The Infected Lungs and Brain Interface in COVID-19: The Impact on Cognitive Function

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Abstract
Many coronavirus disease 2019 (COVID-19)-recovered patients report signs and symptoms and are experiencing neurological, psychiatric, and cognitive problems. However, the exact prevalence and outcome of cognitive sequelae is unclear. Even though the severe acute respiratory syndrome coronavirus 2 has target brain cells through binding to angiotensin-converting enzyme 2 (ACE2) receptor in acute infection, several studies indicate the absence of the virus in the brain of many COVID-19 patients who developed neurological disorders. Thus, the COVID-19 mechanisms for stimulating cognitive dysfunction may include neuroinflammation, which is mediated by a sustained systemic inflammation, a disrupted brain barrier, and severe glial reactivity, especially within the limbic system. This review explores the interplay of infected lungs and brain in COVID-19 and its impact on the cognitive function.

Introduction
In December 2019, the world began to face a pandemic caused by the new coronavirus, discovered in the city of Wuhan, China \cite{1, 2}, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), being the etiologic agent of the coronavirus disease 2019 (COVID-19) \cite{2}. Since its discovery, the virus has had a rapid evolution reaching almost all countries in the world \cite{3}. In March 2020, the World Health Organization (WHO) announced the SARS-CoV-2 virus as a pandemic \cite{2, 4, 5}.

Currently, COVID-19 represents a major challenge to public health and economy, as the host’s immune response is not completely understood \cite{6}. SARS-CoV-2 infection can also affect the CNS. The number of patients with respiratory infection and neurological damage is increasing \cite{7, 8}. Thus, there is a great need for understanding the immune responses to this virus and how it can compromise the brain \cite{9}.

During an innate immune response to a viral infection, pattern recognition receptors, such as Toll-like receptors (TLR) and NOD-like receptors, recognize different mo-
Molecular structures that are characteristic of the invading virus [10, 11]. These molecular structures are known as pathogen-associated molecular patterns (PAMPs). The interaction between PAMPs and pattern recognition receptors triggers the onset of the inflammatory response against the invading virus leading to a signal transduction that involves the activation of the nuclear factor kappa B (NF-kB) [12, 13]. As a consequence, pro-inflammatory mediators are produced like tumor necrosis factor-alpha (TNF-α), interleukin-1β, and interleukin-6 (IL-6), which favor an intense cellular response with the release of secondary mediators [14–16]. This results in the influx of several immune cells, such as macrophages, neutrophils, and T cells from the circulation to the site of infection [10].

Therefore, when the attempt to limit the infection is augmented and sustained, nonspecific oxidative and inflammatory effects will result in cellular damage [10]. SARS-CoV-2 infection leads to low levels of oxygen saturation, being one of the main causes of mortality; although these mechanisms are not fully understood, the excessive synthesis of pro-inflammatory cytokines is considered one of the main contributing factors [17, 18], and a study points the association of a cytokine profile with the severity of COVID-19 disease [19]. Fatality predictors from a recent retrospective multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin [20], suggesting that the mortality may be due to hyperinflammation [21].

Patients with severe disease are more likely to develop neurological symptoms, including loss of taste and smell, as well as encephalitis and cerebrovascular disorders [22]. However, whether neurological complications are actually due to direct viral infection of the nervous system or arise as a result of the immune reaction against the virus in patients who had preexisting deficits or had a certain harmful immune response is still a question to be properly addressed [22]. Thus, this review aimed to provide an overview of the current neurological symptoms associated with COVID-19 as well as to present a perspective between infected lungs and the brain in COVID-19, including the impact on cognitive function.

**Neurological Manifestations after COVID-19 Infection**

The potential of SARS-CoV-2 in causing neuroinflammatory and neurodegenerative manifestations in short- and long-term have become a target of great interest in scientific research [23–25]. Given that neurological dysfunction due to inflammation increases the burden of cognitive impairment [25–27] and the mortality rate [28], our search strategy focused on listing studies concerning the manifestations of cognitive impairment in COVID-19 patients, and the articles are shown in the Table 1.

