiratory disease [35–38], with viral CNS dissemination observed in a later phase. Virions were initially detected in the olfactory bulb and spread to other brain locations, such as the basal brain and spinal cord, in a dose-dependent manner but independently of ACE2 expression. Although no direct cytopathic effect was observed in neuron infection, important microgliosis and immune cell apoptosis were reported [39]. Other authors detected viral antigens in the cortex, cerebellum, and hippocampus in the same model. A higher viral load was found in brain tissues between days five and six after infection, and a differential increase in the levels of proinflammatory cytokines and chemokines was observed in lung and brain tissues. The expression of IL-6 mRNA increased from 10 to 100 times on days 1 and 3 after infection, whereas in the brain it increased from <10 to 500 times between days 3 and 5. Similarly, the expression of TNF- $\alpha$  and IFN- $\gamma$  mRNAs increased  $\sim$ 10 and 15 times, respectively, on day 3, whereas TNF- $\alpha$  and IFN- $\gamma$  levels in the brain increased  $\sim$ 750 times on day 5 after infection. In addition, the expression of mRNA chemokines (CCL2 and CC3) increased 1000 times after 5 days of infection, in correlation with a high local viral load. These data suggested a more intense inflammatory response in the CNS at a later infection stage [40].

### Human cell lines and postmortem studies

Some cell lines, including human cancer lines, have also been used to study SARS-CoV-2 infection, with some limitations and factors that may interfere with antiviral responses (particularly P53, which regulates SARS-CoV-2 replication, or a deficiency in Retinoic Acid-Inducible Gene-1 (RIG-1), which controls the innate immune response) [9,41,42]. Thus, *in vitro* models of SARS-CoV-2 infection using cerebral organoids have gained relevance. In these studies, human-induced pluripotent stem cells-derived Neural Progenitor Cells (NPC) have been found to show neurotropism and permissibility to infection [9,43,44], along with increased cell death rates and transcriptional dysregulation owing to an inflammatory response and cell function deficits [45,46]. In addition to transcriptional dysregulation, an exacerbated inflammation with high serum levels of proinflammatory cytokines/chemokines was reported in postmortem COVID-19 studies [47]. In another study, the single-nucleus transcriptomes from frontal cortex and choroid plexus samples from postmortem COVID-19, it was observed that barrier cells of the choroid plexus recognize and transmit peripheral inflammation into the brain in close relation to the strongest effect in astrocytes and other glia, that taken together point to an activation of inflammatory pathways despite lacking detection of SARS-CoV-2 RNA in those samples [48]. Taken into account that most of postmortem brain tissue from COVID-19 individuals may have inadequate preservation or are immediately fixed for safety reason, it cannot be excluded from the possibility of viral neuroinvasion. In fact, viral RNA transcripts and viral proteins [49–51] have been detected in the brain and other tissues, like endothelial cells within the olfactory bulb [7]. On the other hand, the link between the presence of the virus in the neural–mucosal interface with brain thromboembolic ischemic infarction [52], accompanied by microglial activation, neuronophagia, and low viral levels, also suggests a synergistic effect between systemic inflammation and hypoxia/ischemia [53].

### Conclusions

Taken together, these data on the neuroinflammatory process during COVID-19 and neuroCOVID, along with clinical data of patients with post-COVID syndrome, suggest the possibility of a prolonged viral load or viral reactivation in some convalescent patients, probably by the persistence of immunological sanctuaries (such as neural or even lung tissue), which could explain the early infection signs observed in some convalescents. However, more specific studies are required to deepen this issue.

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### Author's contribution

GC, GF, and ES conceived and designed the review and wrote the article. All authors have read and approved the article for publication.

### Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

- \* of special interest
- \*\* of outstanding interest

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