Studies suggest that patients infected by SARS-CoV-2 may present neurological damage and impaired cognitive function across different phases of recovery. Alemanno et al. [29] evaluated 87 patients at 5–20 days after COVID-19 symptoms onset, and they detected cognitive dysfunctions that included deficits in memory, executive functions, language, orientation, and abstraction; also, patients who received invasive ventilation and sedation presented better cognitive functions, especially the younger individuals.

Jaywant et al. [30] analyzed 57 individuals undergoing inpatient rehabilitation after hospitalization for 43.2 days (±19.2) due to COVID-19. They observed that 81% presented some cognitive deficits (47% had mild impairment while 25% showed moderate impairment), and the main alterations were seen in the domains of attention and executive functions, e.g., rapid visual attention, immediate recall, and information processing speed.

The medium-term effects of SARS-CoV-2 infection on cognition were assessed by Raman et al. [31]. The evaluations performed at 2–3 months post COVID-19 in 58 patients and 30 healthy controls indicated that 28% of the patients presented global cognitive impairment, but the most pronounced deficit was found in the domain of executive/visuospatial. Diminished executive functions (dysexecutive syndrome) were also found by Versace et al. [32] in 12 patients at 9–13 weeks post COVID-19 onset. Similar results were demonstrated by Miskowiak et al. [33] at 3–4 months after disease onset, denoting global cognitive impairment in 38% of the COVID-19-positive individuals (n = 29), while 24% of the patients presented selective impairment, and the main deficits were found in the domains of verbal learning and working memory. Blazhenets et al. [34] evaluated eight COVID-19 patients at the subacute stage of the disease (37 ± 19 days) and at approximately 6 months post disease onset, demonstrating that although there was an improvement in global cognitive function, 5 patients remained below the cut-off value for detection of cognitive impairment.

These cognitive impairments are not limited to symptomatic patients, as found by Amalakanti et al. [35] in a case-control study involving 93 COVID-19 patients and 102 controls, showing that asymptomatic individuals presented an impaired function in the visuoperception,
Table 1. Cognitive impairment manifestation of COVID-19 patients

| Study type                  | Location | n       | Manifestation                                                                 | Ref. |
|-----------------------------|----------|---------|-------------------------------------------------------------------------------|------|
| Retrospective cohort        | France   | 58      | Dysexecutive syndrome: 14/39 (36%)                                           | [35] |
|                             |          |         | Agitation: 40/58 (69%)                                                       |      |
|                             |          |         | Confusion*: 26/40 (65%)                                                     |      |
| Case-control                | India    | 93      | COVID-19 patients presented lower scores in the domains of visuoperception (2.4±0.7 vs. 2.8±0.7); naming (3.6±0.5 vs. 3.9±0.2); fluency (0.9±0.6 vs. 1.6±0.7). Correlated with age | [34] |
| Case-control                | China    | 29      | COVID-19 patients exhibited deficits in attention domains                      | [125]|
| Cross-sectional             | USA      | 57      | Cognitive deficits varied in severity: mild (27; 47%), moderate (14; 25%), severe (5; 9%); delirium during acute hospitalization (37; 66%) | [30] |
| Prospective cohort          | Italy    | 87      | Patients divided into four groups according to the respiratory assistance. MoCAb/MMSEe: group 1: 74.2% deficits/12.9% mild to severe deficit; group 2: 94.4% deficits/55.6% mild to moderate deficits; group 3: 89.6% deficits/48.3% mild to severe deficit; group 4: 77.8% deficits/44.4% moderate deficits. Correlated with age | [29] |
| Case series                 | Italy    | 9       | Low scores* in the domains of attention, calculation, short-term memory, constructional praxis, and written language (3; 33.3%) | [126]|
| Case-control                | Italy    | 12      | COVID-19 patients showed a significantly poorer cognitive performance and smaller scores in different tests (p < 0.001) | [127]|
| Retrospective and prospective cohort | Italy     | 185 | Evaluations performed at 23 [20–29] days post discharge. Cognitive impaired patients: 47 (25.4%). Of these: required hospitalization: 36; were discharged from emergency department: 11 | [128]|
| Retrospective cohort        | USA      | 1,409   | Cognitive dysfunction in different domains: requires prompting (327; 23%), requires assistance, and direction (92; 7%). Confusion: in new and complex situations only (575; 41%), on awakening or at night, during the day/evening, or constantly (85; 6%) | [37] |
| Prospective cohort          | Germany  | 29      | Cognitive impairment in executive abilities, visuoconstruction, memory, and attention: 29 patients. Severity: mild to moderate (14; 54%); severe (4; 15%). Alterations in different domains: memory (7/14); executive functions (6/15) | [129]|
| Prospective case series     | Germany  | 8       | Subacute stage: 37±19 days post COVID-19 onset; chronic stages: 6 months post COVID-19 onset. Global cognitive function improved over time (from subacute to chronic stages), but the mean score was still indicative of cognitive impairment. Persistent deficits cognitive: 5 patients (visuoconstruction, executive functions, memory) | [130]|
| Cross-sectional             | Italy    | 56      | Patients with delirium (14; 25%); higher scores in different tests (p < 0.001) and were older than patients without delirium (p = 0.002) | [36] |
| Prospective cohort          | Denmark  | 29      | Global cognitive impairments (11; 38%) or selective impairment (7; 24%). Deficits in domains of verbal learning and working memory | [33] |
| Prospective cohort          | UK       | 58      | Global cognitive impairmentb (16; 28%) and deficits in the domain of executive/visuospatial (40% vs. 16% in controls) | [31] |
| Case report                 | USA      | 1       | Delirium during acute phase of infection. Delirium and cognitive status did not improve at more than 3 months after diagnosing | [38] |
| Prospective cohort          | Italy    | 266     | Poor performance in different functions of a cognitive test: at least one function (21; 16%), two (22; 17%), three (18; 14%), four (14; 11%), five (7; 5%), and 2 patients (1.5%) showed no good performance at all. Patients with psychopathology at 1-month after discharge performed worse on verbal fluency, information processing, and executive functions at the 3 months assessment, whereas psychopathology at 3 months associated with worse information processing | [131]|
| Prospective cohort          | Germany  | 53      | Cognitive deficits in executive function, attention, language, and delayed recall | [132]|
| Case-control                | Italy    | 12      | Evaluations performed at 9–13 weeks post COVID-19. Diminished executive functions (dysexecutive syndrome) | [32] |
| Randomized clinical trial   | Germany  | 1,030   | Cognitive impairment*: 622 (60.6%)                                           | [133]|
| Prospective cohort          | USA      | 50      | Cognitive deficits in short-term memory (15; 30%) and attention (12; 24%) | [134]|
| Prospective cohort          | Austria  | 23      | Cognitive deficits in concentration, memory, and/or executive functions (4; 29%) | [135]|

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*The Confusion Assessment Method for the ICU (intensive care unit) (CAM-ICU). **Montreal Cognitive Assessment (MoCA) test. ***Continuous Performance Test (CPT). ****Brief Memory and Executive Test (BMET). *****Mini Mental State Evaluation (MMSE). ******Frontal Assessment Battery (FAB). *******Outcome and Assessment Information Set version D-1 (OASIS-D-1). ********Neuropsychological Test Battery (NTB). *******The 4 ’A’s Test (4AT). ********Psychiatry Danish Version (SCID-D). *******Trail Making Test-Part B (TMT-B). *******Brief Assessment of Cognition in Schizophrenia (BACS). ********NIH Toolbox for the Assessment of Neurological and Behavioral Function. *******Tests of Attentional Performance (TAP).
naming, and fluency domains of cognition, and the impairment was worse in older participants.

Confusion and delirium were also observed in several COVID-19 patients. Helms et al. [36] found that 26 of 40 participants (65%) presented confusion during the course of the disease and hospitalization in the ICU. D’Ardes et al. [37] noted that 14 patients (25%) presented delirium and had test results indicative of cognitive impairment. In addition, Bowles et al. [38] demonstrated that in their retrospective cohort confusion was observed in different domains, e.g., in new and complex situations only (575; 41%), and on awakening or at night, during the day/evening, or constantly (85; 6%); cognitive impairments were also detected. In a case report, Payne et al. [39] pointed a case of an 85-year-old patient who experienced confusion and functional decline in the acute phase of the disease, but after more than 3 months from diagnose, the cognitive status and delirium did not return to the baseline.

Cross Talk between Infected Lungs and the Brain in COVID-19

Lung Infection by SARS-CoV-2

A summary of a report of over 70,000 cases of SARS-CoV-2 infection pointed that most cases (81%) were classified as mild (without pneumonia or mild pneumonia), whereas 14% of the cases were considered severe: presence of dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to a fraction of inspired oxygen ratio <300, and lung infiltrates >50% within 24–48 h, and 5% were critical (with respiratory failure, septic shock, and multiple organ dysfunction or failure). The overall case fatality rate was 2.3%; however, patients with comorbidities or those over 70 years old were more susceptible to complications and death [40].

The airborne and persistence of the virus on surfaces explain the rapid spread of COVID-19 infection [41]. The acute clinical features of COVID-19 are fever, cough, myalgia, headache, and sore throat. The following clinical stage was characterized by high fever, shortness of breath, hypoxemia, and atypical pneumonia [42].

SARS-CoV-2 spreads through droplets and secretions from the respiratory tract of an infected person [43]. The SARS-CoV-2 is an enveloped positive-stranded RNA virus. This virus replicates in the cytoplasm of host cells and the viral RNA genome merges with the plasma membrane, releasing viral replicates into the extracellular space [44].

It was recently predicted that SARS-CoV-2 directly attacks type 2 pneumocytes by binding to the human angiotensin-converting enzyme 2 (ACE2) receptor [45], a membrane carboxypeptidase enzyme present in distal airways and alveoli, especially type 2 pneumocytes which have the highest expression of ACE2, along with alveolar macrophages and dendritic cells. For this reason, the surface area of the lung serves as a reservoir for viral binding and replication [46]. ACE2 is also expressed on the vascular endothelium, nasal, oral, nasopharyngeal, and oropharyngeal epithelia, gut epithelia, cardiac pericytes, renal proximal tubular cells and in the skin, reticuloendothelial, and the CNS [47].

Dendritic cells and alveolar macrophages phagocytose the virus-infected epithelial cells and induce alveolar injury and interstitial inflammation [48]. In addition, recruited macrophages release chemokines, increasing capillary permeability, and allowing neutrophils to migrate into the space alveolar. The migration of neutrophils results in the rupture of the alveolar-capillary barrier and the formation of edema due to the migration of blood proteins [49]. In the alveolar space, monocytes are recruited and secrete pro-inflammatory cytokines that induce pneumocyte apoptosis [44]. Also, interstitial edema contributes to alveolar dysfunction [50] and severe impairment of alveolar gas exchange and oxygenation [51]. The massive production of cytokines is involved in this process and is called “cytokine storm.” Cytokine storm results from an inflammatory overreaction that ultimately leads to endothelial cell dysfunction, damage of the vascular barrier, capillary leak, and diffuse alveolar damage [10].

Cytokine Storm after SARS-CoV-2 Infection

Cytokine storm is an umbrella term encompassing several disorders of immune dysregulation characterized by constitutional symptoms, systemic inflammation, and multiorgan dysfunction that can lead to multiorgan failure if inadequately treated [52]. The mortality of hospitalized individuals with pneumonia due to COVID-19 has been attributed mainly to the cytokine storm syndrome [10].

The spike surface glycoprotein S on the SARS-CoV-2 binds to ACE2, and cell entry requires priming of the spike protein by the cellular serine protease TMPRSS2 or other proteases. The alveolar epithelial cells, lymphocytes, and vascular endothelial cells are the primary targets of the virions (Fig. 1). The virus inhibits the production of interferons that are part of cellular defense mechanisms. The viral replication releases a large number of
virions, leading to infection of neighboring target cells and viremia, which then cause an exaggerated pulmonary and systemic inflammatory response, respectively [53, 54]. This explains the clinical presentation of severe COVID-19 that is predominated by acute respiratory distress syndrome, shock, and coagulopathy [53].

Renin cleaves angiotensinogen to produce angiotensin I, which is further cleaved by ACE to produce angiotensin II, having a dual role. By acting through angiotensin II type 1 receptor, it facilitates vasoconstriction, fibrotic remodeling, and inflammation, whereas through angiotensin II type 2 receptor, it leads to vasodilation and growth inhibition. Angiotensin II is cleaved by ACE2 to Ang 1–7, which counteracts the harmful effects of the ACE/Ang II/AT1 axis. Thus, ACE2 primarily plays a key role to physiologically counterbalance ACE and regulate angiotensin II. The internalization of ACE2 after viral interaction leads to its downregulation and consequent upregulation of angiotensin II. The latter, by acting through angiotensin II type 1 receptor, activates the downstream inflammatory pathways, leading to the cytokine storm that adversely affects multiple organs [55].

Specifically, cytokine storm evolves through several pathways, like the NF-κB, janus kinase/signal transducers and activators of transcription (JAK/STAT), and the macrophage activation pathway, triggering the release of interleukin-1β, IL-6, C-X-C motif chemokine ligand 10 (CXCL10), TNF-α, interferon-γ (IFN-γ), macrophage inflammatory protein-1α and -1β, and the vascular endothelial cell growth factor [56]. IL-6 is a key player in the cytokine storm, stimulating several cell types and forming a positive feedback loop [19, 57], and higher IL-6 levels are strongly associated with shorter survival [58]. The large-scale unregulated production of interleukins, particularly IL-6, further stimulates several downstream pathways, increasing the production of acute-phase reactants, like C-reactive protein [59].

Hematological alterations are also related with the cytokine storm. Peripheral blood leukocyte and lymphocyte

![Fig. 1. Schematic of the SARS-CoV-2 infection. (1) The S protein binds to the receptor ACE2. (2) Cleavage of SARS-COV-2 S protein. (3) Activation of S2 domain. (4) The virus-cell fusion process.](image-url)
counts are normal or slightly reduced in early disease, when symptoms tend to be nonspecific [60]. Approximately 7–14 days from the onset of symptoms, the appearance of significant lymphopenia coincides with a decline in clinical status, enhanced levels of inflammatory mediators, and cytokine storm [61].

TNF-α can promote T-cell apoptosis and IL-6 may suppress normal T-cell activation [62]. Additionally, reduced lymphocyte turnover due to the cytokine storm induces atrophy of lymphoid organs. Thus, the SARS-CoV-2 infection may cause lymphopenia resulting in reduced CD4+, CD8+ T-cell counts, and suppressed IFN-γ production [63]. Type 1 IFNs are important in inhibiting the early stage of COVID-19 infection, so a failure in the immune response of type 1 IFNs excessively enhances the activity of the immune system, increasing pro-inflammatory cytokine production [64]. In the CNS, the expression of ACE2 in neurons and glial cells makes the brain vulnerable to COVID-19 infection [65], but the peripheral cytokine storm can be an important factor to the brain alterations.

**Brain Barriers and SARS-CoV-2 Infection**

The CNS has long been described as immunologically privileged due to its natural barriers that separate it from peripheral organs, but this dogma has undergone modifications [66]. Macroscopic examples are the brain meninges [67], but there are also microscopic brain barriers formed by different cells that assist in controlling the influx of substances from the blood into the brain parenchyma [68]. The blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier form these brain barriers [69]. The BBB is located at the level of the endothelial cells within CNS microvessels, while the blood-cerebrospinal fluid barrier is established by the choroid plexus epithelial cells [70].

The cells that compose brain barriers can be stimulated by microorganisms, such as bacteria, or by PAMPs, e.g., gram-negative lipopolysaccharide [71], and by immune or toxic molecules present in peripheral blood, such as interleukins [72] or reactive oxygen species [73]. However, viruses can also activate brain barrier cells [74], as emerging data indicate that neurological complications occur as a consequence of SARS-CoV-2 infection [75] and it could be caused by BBB activation [76]. The activation of endothelial cells from the BBB occurs due to the high expression of ACE2 receptors [77], but it is also known that BBB cells can be infected with the SARS-CoV-2 virus, and after viral replication, virions can be released into the brain parenchyma [78].

Recent studies show different routes of entry for the COVID-19 virus into the CNS [79, 80] (Fig. 2). The first route of entry would be through the olfactory epithelium, crossing the cribriform plate of the ethmoid bone and reaching the olfactory bulb from which it could spread to different areas of the brain [81]. The second route would be through the activation of brain barriers, as already mentioned, which allows the action of a third route. In this third route, infected leukocytes could enter through dysfunctional brain barriers, acting as a vehicle for dissemination within the CNS [82, 83]. And the fourth mechanism would be through the neuronal pathway, in the lower respiratory tract through the vagus nerve, where viruses are transported by endocytosis and exocytosis through neuronal cell bodies [84]. Evidently, viruses can also damage neurons directly or indirectly by stimulating the reaction of microglial cells and astrocytes [85].

However, we intend to show the neuronal damage due to neuroinflammation occurring as a response to peripheral inflammation, independently of brain infection with SARS-CoV-2. A previous study identified that COVID-19 patients presented enhanced levels of inflammatory markers in the blood and cerebrospinal fluid, being the encephalopathy the neurological condition mainly influenced by peripheral inflammation [86]. The SARS-CoV-2 infection can be classified as acute, that is, there is no persistence of the virus in the human body for long periods, indicating that only a section of the neurological changes seen in COVID-19 patients is caused directly by the presence of the virus [87, 88]. In fact, postmortem studies show that a significant rate of individuals diagnosed with COVID-19 who presented neurological disorders tested negative for the presence of the virus in the CNS [89–94].

For a long time, many peripheral infectious diseases were not associated to the changes in the CNS [68], but this concept is rapidly changing due to the COVID-19 pandemic, where many surviving patients show cognitive and functional changes [89]. We support the idea that the cytokine storm may be intrinsically involved in early and long-term neurological damage, during SARS-CoV-2 infection and after COVID-19 recovery [95, 96]. In addition, the activation of brain barriers is possibly the most accurate mechanism for enhancing neurological damage in COVID-19 individuals [75, 97] since in response to stressful events, such as infections or release of inflammatory mediators, the characteristics of these barriers can be altered, leading to edema and recruitment of inflammatory cells and the release of toxic metabolites into the brain parenchyma [70].
Abdominal sepsis is an example that illustrates what is been proposed to happen in COVID-19: peripheral pro-inflammatory cytokines, along with oxidative stress, stimulate the expression of extracellular matrix metalloproteinases that degrade the tight junctions of the BBB and impair its functioning [98, 99]. Increased expression of the type 1 adhesion molecule, responsible for the scrolling and infiltration of leukocytes in the cerebral microvasculature, was verified in experimental sepsis [100]. In addition, an increasing permeability of BBB can lead to the activation of glial cells and the production of cytotoxic mediators which in turn act on the brain barriers, propagating the damage. Thus, brain barriers permeability is not only a cause but a consequence of brain injury in sepsis [68]. In summary, neurological damage can arise regardless of the presence of the virus, considering that peripheral mediators can access glial cells and induce their reactivity, and these in turn initiate and maintain neuroinflammation, which in excess causes more cellular damage (Fig. 3).

**Fig. 2.** Routes of entry for the COVID-19 virus in the CNS. (1) The first route of entry would be through the olfactory epithelium, crossing the cribriform plate of the ethmoid bone and reaching the olfactory bulb from which it could spread to different areas of the brain. (2) The second route would be through the activation and permeability of BBB. The virus in the bloodstream may infect the peripheral immune cells and cause the cytokine storm. Cytokines can signal and alter the structure of BBB, and infected leukocytes could enter the CNS through dysfunctional brain barriers, acting as a vehicle for dissemination within the CNS or aggravate cytokine production within the CNS. (3) Another mechanism would be through the neuronal pathway in the lower respiratory tract through the vagus nerve, where viruses are transported by endocytosis and exocytosis through neuronal cell bodies.
mote self-remodeling and can attack stressed neurons [102]. Along with microglia, the astrocytes are involved in physiological and pathological activities within the CNS [103]. These activities include not only the formation and maturation of synapses [104] but also the maintenance, pruning and remodeling of synaptic transmis-
sion, and plasticity [105]. Astrocytes are capable of releasing several neurotrophic factors that assist in neuron differentiation and survival [106].

Microglia and astrocytes become reactive to inflammatory processes mainly because of vascular alterations in the brain that may lead to hypoxia and cytokine storm, and these alterations can arise from a direct CNS viral infection or a systemic inflammation due to a peripheral organ dysfunction (Fig. 3) [7]. As seen in sepsis [107], COVID-19 patients can experience cognitive impairment, since the systemic inflammation and the acute respiratory distress syndrome together produce a wide range of insults that favors glial cells activation, BBB disruption, and neurodegeneration, being the hippocampus highly susceptible [108].

In the brain, ACE2 receptors are present on neurons and glial cells [109], but it has been also discovered in substantia nigra, ventricles, middle temporal gyrus, the posterior cingulate cortex, and the olfactory bulb. Such widespread expression in the brain has reinforced that SARS-CoV-2 can infect neurons and glial cells in the CNS [109, 110].

A case report of a SARS-CoV-2 patient with cerebellar hemorrhage showed microglial nodules and neuroophagia bilaterally and in the cerebellar dentate nuclei, as highlighted by CD68 immunostains, and also CD8+ cells in microglial nodules [111]. COVID-19 infection induces severe hypoxia conditions, which potentiate and exacerbate microglia responsiveness and delays its shift to a surveillant state important for tissue repair. This is a possible pathway for the pathogenicity of COVID-19 and the complications in tissues sensible of oxygenation variation, such as the brain, and tissue damage as observed in severe patients of COVID-19 [112].

Moreover, pathogens are able to directly induce astrocytes to become reactive, such as herpes simplex virus type 2 [113], Japanese encephalitis virus [74], and more recently, SARS-CoV-2 [89], since astrocytes express ACE2 receptors, though in a lower concentration than in neurons [114]. In August 2020, the first preclinical evidence emerged indicating that coronaviruses can stimulate the release of pro-inflammatory cytokines in type I astrocytes. Evidences of astrocyte activation have been identified in the plasma, brain, and cerebrospinal fluid of patients with COVID-19 [115–117].

Another important evidence emerged when a postmortem study found similar histopathological alterations among COVID-19 patients and sepsis patients [118], supporting the hypothesis that not only the presence of the virus [119] but also the cytokine storm contributes to neurological damage after COVID-19, in the same way that occurs during sepsis [68]: peripheral COVID-19 infection induces an expressive release of cytokines, which can subsequently compromise the BBB and cause the reactivity of microglia- and astrocyte-borne TLR, stimulating these cells to release toxic substances and inflammatory mediators, thus leading to neuronal tissue damage without the presence of the virus in situ [77]. In fact, some works show that most of the patients with neurological alterations due to COVID-19 did not present the virus in the CNS [89, 118, 120, 121].

Independently of the reason, COVID-19 survivors are at a high risk of developing long-term neurological alterations either because of an aggravated pre-existing disorder or by triggering a new one [36]. Researchers pointed that SARS-CoV-2 infection, by causing several cellular imbalances, oxidative stress, and mitochondrial and lysosomal dysfunctions, would prone the cells to be less infection-resistant, thus in the long-term it may accelerate aging of the immune system and disturbed tissues [122], and this would explain the reason COVID-19 survivors are susceptible to the development or worsening of Parkinson’s disease [123], especially because the cortex and substantia nigra are the two brain regions with higher SARS-CoV-2 penetration and the most frequently associated with neurodegenerative diseases [124].

As seen in other infections, like sepsis [68], reactive microglia and astrocytes are a part of the neuroinflammation cascade, a process that can be beneficial in eliminating pathogens; however, when exacerbated or sustained, it tends to be detrimental, which generates imbalances in neurotransmitters and causes short- and long-term clinical manifestations, and these pathophysiological mechanisms may also be involved in the neurological manifestations of COVID-19 survivors.

Conclusion

Overall, the findings discussed in this review indicate that the systemic inflammatory response induced by SARS-CoV-2 seems enough to set off the alarms on its potential association with neuroinflammation, regardless of the presence of the virus in the brain. This interplay between periphery and brain is controlled by brain barriers, and the exposure to SARS-CoV-2 virus can disrupt this control, damaging this important protection against the deleterious consequences of systemic inflammation and favoring the entry of pro-inflammatory cytokines and peripheral immune cells into the CNS. Therefore, gli-
al responsiveness displays an exaggerated release of pro-inflammatory mediators that induces synaptic loss and demyelination, reinforcing the evidence that neuroinflammation associated with COVID-19 is involved in subsequent neurodegeneration and cognitive decline.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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